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Extended Research Article

The feasibility of risk-stratified screening as routine practice in the NHS Breast Screening Programme in England: the PROCAS2 research programme

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Disclaimer: This article contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

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Abstract

Background: Screening for breast cancer produces benefits through cancers being detected earlier, thereby reducing premature deaths and the need for more intensive treatment. As with all screening, it can also produce harms such as false-positive screening test results. One way to improve the ratio of benefits to harms is through risk stratification. The main potential benefits of risk-stratified screening are via identifying women who are currently unaware that they are at increased risk and who can be offered more frequent screening and medicines for breast cancer prevention. However, it is unclear if these benefits would materialise in routine practice, whether additional harms would materialise and whether risk stratification is cost-effective.

Objectives: Our aims were to develop a risk-stratification system, BC-Predict, and to evaluate its feasibility when delivered as part of the National Health Service Breast Screening Programme. Specific objectives were to: (1) automate BC-Predict informatics systems and integrate into National Health Service Breast Screening Programme; (2) optimise to be acceptable to women who were offered it and healthcare professionals delivering it; (3) assess feasibility of BC-Predict, including estimates of benefits and harms; (4) identify likely cost-effectiveness and (5) engage key stakeholders to consider how risk stratification should be taken forward.

Design and methods: The PROCAS2-Collator software was created to control the workflow of BC-Predict, and qualitative methods were used to develop patient-facing materials, care pathways and study procedures.

The main feasibility study involved women being offered BC-Predict as part of routine National Health Service Breast Screening Programme, with a comparison group of standard National Health Service Breast Screening Programme.

Setting and participants: The BC-Predict was offered at seven screening sites (three screening centres), with the comparison standard National Health Service Breast Screening Programme organised by two sites (one screening centre), within North West England. Participants were all women offered the National Health Service Breast Screening Programme at participating sites, with nested qualitative work with healthcare providers from the same screening centres.

Intervention: The BC-Predict risk-stratification system, offered to women when invited to the National Health Service Breast Screening Programme, calculated the 10-year risk based on the Tyrer–Cuzick model and produced risk feedback letters after negative screening test results were received. Women at high risk (≥ 8% 10-year risk) or moderate risk (≥ 5% to < 8% 10-year risk) were thereby encouraged to make telephone appointments to discuss prevention and early detection options.

Main outcome measures: Uptake of BC-Predict and subsequent prevention and early detection offers. BC-Predict was costed using a National Health Service perspective, and a decision-analytic model-based cost-effectiveness analysis was technically verified with validation.

Results: The BC-Predict was offered to 19,464 women, where 14,661 women attended screening (60.7%). Only 2429 women (12.5%) who were eligible took up the offer of BC-Predict. Uptake was substantially higher when women were personally approached at the study site: 137/263 (52.1%). Attendance at the telephone risk appointments offered was also lower than expected: 80/197 (40.6%) of high-risk and 68/379 (17.9%) of moderate-risk women. Of those who took up risk appointments, 105/148 (71%) women received a prescription for preventive medication and 63/80 (79%) accepted additional mammography. The cost-effectiveness analysis indicated that risk-based screening using self-reported risk factors and mammographic density provided 0.004 incremental quality-adjusted life-years per woman screened at an additional cost of £42 when compared to the current NHSBSP using 3-yearly screening (incremental cost-effectiveness ratio of £10,500 per QALY). Comparing this ICER with a cost-effectiveness threshold of £20,000 per QALY, suggests that replacing the current NHSBSP with risk-based screening could be a good use of the NHS budget.

A nested questionnaire study found no effects on general anxiety or cancer-related worry for women who were offered BC-Predict. Thematic analyses of qualitative interviews revealed women were positive about BC-Predict, with only transient increases in worry reported by high-risk women. Healthcare professionals who were involved with the

implementation were generally enthusiastic about the risk-stratified screening. The agenda-setting meeting identified a consensual view that risk-stratified screening is likely to happen eventually and that there is a need to develop plans to prepare for it.

Limitations: The study was not randomised and was dramatically impacted by the COVID-19 pandemic, with uptake of the study and of risk appointments in those identified as moderate or high risk almost certainly affected. As such, generalisability of the results will need to be reassessed after the results from the My Personalised Breast Screening trial are available.

Conclusions: The present work suggests that risk-stratified screening for breast cancer is feasible, acceptable and likely to be a cost-effective use of the healthcare budget. Key stakeholders at all stages viewed risk-stratified screening as generally desirable and inevitable.

Future work: The My Personalised Breast Screening trial has recruited over 50,000 women to examine the effectiveness of risk-stratified screening at preventing later-stage (2+) breast cancers. It is timely to consider information technology and workforce needs now and how best to engage women, especially those who are currently underserved by the existing National Health Service Breast Screening Programme.

Study registration: This study is registered as clinicaltrials.gov NCT04359420.

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Report Supplementary Material 1 BC-Predict technical report

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/HGDW6751).

Supplementary material has been provided by the authors to support the article and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed

The supplementary materials (which include but are not limited to related publications, patient information leaflets and questionnaires) are provided to support and contextualise the publication. Every effort has been made to obtain the necessary permissions for reproduction, to credit original sources appropriately, and to respect copyright requirements. However, despite our diligence, we acknowledge the possibility of unintentional omissions or errors and we welcome notifications of any concerns regarding copyright or permissions.

List of abbreviations

ANCOVA	analysis of variance
BC	breast cancer
CAG	confidential advisory group
DNA	deoxyribonucleic acid
FHPC	family history, risk and prevention clinic
GDPR	General Data Protection Regulation
GP	general practitioner
HCP	healthcare professional
IMD	Index of Multiple Deprivation
IT	information technology
MyPeBS	My Personalised Breast Screening
NHSBSP	National Health Service Breast Screening Programme
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PPI	patient and public involvement
PPIE	patient and public involvement and engagement
PROCAS	Predicting-Risk-Of-Cancer-At-Screening
QALY	quality-adjusted life-years
SES	socioeconomic status
SNP	single-nucleotide polymorphism
UKNSC	UK National Screening Committee
WP	work package

Plain language summary

The National Health Service Breast Screening Programme invites all women aged 50–70 years to have 3-yearly mammograms. The majority of women in this group who should be offered additional health care (more frequent mammograms and risk-reducing medication) based on their breast cancer risk are unaware of this risk. We created an online breast cancer risk assessment intervention (BC-Predict) to estimate 10-year breast cancer risk, based on a self-report questionnaire, alongside mammogram information and deoxyribonucleic acid from a saliva sample.

We produced written risk feedback information that was sent to women who wanted risk feedback after completing BC-Predict in the following categories: below average, average, moderate or high risk. Moderate- and high-risk women were encouraged to make a risk appointment with a healthcare professional. We ran focus groups with healthcare professionals at the National Health Service Breast Screening Programme centres, taking part in our study, to try to minimise concerns they had about BC-Predict. We interviewed British-Pakistani women to try to ensure that BC-Predict was usable by them.

The BC-Predict was offered to 19,464 women from three National Health Service Breast Screening Programme centres alongside their 3-yearly mammogram invitation. Overall, 2429 women took part and 148/576 (25.7%) moderate- or high-risk women accepted the invitation for risk appointments. All these numbers were lower than in previous research. Of the women who were at moderate or high risk and made appointments to discuss risk, 105/148 (71%) women received a prescription for preventive medication and 63/80 (79%) accepted additional mammography. Questionnaires found no changes in anxiety or cancer-related worry. Interviews with 40 women who received BC-Predict risk feedback were positive about it, though some had short-term concerns. The economic analysis, comparing the NHS costs and health benefits of Predict-EC with the current national breast screening programme, indicates that risk-based breast screening could be a good use of the NHS budget.

It is possible to include breast cancer risk assessment in the National Health Service Breast Screening Programme. Further work should focus on finding out how best to increase uptake, especially in more underserved communities.

Scientific summary

Background

Screening for breast cancer (BC) provides benefits in terms of preventing premature deaths and less invasive treatment being needed due to BCs being detected earlier. In line with all screening, it also produces harms such as overdiagnosis and false-positive screening test results. One way to improve the balance of benefits to harms, that has been proposed, is risk stratification. National Institute for Health and Care Excellence provides guidance related to the management of women at increased risk of BC, which indicates that women at higher risk should be offered more frequent screening and risk-reducing medication. However, the majority of women at increased risk do not have a strong family history of BC and are unaware of their risk. Providing women at screening, with the option of having their risk assessed, would allow higher-risk women to receive these offers. However, it is not clear if women would take up services in routine practice to gain these benefits, or whether additional harms would outweigh any benefits.

The present programme of work concerned a risk-stratification system, BC-Predict, to be offered to women when invited to the National Health Service Breast Screening Programme (NHSBSP). It calculates 10-year BC risk based on the validated Tyrer–Cuzick model, which combines information about self-reports of family history and factors that affect lifetime hormone levels with mammographic density from mammography and, in a subsample, single-nucleotide polymorphisms (SNPs) derived from saliva. Risk assessments identified women as belonging to one of the following categories: below average, average, above average (moderate) or high risk. The BC-Predict system then produces risk feedback letters and advice related to preventive options, which are sent to women participants and their general practitioner. Women at high risk (≥ 8% 10-year) or moderate risk (≥ 5% to < 8% 10-year) were thereby invited to make a telephone appointment to discuss prevention and early detection options at a family history, risk and prevention clinic (FHPC).

Aims and objectives

The aims of the present programme were to develop the BC-Predict system and to evaluate its feasibility when delivered as part of the NHSBSP. Specific objectives were to: (1) ensure that BC-Predict informatics systems functioned as intended; (2) ensure that it was acceptable to women who were offered it and healthcare professionals (HCPs) delivering it; (3) assess multiple aspects of feasibility of BC-Predict when rolled out in real time in screening centres in North West England, including benefits such as uptake of BC-Predict, risk consultations and chemoprevention harms, such as increased anxiety of women taking up BC-Predict; (4) identify key drivers underpinning the relative cost-effectiveness of embedding BC-Predict into the NHSBSP and (5) engage key stakeholders in an agenda-setting meeting to identify how risk stratification should best be taken forward.

Methods

The PROCAS2-Collator software was created to control the workflow of BC-Predict, including integration of information on risk factors (self-reported information on family history and hormone-related factors, e.g. age at first pregnancy, via questionnaire; mammographic density; and in a subsample, SNPs from saliva). Letters informed participating women of their risk categories and the implications of this. Qualitative methods were used to develop patient-facing materials, and BC-Predict care pathways and study procedures, with (1) women who had taken part in an earlier study where they received BC risk estimates, (2) British-Pakistani women from a deprived location and (3) HCPs from multiple professional backgrounds who were preparing to deliver BC-Predict.

The main feasibility study involved the offer of BC-Predict to women as part of routine NHSBSP, with a comparison group of standard NHSBSP, and it was registered with clinicaltrials.gov (NCT04359420). Inclusion criteria for BC-Predict were women born biologically female, invited for 3-yearly mammographic breast screening, able to provide informed consent and complete a self-report risk assessment questionnaire. Uptake of BC-Predict and subsequent offers of risk

review appointment, enhanced screening and preventive medication were recorded. A nested questionnaire study with 662 women examined changes in potential psychological harms, relative to women offered standard of care NHSBSP, at baseline (screening appointment) and 3 months and 6 months later. Further nested qualitative studies examined the experiences of women who received each of the four risk results after they had completed the BC-Predict pathway and participating HCPs after their centres finished offering BC-Predict.

The cost of delivering BC-Predict in the NHS was calculated, and a decision-analytic model-based cost-effectiveness analysis was technically verified and validation of the model was carried out. A final meeting involved analysis of discussions of key stakeholders in BC screening to develop a risk-stratified breast screening implementation agenda.

Results

Development of BC-Predict software, materials, care pathways and procedures

The PROCAS2-Collator software was developed and tested through an iterative series of pilots, with study team and services users to assess whether it was functioning as intended. A series of think-aloud interviews with 57 women developed and refined materials for use with women within each risk category. Women found these materials to be clear and appropriately pitched. The materials addressed concerns, such as users wanting materials to be framed in terms of the greater majority of women who do not develop cancer, and what women could do to reduce their risk.

Interviews were conducted with 19 British-Pakistani women, of whom 14 required a translator. Although there was enthusiasm for risk-stratified screening, a number of misunderstandings were identified, such as believing that breast screening is for those who present with symptoms. The information materials were therefore translated and made available in multiple languages and offered along with all BC-Predict invites.

Focus groups with 29 HCPs who would shortly be delivering BC-Predict identified concerns over capacity limitations in a service that was already stretched and concerns about increasing anxiety in some women and exacerbating existing inequalities in screening. This work fed into developing and refining procedures and care pathways for BC-Predict. For example, the creation of a BC-Predict study hotline and centralised risk discussion appointments at a single regional FHPC centre.

Main feasibility study: uptake rates

The BC-Predict was offered to 19,464 women at seven screening sites organised by three screening centres, of whom 14,661 women attended screening (60.7%). Of the invited cohort, only 2429 women (12.5%) took up the offer of BC-Predict. Of those who attended the screening, 16.6% accepted the offer of BC-Predict. This figure was substantially higher when women were personally approached at the study site. When personally approached, 137/263 (52.0%) women took up the offer of BC-Predict, and 79/125 (63.2%) of women took up BC-Predict when approached and were offered a paper questionnaire instead of requiring completion of an online form. Overall uptake was lower in women living in more deprived locations, as assessed by the Index of Multiple Deprivation. Telephone risk appointments were taken up by 80/197 (40.6%) of high-risk and 68/379 (17.9%) of moderate-risk women. Of those who took up risk appointments, 105/148 (71%) women accepted the offer of a prescription for risk-reducing medication. There was also a high uptake of additional screening in 107/148 (72.3%) women.

Main feasibility study: impact on women offered BC-Predict and healthcare professionals

There were no changes in the questionnaire ratings of general anxiety and cancer-related worry for women who were offered BC-Predict compared to women who were offered standard NHSBSP. Questionnaire scores were typical of those found in other studies of NHSBSP samples. Within BC-Predict, women, who were told that they were at high risk, rated their own risk higher and reported more cancer worry at 6 months than the women who were informed of being at lower risk, but changes were modest in size. A thematic analysis of 40 interviews with women within each of the four risk results revealed that women were positive about BC-Predict. Women who did not expect to be at high or moderate risk reported that they felt transient increases in worry, when found to be so, but that these adverse effects did not last. Fourteen HCPs working in the NHSBSP who were interviewed after their involvement with BC-Predict were generally

more enthusiastic about having implemented the risk-stratified screening. Major increases in workload, which were a concern prior to implementation, did not materialise.

Main feasibility study: cost-effectiveness analysis

The cost of estimating a woman's risk of BC was calculated to be relatively small, with an expected cost of £8.46 per woman for the approach used in BC-Predict. The addition of SNPs would result in an appreciably higher cost of £88.87. The cost-effectiveness analysis indicated that risk-based screening, using self-reported risk factors and mammographic density, was a more cost-effective use of resources than the 3-yearly screening, 2-yearly screening or no screening. At higher cost-effectiveness thresholds, the 2-yearly screening (as is routine in many other European countries) was equally as cost-effective as risk-stratified screening, but it was associated with a higher number of screens per woman (8.24 vs. 6.00) and therefore was an additional burden on the NHSBSP.

Agenda-setting meeting

A meeting at the end of the programme, an agenda-setting meeting involving key stakeholders, including HCPs, academic experts, patient and public involvement contributors and NHSBSP staff, was held. The meeting identified a consensual view that risk-stratified screening would happen eventually, pending results of the My Personalised Breast Screening (MyPeBS) effectiveness trial and the need to develop plans to prepare for it. These stakeholders identified the following recommendations for research:

1. identify procedures for how best to engage women
2. identify how best to promote uptake by women who are currently underserved by existing NHSBSP, notably women from minority ethnic populations and those living in more deprived areas
3. how to organise risk-stratified screening to avoid placing any additional burden on NHS staff and to consider further the role of general practice
4. consider feasibility of extending screening intervals of women at lower risk, for new service to not require additional funding
5. validate risk prediction algorithms for other ethnic groups and over longer follow-up periods
6. consider whether risk assessments that consider other diseases alongside BC would be valuable to women.

Conclusions

The present work has indicated that risk-stratified screening for BC is feasible as part of the NHSBSP. It was acceptable with no major harms to women who were offered it, and HCPs were involved in its delivery.

We originally anticipated offering BC-Predict to 18,700 women, and on the basis of Predicting-Risk-Of-Cancer-At-Screening results, we anticipated that 8000 women would consent to BC-Predict, of whom 1169 would be seriously considered for chemoprevention and 117 women would take it up. Thus, although the uptake of BC-Predict was lower than expected, this was partly attributable to coronavirus disease discovered in 2019 affecting the NHSBSP during the duration of the study. By contrast, risk-stratified screening also resulted in a higher uptake of medicines to reduce the risk of BC than previously reported, so the number taking up medication in the present study (n = 105) was only slightly below the number (n = 117) that was originally expected. Given this, and as chemoprevention produces NHS cost savings, a validated decision-analytic model indicated that a risk-stratified approach to BC screening is likely to be the most cost-effective option or equally as cost-effective as a 2-yearly screening. However, current capacity constraints in the NHSBSP, including the number of available radiographers, and the requirement for significantly more screening appointments in a 2-yearly approach may prove difficult to accommodate.

The MyPeBS trial has recruited over 50,000 women to examine the effectiveness of risk-stratified screening for reducing later-stage (2+) BCs, which should report by 2027. It is timely to consider plans for this, including considering information technology and workforce needs to allow roll-out in anticipation of these trial results. There is a need for further research to address how to increase the uptake, promote informed choices and to avoid exacerbating inequalities further.

Study registration

This study is registered as clinicaltrials.gov NCT04359420.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Programme Grants for Applied Research programme (NIHR award ref.: RP-PG-1214-20016) and is published in full in *Programme Grants for Applied Research*; Vol. 13, No. 13. See the NIHR Funding and Awards website for further award information.

Synopsis

Introduction and overview of the programme

The National Health Service Breast Screening Programme (NHSBSP) aims to detect breast cancers (BCs) early, but only 32% are detected by this route.[4] It has been repeatedly argued that the NHSBSP produces comparatively few benefits that may be outweighed by harms such as false-positive test results and overdiagnosis.[5] One approach to improve the balance of benefits to harms of breast screening is to stratify the offer received at screening by women's risk status.[6]

In 2013, National Institute for Health and Care Excellence (NICE) indicated that women at high risk of BC should have more frequent screening by mammography (annual mammography between ages 40 and 60 years) to detect BC at an earlier stage, and they offered chemoprevention therapy to reduce the risk of being diagnosed with BC.[7] However, NICE guidelines cannot currently be implemented, with most women undergoing screening in the NHSBSP as they are not currently informed of their risks. So far, only about one in six women (0.5% of population) who are in the high-risk category (defined by NICE as ≥ 8% 10-year risk of BC) have actively identified themselves as high risk by attending family history, risk and prevention clinics (FHPCs).[8,9]

The Predicting-Risk-Of-Cancer-At-Screening (PROCAS-1) National Institute for Health and Care Research (NIHR) programme grant showed that it was possible to accurately calculate the individual risk of 58,000 women developing BC through self-report questions and information on breast density derived from mammography.[10] In contrast to the 0.5% of the population who have a 10-year BC risk of ≥ 8%, PROCAS-1 showed that at least 3% of women are at high risk when all risk factors, including mammographic density, are assessed, and a further 10% are at moderate risk (5–8% 10-year risk).[8,9] This means that there are around an additional 450,000 women in England (aged 30–70 years) at high risk that NICE-guidance indicates *should* be offered chemoprevention and annual mammography.

The rationale underpinning the present programme of research was that defining an intervention, BC-Predict, that provides women with their BC risk shortly after receiving a negative NHSBSP screening test result will direct women to appropriate follow-up in terms of care pathways involving chemoprevention and increased mammography for high-risk women. Such an intervention must be evaluated in terms of the balance of potential benefits and harms and NHS costs.[11]

The present programme of research took as its focus issues concerning the feasibility of risk-stratified screening for BC; that is, not how effective is such screening, but what are the key issues that need to be considered in developing such a screening programme to allow it to be routinely implemented into the NHSBSP. Further, a required large-scale definitive evaluation which aims to show superiority of risk-stratified screening would require hundreds of thousands of women to have sufficient power to detect its effect on BC incidence and stage. Such an evaluation could only be done at reasonable cost as part of a large-scale implementation: a stand-alone randomised trial would cost tens of millions of Great British pounds. Given this, and in line with the Medical Research Council Framework for Developing and Evaluating Complex Interventions,[12] the present research aimed to resolve key uncertainties regarding the feasibility of integrating BC-Predict into the NHS and the feasibility of a definitive study of implementing BC-Predict to assess whether the intervention translates into measurable patient benefits and is a cost-effective use of NHS resources.

The present programme of research had the following overall shape. First, developmental work was carried out to ensure that the informatics procedures to integrate information regarding BC risk worked properly. Further developmental work was carried out to ensure that written materials were acceptable to women in receipt of a variety

of risk estimates. Relatedly, care pathways and study procedures had to be refined from the first PROCAS study to ensure that they were acceptable to women and healthcare professionals (HCPs).

These two streams of developmental work fed into the main BC-Predict feasibility study. This study evaluated the effects of BC-Predict in comparison with the usual NHSBSP in three screening centres. Outcomes included uptake of: FHPC appointments, chemoprevention, additional screening and other outcomes, including anxiety, as well as a process evaluation using qualitative methods, with both women accepting BC-Predict and HCPs delivering it. A nested micro-costing study and technical verification and validation of a decision-analytic model-based cost-effectiveness analysis considered embedding BC-Predict into the NHSBSP. Finally, the programme concluded with a final meeting with key stakeholders to set the agenda for future potential implementation of risk-stratified screening within the NHSBSP.

A schematic showing the relationships between the earlier developmental work, the main feasibility study and embedded economic analysis and consequent agenda-setting meeting is shown in *Figure 1*.

Developing automatic systems

Aim

The aim of this work package (WP) was to automate the workflow of the BC-Predict process to reduce the amount of manual administrative processes and allow the creation of real-time reports to see the overall progress of the patients' data through the process. The main detail for this WP is included as a technical report as in *Report Supplementary Material 1*.

Method

The BC-Predict process had three suppliers of software: Volpara Solutions (website), CRA Health (website) and the Digital Health Software team at The University of Manchester (website). Volpara's software (Volpara Health: www.volparahealth.com/) ran on the scanners in the hospitals, intercepting the images for the patients invited to the study and then calculating the breast density score. CRA Health supplied a questionnaire web application that asked the patient about certain aspects of their own health history and family health history. It then used the results along with the density score from Volpara to calculate an individual risk score and generate a risk letter.

The PROCAS2-Collator software created by the Digital Health Software team is the software that stood in the middle and co-ordinated the workflow of the research project. The main piece of software from an administrative or research user's point of view is a web application. There are also a number of small programs that operate without user interaction, which co-ordinate the communication between the three applications and the storage.

Members of the research team based at the Manchester University NHS Foundation Trust operated the BC-Predict research workflow.

The research team informed the Collator software of the patients who were invited by uploading a spreadsheet with the information. At this stage, just a minimum of the NHS number was required (as that is used as the identifier in the scanners). The invitee used CRA's software to consent to join the study, and once that consent occurred, a number of automatic and manual processes were initiated. Firstly, the images from the scanner were processed by the Volpara breast density calculator, and the results were sent to both Collator and CRA. If the images were not immediately available (i.e. the patient consented to the study sometime before their appointment), the process waited until they arrived from the scanners.

The CRA software combined the result from Volpara and the answers to the questions asked by CRA to produce a risk score and the text of a letter to send to the patient to highlight the risk score. This risk score represented the likelihood of developing BC over the next 10 years. The score and letter text were sent to Collator.

Within Collator, the patient's name and address were added and were then merged with the letter. The letter was exported then sent to the patient and their general practitioner (GP).

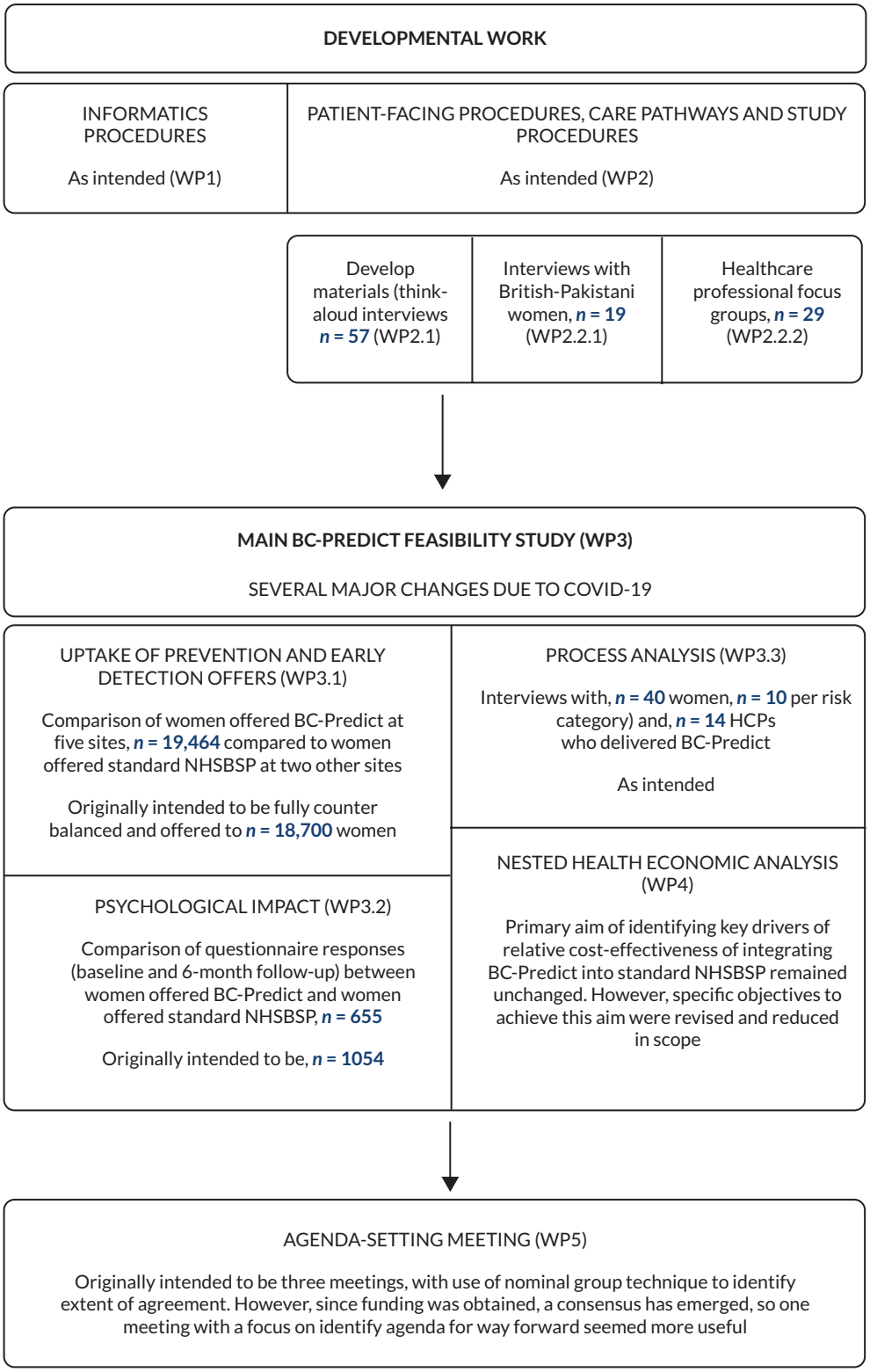

FIGURE 1 Research pathway diagram showing overall plan of programme, with deviations from original plan noted. COVID, coronavirus disease discovered in 2019.

The researchers could use Collator to view the progress of patients through the system, that is, they can see when their results were available and when to export their letter. They also had access to a number of reports that effectively allowed them to export the database, in an anonymised fashion, to allow them to study the data.

Key findings

The link between CRA and Collator worked very well from a technical point of view. During the entire 3-year period of operation, almost 3000 patients were processed through the system, and there were no errors attributable to the communication link.

The dashboard was popular, as it was very easy to get a list of patients for which the researchers needed to perform an action such as export a letter or follow up, because they had consented but not attended their appointment. Any problems with the data flow could be detected relatively quickly too.

Not all the processes could be easily automated and so this could perhaps be considered for future iterations of the project. The process of getting the patient information from the National Breast Screening System database was a manual one as there was no automatic way of doing it, so sometimes incorrect details of invited patients could be uploaded to Collator by human error. This caused a problem if the wrong NHS number was used, as Collator/Volpara would not be expecting their images and so would not record the data. This caused extra administrative overhead in order to fix the problem and push the images through again. The upload process to the CRA software could be made automatic too to reduce the level of administrative interaction with that software.

Limitations

An error in the CRA survey software made it impossible to distinguish between those patients of a White ethnicity or South Asian ethnicity, as both ethnic groups were recorded as White.

Interactions with the programme

The software provided the data necessary for WP2 and WP3 to both operate more efficiently and analyse the results easily. The intent of the programme was to show that the whole patient recruitment and operational process could be conducted online, and therefore the software was key to the process.

Developing and refining the BC-Predict intervention

Research aims

The key aim of this WP was to develop and refine the risk-stratification system that was used in the first PROCAS study[10] to be suitable for the assessment and delivery of risk estimates to women, who were offered NHSBSP appointments, and to provide appropriate care pathways for women at higher risk. Key concerns were that the system should be feasible, in terms of not causing distress or confusing to women, to be workable for NHS staff involved in its delivery and to avoid exacerbating inequalities to women from ethnic minority of lower socioeconomic status (SES) backgrounds.

Specific objectives were therefore:

1. to refine risk communication materials from PROCAS-1
2. to identify and overcome barriers to uptake of BC-Predict for ethnic minority and lower SES women
3. to optimise service delivery through developing appropriate care pathways within the NHSBSP and FHPCs.

Methods

Three pieces of work were undertaken, with somewhat overlapping objectives.

Think-aloud study

We used a three-step process in the development, refinement and acceptability of BC risk information materials.[13] All participants were women who were recruited through previous participation in the PROCAS-1 study, where they provided risk information and received risk estimates some years later.

The first step involved 18 women being presented with initial drafts of risk letters and accompanying information leaflets based on Cancer Research UK BC leaflets.[14] In line with recommendations on developing communications about cancer screening programmes,[15] the information aimed to provide accurate information about risk[16] and promote informed choices about screening. Participants were asked to independently read the version in line with their own risk and to 'think aloud' while doing so, verbalising their thoughts to indicate where there are difficulties in comprehension or misunderstandings.[17] At the end of this process, each woman was then briefly interviewed to elicit further thoughts, questions or comments about the information they had received. The information was then revised following feedback. Two further steps involved another 19 women and then a further 18 women being presented with revised letters and leaflets that were revised based on earlier steps and to again read and think aloud. At all stages, data were analysed deductively using thematic analysis from a realist perspective.[18]

Interviews with British-Pakistani women

As we wanted to elicit the views of ethnic minority women and women from low SES backgrounds, we chose to base this research in East Lancashire.[19,20] East Lancashire was one of the BC-Predict centres, and women in this area had a low uptake to the NHSBSP.[21] East Lancashire had a large community of British-Pakistani women[22] who were seen as one of the most 'underserved' communities by BC screening. Prior to commencing recruitment, the research team spent an extensive amount of time exploring the best and most effective ways to reach these 'underserved' communities. By speaking with a patient and public involvement and engagement (PPIE) group and community workers, the following strategies for recruitment were devised: (1) holding a community event and advertising the said event via commonly spoken languages in the area; (2) communicating the research study via contacts in the area (i.e. genetic counsellors) who were trusted by women and (3) providing interpreters.

In total, the researchers interviewed 19 women from the British-Pakistani community in East Lancashire about their views of BC screening generally and risk-stratified screening in particular. Of these women, 14 required an NHS-approved interpreter. The analysis of the interviews was conducted in two halves to reflect the two halves of the interview schedule. The analysis method chosen was thematic analysis, which was conducted from a realist perspective.[18] Coding was iterative using a hybrid approach of inductive and deductive analysis.

Healthcare professional focus group study

We elicited the views of those HCPs from the three screening centres, who would be responsible for delivering the BC-Predict intervention in the main study (described in the next section): Greater Manchester, East Lancashire and Macclesfield.[23] We recruited 29 HCPs with a variety of professional backgrounds, who took part in four focus groups. Before each focus group, a senior member of the research team gave a brief presentation of the BC-Predict intervention rationale and anticipated care pathways, followed by questions and discussion with the HCPs. The senior members of the team then left, and the focus groups were conducted by a different member of the research team. An inductive-manifest thematic analysis was conducted to analyse the resulting transcribed focus groups.

Limitations

The major limitation of the focus group study was a lack of diversity in participants, which may be due to the participants previously selecting into the NHSBSP and PROCAS-1 study as well as into this specific project. This limitation provided a clear justification for, and was somewhat overcome by, the interview study with the British-Pakistani women. This interview study with the British-Pakistani women involved women who all said they had been to breast screening at least once. Therefore, the views of those who disengage from breast screening may not have been fully captured. However, as the NHS does not routinely collect ethnicity and language spoken data, there was no way to reliably engage women who do not attend for breast screening. Clearly, we also only interviewed women from one particular ethnic group, and the views of women from other ethnic groups were not represented, including White women from lower SES backgrounds.

A particular challenge of the interviews with British-Pakistani women was that an interpreter was employed for 14 interviews. This resulted in the researchers not being entirely sure that the interpreter was translating verbatim. However, to mitigate this issue, the interpreter was briefed before every interview about their role and the aim of the research. Further, the research team involved researchers from exclusively White backgrounds, so some nuance and cultural issues may not have been fully elicited or appreciated by the research team.

The study with HCPs was limited by risk stratification being a hypothetical intervention for the interviewees at this stage. It should be noted, however, that the participants in the present study were aware that they would be implementing the care pathways discussed in the near future, which clearly focused minds on how to make the pathways work. Recruitment of primary care participants proved challenging, and their views may not have been well represented.

Key findings

Think-aloud study

The study had two main outputs; first, a set of revised materials (both leaflets and letters) for use with women within each risk category that women found to be clear and appropriately pitched. The potential for this information to induce anxiety was noted, and several suggestions were made for how this information could be framed to avoid this, for example focusing on the great majority of women who do not develop BC even in the higher-risk categories. The thematic analysis also identified some wider issues for communicating BC risk. First, the participants wanted to know about what were the factors specific to them personally which drove their risk rather than what are the main factors for women generally. Relatedly, they wanted to know what they could do to reduce their risk. In line with this, the women wanted to know where to contact if they wanted more information.

Interviews with British-Pakistani women

The thematic analysis identified a number of issues specific to this population, which applied to both screening, in general,[19] and risk-stratified screening.[20] One of the most problematic areas discussed was the language barrier between themselves and their HCP. Women described that often information would be missed as well as feeling a loss of privacy and autonomy when family members have to attend to act as a translator. A loss of privacy was also described when invites for screening are provided in English, as family members would have to read the invite on their female relative's behalf. For those unable to access the information, the invite was simply discarded. A number of misunderstandings were identified, such as believing that breast screening is for those who present with symptoms. In relation to risk-stratified screening, the interviewees were generally positive and expressed a desire to know their personal risk of BC. However, a number of barriers to access were anticipated, including language barriers and online completion of a self-report risk assessment questionnaire.

Healthcare professional focus group study

Healthcare professionals that took part in the focus groups also viewed the implementation of risk-stratified care as a positive way forward, but the discussion focused on a number of concerns. First, they emphasised that the current breast services have serious capacity limitations, and a major concern was that any innovations could lead to further demand on services that are already stretched. Second, they were concerned about how to convey risk information to women without inducing anxiety that was manageable, given the resource constraints. Third, the HCPs were concerned about the effects that risk stratification could have on inequalities. That is, the lower attendance at screening of many ethnic minority women was already seen as being a problem, and risk stratification was seen as potentially reducing screening uptake. The possibility of risk stratification not being taken up by lower SES or ethnic minority women was also flagged as being a potential downside to this approach.

Inter-relation with other parts of the programme

The findings of these three pieces of qualitative research helped refine the materials, care pathways and procedures that were used in the first PROCAS study. Together, this information helped develop these materials, pathways and procedures for the main BC-Predict study to produce a workable model of how to conduct risk-stratified screening for the main BC-Predict study.

The overall care pathway for women participating in BC-Predict and how this differs from standard NHSBSP are described in detail in *Report Supplementary Material 1*. The key features of BC-Predict were that risk estimation can be offered in real time to women invited to the NHSBSP via an online web system to allow consent and self-report measures to be provided. Women who receive a clear mammogram result are then sent a letter providing their 10-year BC risk within 6–8 weeks after their mammogram. Thus, all women were informed about their personal risk estimates. Those women at moderate

(> 5% but < 8% 10-year risk) or high (≥ 8% 10-year) risk are encouraged to attend a consultation at a Family History and Risk Prevention (FHRP) clinic to discuss the offer of more frequent screening and chemoprevention.

Following this qualitative research, the risk materials were refined, for example to convey that the majority of women do not develop BC. Researchers ensured that information materials were produced in different languages should these have been requested. More information was included on what women could do to reduce their risk and how to gain more information. For some of the duration of the main BC-Predict feasibility study, having a person attend the screening sites to explain the study and help women complete the online web system or elicit the information for risk estimation on paper forms was carried out and uptake was noted (see *Main BC-Predict feasibility study*). A study helpline was set up within office hours to answer any outstanding questions for all women. The letters and leaflets for women at moderate or high risk about how they should obtain timely consultations with FHPCs were emphasised. More broadly, invites from the NHSBSP in Greater Manchester also explained that mammograms would be performed by a female HCP.

The care pathways were also set up to make the running of BC-Predict fit with HCPs' existing working patterns. The study procedures were designed so that minimal additional actions were required by screening staff as the helpline handled queries. The offer of an appointment with little delay for moderate- and high-risk women was intended to reduce a period of waiting for women who may have been concerned by the results they received. Importantly, an agreement was reached within the area that chemoprevention could be prescribed for an initial period of 2 months by the FHPCs, with GPs being informed and asked to approve repeat prescriptions rather than carry out initial consultations and prescribing which required specialist knowledge that few GPs may have possessed.

Main BC-Predict feasibility study

Research aims

The overall aim of this WP was to establish the effects of rolling out BC-Predict at three NHSBSP centres in North England on potential benefits and harms, including assessing views of HCPs delivering BC-Predict and women who participated in it. Specific objectives were:

1. to quantify important potential benefits:
    a. screening attendance at first offered screening episode or within 180 days
    b. uptake of BC-Predict among women who were offered it
    c. uptake of risk consultation (for those eligible)
    d. uptake of chemoprevention (for those offered it)
    e. uptake of additional mammography (for those offered it)

2. to quantify important potential harms:
    a. lower uptake of NHSBSP among women offered BC-Predict
    b. increased worry about BC
    c. increased general state anxiety

3. to explore views on the acceptability of BC-Predict with:
    a. BC-Predict service users
    b. HCPs working in the NHSBSP, FHRP clinics and general practice.

Methods

The present study employed a non-randomised controlled trial of the effects of offering women either standard NHSBSP or BC-Predict alongside the NHSBSP offer of mammography screening (*Figure 2*). There were three elements to this trial, which are reported in turn: (1) trial of effects of BC-Predict on healthcare uptake, (2) nested questionnaire study and (3) two nested qualitative studies. The protocol for all elements for this non-randomised controlled trial was pre-registered.[1]

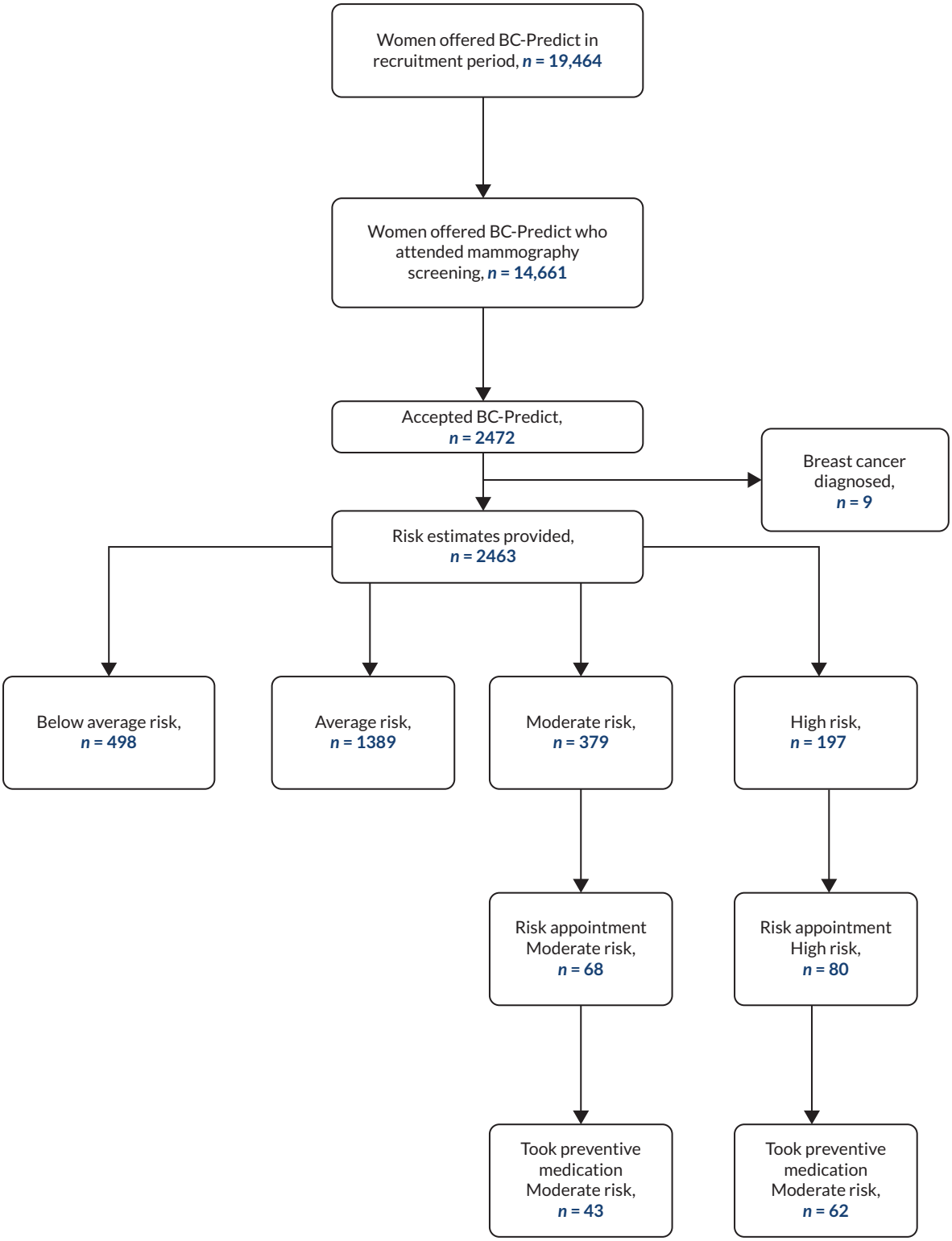

FIGURE 2 Flow of participants through the BC-Predict pathway during main feasibility study, showing risk estimates provided and uptake of additional services. Reproduced with permission from Evans *et al.*[2] and French *et al.*[3] These are Open Access articles distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

Trial of effects of BC-Predict on healthcare uptake

Design

All women involved with the PROCAS2 study were invited from seven NHSBSP sites run by three centres in North West England,[2] with women from five participating sites also being offered BC-Predict and women from two other sites being offered only standard NHSBSP. Nested within the BC-Predict arm was a further non-randomised factor, whereby various changes were made to methods of recruitment, including changes to the information sheets and invitation letters, and variations in uptake rates were noted.

After a pilot phase, BC-Predict started in September 2019 in two Greater Manchester sites (Trafford, Withington Community). The intended start was delayed in the two Macclesfield sites. A research practitioner was utilised from January to March 2020 to aid recruitment on site and to offer the single nucleotide polymorphism – polygenic risk score (SNP-PRS). The study was seriously disrupted by the coronavirus disease discovered in 2019 (COVID-19) pandemic, with a full shutdown occurring in England on 21 March 2020 and only reopening on 1 August 2020. It was not possible to offer saliva testing from this point. Also, screening invitations were severely curtailed due to needs for social distancing and cleaning of equipment after each woman was screened. Therefore, recruitment did not finish in the first two sites until 2 September 2020. The switch over to Oldham in Greater Manchester, the Macclesfield sites and the two East Lancashire sites occurred on 3 September 2020 and 15 September 2020 and 2 February 2021, respectively. The trial was extended to 9 July 2021 at all the second phase sites to adjust for the reduced invitation rates for screening. From August 2020, women did not receive an actual appointment for mammography but rather an invite to make an appointment.

Participants

All women who had mammograms scheduled at one of the seven participating sites in the study period were included. Additional inclusion criteria were that the participant was born biologically female and was able to provide informed consent. Exclusion criteria were that the participant previously had BC or had a bilateral mastectomy.

Procedure

All women were invited to have a mammogram by the NHSBSP during the recruitment period. During the COVID-19 pandemic, the NHSBSP programme changed the breast screening invitations to open-invite letter, and this was continued for the duration of the present study rather than previous usual practice of sending pre-allocated appointments.

Women in the BC-Predict arm who took up the offer of BC-Predict and who received a clear mammogram result were sent a letter in the post, providing their 10-year BC risk approximately 6–8 weeks after their mammogram. The risk feedback letter informed women that they are at 'high' (≥ 8% 10-year risk), 'above average (moderate)' (≥ 5% but < 8% 10-year risk), 'average' (≥ 2% but < 5% 10-year risk) or 'below average' risk (< 2% 10-year risk).

Each letter explained how the risk estimates were derived and the implications of these along with a leaflet providing additional detail on BC risk factors, signs and symptoms of BC and how risk might be managed. Women at 'high' or 'above average (moderate)' risk were also encouraged to make an appointment at a Family History and Risk Prevention Clinic to talk about managing their risk.

Measures and analysis

The following outcomes were assessed:

1. screening attendance at first offered screening episode or within 180 days by screening site
2. time to provision of results from BC-Predict and proportion over 8-week threshold
3. subsequent consultation in FHRP clinics (and mode: telephone only as face-to-face meeting not possible due to COVID-19)
4. subsequent enrolment for more frequent mammographies for those receiving a moderate- or high-risk appointment
5. subsequent prescription of chemoprevention for those receiving a moderate- or high-risk appointment.

Comparisons by two-sided chi-squared tests were used to assess the differences in uptake using Fisher's exact test and trends by Mantel–Haenszel chi-squared test for linear trend.

Nested questionnaire study

Design

A questionnaire study was nested within the main BC-Predict trial,[3] with only half of women at the five sites offering BC-Predict being invited (the first half of women on the daily list received from each site), whereas all women at the two sites offering only standard NHSBSP were invited.

Participants

Women who had mammograms scheduled at one of the seven participating sites in the 8-month recruitment period for this nested questionnaire study (November 2020–July 2021) were eligible (although one site did not begin recruitment until February 2021).

Procedure

Women were asked to complete questionnaires at baseline, 3 months and 6 months online using a unique study identification number on SmartSurvey (www.smartsurvey.co.uk/). Paper copies were available on request. For women in both BC-Predict and standard NHSBSP groups, the invitation to complete the baseline questionnaire was sent approximately 7 days after their first offered mammogram appointment. Women in both experimental groups only received follow-up questionnaire invites via letter once they had received a clear mammogram result and BC status was negative.

Measures

The key measures that were administered were as follows.

Perceived relative risk of developing BC was assessed with a single-item that asked women to rate their risk of developing BC in the next 10 years compared with other women of their age, from 'much lower', 'a bit lower', 'about the same', 'a bit higher' and 'much higher'.[24]

State anxiety was assessed using the six-item short form[25] of the Spielberger State-trait Anxiety Inventory,[26] with participants responding to six emotion adjectives (e.g. 'upset') about their present feelings by selecting one of the following response options: 'not at all', 'somewhat', 'moderately' and 'very much' (α = 0.86).

Breast cancer worry was assessed using the Lerman Cancer Worry Scale,[27] consisting of six statements such as: 'How often have you thought about your chances of getting cancer?'. Participants endorsed one of the following response options: 'never', 'rarely', 'sometimes' and 'almost all the time' (α = 0.87).

Demographic and clinical information was obtained using information from the BC-Predict questionnaire that was used to estimate BC risk for women in that experimental group. This was supplemented by core demographic and clinical information that was provided at the aggregate levels using a confidential advisory group (CAG) approval, which therefore did not require consent for the wider PROCAS2 study. *Area deprivation* was assessed for all women invited using the Index of Multiple Deprivation (IMD) deciles derived from postcodes of women invited, which indicated area deprivation in deciles from 1 (most deprived) to 10 (least deprived).[28]

Data analysis

Comparisons of the responses of women who were offered BC-Predict with women who were offered standard NHSBSP were carried out. Analysis of variance (ANCOVA) was used, with baseline responses to the same questionnaires, age and IMD as covariates. Analyses were conducted on all questionnaire measures at 3 months and 6 months, with the 6-month state anxiety measure being the a priori primary outcome for this nested study.[3] ANCOVA was also used to compare responses of the four groups of women in the BC-Predict group provided with different risk estimates (i.e. high, moderate, average and below average) at follow-up.

Two nested qualitative studies

Patient interviews: design, sample, recruitment and data collection

A purposive sample of below-average-, average-, moderate- and high-risk women who had received BC-Predict was invited to participate in a semistructured interview, with the aim of recruiting approximately equal numbers of women who received each risk result.[29,30] Below-average- and average-risk women were invited for interview 1 month after receiving their risk feedback letter. Moderate-risk and high-risk women will be invited for interview 6 months after receiving their risk feedback letter. This allowed women in the moderate- and high-risk groups the chance to explore extra screening options or medications prior to the interview.

Data were collected by semistructured interview either face to face or over the phone, audio-recorded and transcribed verbatim. All interviews covered core issues, including acceptability of BC-Predict and lifestyle modifications. Other issues covered are those that are most relevant to the risk estimate communicated, for example uptake of chemoprevention (e.g. GP advice) in higher-risk women and reassurance in below-average-risk women.

Healthcare professional focus groups: design, sample, recruitment and data collection

General practice, radiology and FHRP clinic staff were invited to participate in individual interviews after BC-Predict was stopped being provided in each location. Interviews were conducted face to face or virtually. They considered views on how well prepared they and the associated staff were for implementing BC-Predict, along with views on acceptability of BC-Predict and how its implementation could be facilitated when widely implemented. Focus groups were audio-recorded and transcribed verbatim.

Data analysis

For both groups, data were analysed using a manifest-level approach to thematic analysis. Thematic analysis is a common qualitative analysis method that results in a complex, yet accessible account of the data.[18] Themes were generated at the manifest (or explicit) level. Data were stored and organised within NVivo software (QSR International, Warrington, UK).

Limitations

There are some limitations to the present research. The study was not randomised and was dramatically impacted by the coronavirus disease discovered in 2019 pandemic, with uptake of the study and of risk appointments in those identified at moderate or high risk almost certainly affected. As such, generalisability of the results may need to be reassessed after the results from the My Personal Breast Screening (MyPeBS) trial[31] are available. We were unable to use the original counterbalanced design, which would have allowed a better estimation of differences between BC-Predict and NHSBSP rates, and could not answer the question of whether there were lower rates for screening uptake (although there was no evidence of this in PROCAS-1).[32] Thus, for these two reasons, key assumptions underlying the original sample size calculations[1] did not apply.

In the nested questionnaire study, the major limitation was the 11.2% questionnaire response rate of women invited to participate. This rate was attributable to multiple factors, including lower uptake to NHSBSP during this period, as women were required to actively make an appointment rather than be allocated an appointment. Although the low response rate increases the risk of response bias, the approach in the present study of inviting everyone who was offered BC-Predict or standard NHSBSP did not involve the selection biases of previous studies. It should also be noted that women were equally likely to participate if they were offered BC-Predict or NHSBSP, which suggests that there was no evidence of differential response biases, which is probably a more important threat to the validity of conclusions than the low response rate per se.

The other potential limitation of the present research was that the comparison group was not well matched on deprivation indices with the BC-Predict group. Despite this, it should be noted that there was a good spread of women in all 10 IMD deciles across both the BC-Predict and NHSBSP groups, albeit with the least deprived deciles of women over-represented in the BC-Predict group. Importantly, all analyses reported controlled for IMD, which was not strongly related to the outcome variables.

Key findings

Trial of effects of BC-Predict on healthcare uptake

The overall flow of participants through BC-Predict is shown in *Figure 2*.

Uptake of screening and BC-Predict

Attendance at mammography appointments at both BC-Predict and standard NHSBSP sites was lower than in the pre-pandemic era (~70%), with only 60.7% mean attendance (*Table 1*). Uptake to BC-Predict (n = 2429) was much lower than expected based on the first PROCAS study,[10] at 12.5% of invitees (adjusted to 9.6% when adjustments were made for phase 2) and 16.6% of those who attended for mammography.

Uptake of BC-Predict was much higher in women directly approached at the Withington Community study site (*Table 2*).

The effects of women being directly approached was further enhanced by the offer of a paper questionnaire rather than using the online tool. Uptake increased to 79/125 (63.2%) despite overall Withington Community recruitment being only 12.5% of those attending screening ($p < 0.0001$). Indeed, excluding the 109 recruited onsite who had not already consented to BC-Predict uptake of those attending for screening without a direct approach was only 296/3244 (9.1%). Of those who were offered the paper questionnaire, 75% chose that option.

Both screening attendance and BC-Predict uptake were highest in Macclesfield, which has a much lower mean deprivation score (*Table 1*). Overall uptake was related inversely to the IMD mean scores (*Table 1*). We were not able to assess uptake by ethnicity as the screening invitations do not have ethnicity recorded. Of 2347 (96.6%) women

TABLE 1 Recruitment to BC-Predict by screening area

	Phase 1		Phase 2 +				
Site	Trafford	Withington community	Oldham	East Lancashire:	Macclesfield	Stockport	Total
IMD[a]	209 of 371	2	29	11	228	130	–
Position rank in study	5	1	3	2	6	4	–
Joined BC-Predict	445	405	256	237	510	576	2429
Invited	3750	6120	2149	2536	2247	2662	19,464
Percentage of uptake	11.87	6.62	11.91	9.35	22.70	21.64	12.48
Uptake screening overall, %	63	53	55	53.40	63.80	63.80	60.7
Uptake of self-made mammography appointments	N/A	N/A	92.43%	93.12%	95.36%	96.31%	94.39%
Uptake of those attending screening, %	18.84	12.49	12.89	10.04	23.80	22.47	16.57
Number attending screening	2363	3244	1986	2362	2143	2564	14,661
Adjusted number of those invited for screening[b]	3750	6120	3907	4749	3521	4172	26,219
Adjusted overall uptake[b]	11.87%	6.62%	6.55%	4.99%	14.48%	13.81%	9.26%

N/A, not applicable.
a Position rank from highest deprivation to lowest in English local councils.
b Adjustments required for overall uptake of BC-Predict in phase 2 to account for invites only going to those who made mammography appointments.

TABLE 2 Uptake of BC-Predict in those personally approached at study site

Women	All	Offered paper questionnaire[a]
BC-Predict women attended (*n*)	305	145
BC-Predict women approached (*n*)	263	125
Percentage of BC-P women approached	86.23	86.21
Women consented prior to clinic date (*n*)	23	16
Percentage with prior recruitment	8.75	12.80
Women provided a saliva sample (*n*)	132	68
Percentage of women uptake to SNP	50.19	54.40
Overall recruitment to BC-Predict	52.00	63.20

a 51/68 (75%) women offered paper questionnaire opted for paper.

Source
Reproduced with permission from Evans *et al.*[2] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The table includes minor additions and formatting changes to the original text.

self-reporting ethnicity, 202 (86%) were White British. This reflects a higher minority ethnic proportion than the 9% in PROCAS-1.[10]

Uptake of FHRP appointments, chemoprevention and additional screening

Attendance at risk appointments which were exclusively provided remotely was also lower than expected, with 80/197 (40.6%) of high-risk women and 68/379 (17.9%) of women assessed at moderate risk taking up the offer of an appointment (*Table 3*). However, the uptake of chemoprevention among women taking up the offer of a risk appointment was far higher than expected (*Table 3*). The overall uptake of chemoprevention in those offered BC-Predict (105/15,080; 0.7%) was significantly higher than the zero uptake in the control arm ($p < 0.0001$). There was also high uptake of additional mammography at 78.8% and 64.7% in the high- and moderate-risk women taking up a risk appointment.

Time to results

For women not having a SNP-PRS, 76.8% received their BC-Predict results within 8 weeks of attending for mammography (*Table 4*). For those undergoing genotyping, this was 64.4%. Many of the single-nucleotide polymorphism (SNP) results were delayed due to delays in women submitting their saliva sample.

Nested questionnaire study

There were no statistically significant differences in comparative risk perceptions, general state anxiety or cancer worry between women offered BC-Predict and women offered standard NHSBSP at both 3-month follow-up (*Table 5*) or 6-month follow-up (*Table 6*).

By contrast, differences were apparent at follow-up when comparing responses of the four groups of women who took up BC-Predict and were provided with different risk estimates (i.e. high, moderate, average and below average) (*Table 7*). First, perceptions of risk changed in line with the risk estimates provided: risk perceptions increased in women who were told they were at higher risk and decreased in women who were told they were at lower risk. Cancer worry changed in line with the risk estimates provided at 6 months but not at 3 months, with women informed that they were at higher risk, showing an increase in cancer worry, and women informed that they were at lower risk, showing a decrease in cancer worry. For state anxiety, there was a large increase in women who were told they were at below average risk relative to other groups, which was apparent at 6 months but not at 3 months.

TABLE 3 Uptake of risk appointments, chemoprevention and additional screening

	High	Mod	Average	Low	Total
N	197	379	1389	498	2463
%	8.00	15.40	56.40	20.20	100
Risk appointment	80	68	1	0	149
%	40.60%	17.90%	0.07%	0.00%	6.05%
p-value	$p < 0.0001$	Reference			
Chemoprevention	62	43	0	0	105
% of all	31.50	11.30	0.00	0.00	4.26
p-value	$p < 0.0001$	Reference			
Percentage seen	77.50	63.20	0.00		70.47
Additional screening, NHS	46	11			57
Additional screening, private	17	33			50
Total	63	44			107
Percentage uptake additional screening of those seen	78.75	64.71			71.81

Source
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TABLE 4 Results delivered within 8 weeks for those in main study without deoxyribonucleaic acid (DNA) testing

Site	Within-risk feedback time frame	Outside-of-risk feedback time frame	Total	Proportion within 8 weeks, %	*p-value*
Withington[a] phase 1	118	111	229	51.53	< 0.0001
Trafford/Wythenshawe van[a] phase 1	189	71	260	72.69	< 0.0001
Oldham[a] phase 2	152	4	156	97.44	Reference
East Lancashire	203	77	280	72.50	
Macclesfield	882	204	1086	81.22	
Total	1544	467	2011	76.78	

a Greater Manchester sites.

Source
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Two nested qualitative studies

In total, 40 women who took part in BC-Predict were interviewed. Ten women were at low risk (< 2%), 9 were at average risk (2–4.99%), 11 were at above average/moderate risk (5–7.99%) and 10 were at high risk (≥ 8%). Interviews lasted between 23 and 79 minutes (median 44 minutes) and two themes were produced: (1) risk expectations: What's my story? Highlighting that women have pre-existing perceptions of their risk and when feedback was discordant, this can cause temporary distress and (2) being a good (woman) citizen where women were positive about risk assessment in order to support other women and the wider healthcare system but may feel judged about their risk if viewed as non-modifiable.

TABLE 5 Self-report measures [mean (SD)], at baseline and 3 months post screening, with statistical tests to assess if there are differences in changes between women offered NHSBSP and BC-Predict (*N* = 655)

	Baseline, women offered NHSBSP (*n* = 301)	3 months, women offered NHSBSP (*n* = 222)	Baseline, women offered BC-Predict (*n* = 355)	3 months, women offered BC-Predict (*n* = 289)	Differences between groups at 3 months: test statistics (with *p-values*)
Comparative risk perceptions	3.08 (0.75), *n* = 299	3.07 (0.75), *n* = 222	2.91 (0.80), *n* = 355	3.04 (0.92), *n* = 288	*F*(1502) = 1.207, *p* = 0.273
State anxiety	10.20 (3.80), *n* = 301	10.56 (3.84), *n* = 221	10.06 (3.67), *n* = 355	10.35 (3.81), *n* = 288	*F*(1502) = 0.017, *p* = 0.896
State anxiety (cases)[a]	46 (15.3%)	41 (18.6%)	45 (12.7%)	39 (13.5%)	*X*2 (1) = 1.01, *p* = 0.314
Cancer worry	12.50 (3.20), *n* = 300	12.09 (2.97), *n* = 222	12.00 (3.02), *n* = 355	11.97 (2.94), *n* = 289	*F*(1504) = 1.467, *p* = 0.226

SD, standard deviation.
a NB. Logistic regression, as outcome variable is dichotomous.

Source
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TABLE 6 Self-report measures [mean (SD)] (at baseline and 6 months post screening), with statistical tests to assess if there are differences in changes between women offered NHSBSP and BC-Predict (*N* = 655)

	Baseline, women offered NHSBSP (*n* = 301)	6 months, women offered NHSBSP (*n* = 213)	Baseline, women offered BC-Predict (*n* = 355)	6 months, women offered BC-Predict (*n* = 260)	Differences between groups at 6 months: test statistics (with *p*-values)
Comparative risk perceptions	3.08 (0.75), *n* = 299	3.12 (0.75), *n* = 213	2.91 (0.80), *n* = 355	3.08 (0.95), *n* = 259	*F*(1464) = 1.019, *p* = 0.313
State anxiety	10.20 (3.80), *n* = 301	11.10 (4.19), *n* = 211	10.06 (3.67), *n* = 355	10.54 (3.77), *n* = 260	*F*(1462) = 1.314, *p* = 0.252
State anxiety (cases)[a]	46 (15.3%)	42 (19.9%)	45 (12.7%)	42 (16.2%)	*X*2 (1) = 0.76, *p* = 0.384
Cancer worry	12.50 (3.20), *n* = 300	12.24 (3.03), *n* = 213	12.00 (3.02), *n* = 355	11.85 (3.04), *n* = 259	*F*(1465) = 0.418, *p* = 0.518

a NB. Logistic regression, as outcome variable is dichotomous.

Women spoke about their experience based on risk expectations, with accounts centring on viewing this information as something that might shape their future. When their risk feedback was unexpected, this was often received with initial but transient worry. When risk was incongruent with expectations, women recalled initial alarm before finding the statistical information contained in their letter comforting. Although there appeared to be no negative impact, this was a reflective period for some whose family members have had cancer.

Overall, the offer of risk assessment was often viewed as something that women *should* do regardless of risk category received in order to both support the healthcare system and benefit women more widely. Even for those who were apprehensive about feedback, taking part in BC-Predict allowed the women to feel that they had positively contributed to society.

TABLE 7 Self-report measures [mean (SD)], at baseline and follow-up (3 months and 6 months post screening) with statistical tests to assess if differences in changes according to risk estimate provided to women (*n* = 184)

		Baseline (*n* = 184)	3 months (*n* = 157)	6 months (*n* = 153)	Differences between groups at 3 months	Differences between groups at 6 months
Comparative risk perceptions	Total	2.82 (0.87), *n* = 184	3.05 (1.02), *n* = 157	3.07 (1.05), *n* = 153	**$F(3150) = 35.84$, $p < 0.001$**	**$F(3146) = 28.56$, $p < 0.001$**
	High	3.23 (1.02), *n* = 22	4.24 (0.77), *n* = 21	4.32 (0.75), *n* = 19		
	Moderate	3.15 (0.82), *n* = 27	3.95 (0.50), *n* = 21	3.86 (0.89), *n* = 22		
	Average	2.70 (0.86), *n* = 114	2.79 (0.77), *n* = 99	2.81 (0.74), *n* = 94		
	Below average	2.57 (0.60), *n* = 21	1.94 (0.93), *n* = 16	2.17 (1.20), *n* = 18		
State anxiety	Total	9.75 (3.56), *n* = 184	9.95 (3.58), *n* = 157	10.39 (3.75), *n* = 153	$F(3150) = 0.94$ $p = 0.423$	**$F(3146) = 3.73$ $p = 0.013$**
	High	9.00 (2.91), *n* = 22	9.00 (2.70), *n* = 21	9.84 (3.56), *n* = 19		
	Moderate	10.15 (4.29), *n* = 27	10.62 (4.50), *n* = 21	10.73 (3.72), *n* = 22		
	Average	9.62 (3.29), *n* = 114	9.82 (3.50), *n* = 99	9.80 (3.29), *n* = 94		
	Below average	10.76 (4.41), *n* = 21	11.13 (3.77), *n* = 16	13.67 (4.75), *n* = 18		
Cancer worry	Total	11.69 (2.83), *n* = 184	11.84 (2.74), *n* = 157	11.54 (2.77), *n* = 153	$F(3150) = 1.20$, $p = 0.311$	**$F(3146) = 4.15$ $p = 0.008$**
	High	12.77 (2.74), *n* = 22	13.10 (3.10), *n* = 21	13.21 (2.37), *n* = 19		
	Moderate	11.52 (2.86), *n* = 27	12.57 (2.42), *n* = 21	12.14 (2.75), *n* = 22		
	Average	11.76 (2.84), *n* = 114	11.65 (2.68), *n* = 99	11.35 (2.72), *n* = 94		
	Below average	10.38 (2.40), *n* = 21	10.44 (2.31), *n* = 16	10.06 (2.60), *n* = 18		

Women described the feedback from BC-Predict as empowering 'information about how they could reduce their risk' or maintain a lower risk. Low- and average-risk women viewed attending future mammograms as 'a responsible thing to do'; Evelyn, Low. However, many acknowledged that subsequent risk management via health behaviours is an ongoing responsibility and may be difficult to sustain within the context of a busy life, or if the factors listed as contributors to their risk are non-modifiable.

Fourteen semistructured interviews were conducted with HCPs working across three NHSBSP centres that implemented BC-Predict. The participants included screening office managers (n = 3), screening programme managers (n = 2), nurses from FHRP clinics (n = 2), doctors from FHRCs (n = 2), radiologists (n = 2) and radiographers (n = 3). Some participants took part in up to two previous focus group studies earlier to the PROCAS2 programme and prior to the implementation of BC-Predict.[23,33] Interviews lasted between 24 and 60 minutes (median 44 minutes).

Three themes were produced. Most importantly, *acceptability of BC-Predict and risk-based screening* identified that risk stratification was perceived as a beneficial step for both services and women. A strong consensus across sites and professions was that implementing risk-stratified screening was a positive step for the next generation of breast screening, with an individualised risk assessment perceived as more logical than providing the same screening for all women regardless of their risk. HCPs across the pathway reported low burden of running the BC-Predict trial on routine tasks, but with some residual concerns.

Barriers to implementation comprised capacity constraints of services, including the inadequacy of current information technology (IT) systems, to manage women with different risk profiles. *Facilitators to implementation* included the continuation of stakeholder consultation across the pathway to inform implementation and dedicated risk screening administration staff, a push for mammography recruitment and guidance for screening services. Telephone helplines, integrating GPs and supporting access for all language needs were emphasised.

Inter-relation with other parts of the programme

The present feasibility study is the first to report the feasibility and impact of real-time BC risk feedback based on the mammographic density and standard risks on a population basis. The present research has found that it is feasible to set up risk estimation, including automatic measures of mammographic density, in several NHSBSP sites and provide risk feedback in a timely manner. Uptake rates to the study overall were generally low, with lower uptake among lower SES women. However, uptake rates were highly sensitive to the changes in recruitment strategies. Importantly, chemoprevention was considerably higher than has been found in previous research studies.

Importantly, we were able to incorporate an automatic measure of mammographic density (Volpara) into the risk algorithm without the need for direct human involvement. This did require fitting of an aerial to the mobile screening, which had to be removed and refitted each time the vans moved site.

Although uptake of the provision of risk information was lower than expected and was much lower than in PROCAS-1,[10] where women were only required to complete a short paper questionnaire, this may also have been hampered by the pandemic. Nonetheless, we were able to show that, even in the lowest recruitment site, we were able to boost recruitment from only 9.1% of those attending for screening to 63.2% if a health practitioner was onsite to explain the study and offer a paper questionnaire. We have shown not only the expected lower uptake in higher deprivation areas but also that this can potentially be addressed by use of a health practitioner and provision of the option of a paper questionnaire. That is, even among women from lower SES backgrounds, the obstacles to recruitment can be overcome with appropriate recruitment strategies rather than reflecting any intrinsic resistance to risk-stratified screening per se.

While the overall uptake of risk appointments was also lower than expected, with only just over 40% of those at high risk taking up an appointment, the uptake of a prescription of chemoprevention was exceptionally high at 77.5%. This is massively higher than the average 10–11% uptake in our FHRP clinics utilising the same clinicians.[34,35] This may reflect a greater willingness to do something active about their risk in women newly identified as being at increased risk compared to those who may have known their risk for many years. Uptake was significantly higher in high-risk than moderate-risk women, both of a risk appointment ($p < 0.0001$) and of chemoprevention ($p < 0.0001$), as expected from our previous work.[10,34,35]

Both of our nested questionnaire and qualitative substudies show that there is no evidence of adverse effects on anxiety beyond transient cancer worry.[3,29] Further, evidence from interviews with HCPs[30] shows that the practice of delivering risk-stratified screening was much less burdensome than what they had anticipated prior to delivery.[23]

Health economic analyses

This section describes three studies to address the overall aim to generate economic evidence to inform the introduction of implementing risk stratification into a NHS-BSP.

Study 1: calculating the cost of risk stratification

Background

A published early economic analysis of a risk-stratified screening strategy indicated that it was a potentially cost-effective use of healthcare resources.[36,37] This analysis used an estimate for the cost of the stratification strategy using a range of pragmatic assumptions. The incremental cost-effectiveness of the stratified screening programmes was found to be dependent on the cost of stratification, and it is therefore important to produce a more accurate estimate. The aim of this study was to identify and quantify the resource use and associated costs required to introduce a BC risk-stratification approach into the NBSP.

Method

A micro-costing study assumed the NHS (service provider) perspective to identify the resource use and cost per individual (£; 2021 price year) of providing a risk-stratification strategy as part of the NBSP. Micro-costing is a method that uses the detailed recording (bottom-up) of all resource use to ensure transparency and accuracy.[38] Following a published approach, this micro-costing study employed four stages: identifying the risk-stratification pathway for the different exemplar applications; identifying the resources used in the risk-stratification pathway; identifying unit costs for the resource use and data analysis.[39] The data for this study were informed by expert opinion that contributed to defining the required risk-stratification pathways (consultant oncologist and consultant geneticist) and the proportion of individuals who followed each option within the specified risk-stratification pathway. Unit costs (£; 2021) were derived from relevant published sources. A probabilistic sensitivity analysis was undertaken to understand the key drivers of the cost of risk stratification. In addition, a scenario analysis was used to understand the impact of batching of deoxyribonucleic acid (DNA) samples, which is a key implementation issue when using SNP testing as part of the risk-stratification strategy.

Results

The cost of risk stratification was estimated for three strategies: £5.49 for the Tyrer–Cuzick strategy; £8.46 for the Tyrer–Cuzick with Volpara breast density measurement strategy; £88.87 for the Tyrer–Cuzick with Volpara breast density measurement and SNP testing strategy. In the Tyrer–Cuzick, and Tyrer–Cuzick with Volpara breast density measurement strategy, the key cost drivers were the organisation and conduct of the risk feedback consultation (45% and 52% of cost, respectively) and the generation and sending of the risk letter (44% and 29% of the cost, respectively).

The cost of providing the risk-stratification strategy at a woman's first attendance at BC screening in the BC-Predict trial was estimated to be higher due to problems with implementation: £15.26 for the Tyrer–Cuzick strategy; £20.56 for the Tyrer–Cuzick with Volpara breast density measurement strategy; £101.10 for the Tyrer–Cuzick with Volpara breast density measurement and SNP testing strategy.

Study 2: update, technical verification and validation of a decision-analytic model-based cost-effectiveness analysis

Background

One approach to generating evidence on the cost-effectiveness of a risk-stratified NBSP in the absence of a large trial is to use a decision-analytic model-based analysis.[40,41] Gray *et al*. started the process for producing economic evidence to inform the introduction of a risk-based NBSP by constructing an early economic model.[37] This early analysis was only

the first stage in an iterative process and updates will be required as new data emerge.[42] Tappenden and Chilcott have outlined the stages of model development for the purpose of informing resource allocation decision-making, stating the importance of cycles of model checking and validation.[43] A fundamental component supporting the process of validation is the need for transparency in the decision-analytic model structure and use of data.[44,45] Technical verification, that checks whether the model has been built using software in a way to generate accurate results, is needed to support the validation process.[46] The aim of this study was to design and report the validation, technical verification and update of a published decision-analytic model designed to conduct a cost-effectiveness analysis of a risk-based NBSP in the UK setting. It is publicly available as a *medRxiv* preprint.[40]

Method

The process of decision-analytic model validation in this study followed the format used by Hammerschmidt *et al*. and Haji Ali Afzali *et al*.[47,48] In the absence of a standardised approach to decision model validation, these formats were identified from a literature review using pearl growing to identify relevant papers to inform the discrete steps to guide the process of validation of a published decision-analytic model-based cost-effectiveness analysis.[49–51] The pearl in this study was published by the ISPOR-SMDM Modeling Good Research Practices Task Force–4.[52]

The first step of validation involved an analyst producing a technical document that summarised the main components of the model. This document was then verified by the original analyst who produced the model (Gray). Another analyst then reprogrammed the model in R (The R Foundation for Statistical Computing, Vienna, Austria) to detect any possible errors. Formal technical verification of the R script and model outputs was then conducted by an analyst independent of the research team. The final step involved using systematic reviews to identify whether updates to key model parameters (natural history, utility values and cost data) were required. Patient input (three women with experience of BC) was used to verify any newly identified utility values. The results of the micro-costing study were used to update the cost of the risk-stratification strategy.

Results

The process of duplicating the model using R software identified two minor bugs in the script, but these did not affect the results produced by the decision-analytic model. The independent technical verification identified four minor coding errors in the model and also identified some areas for improvement, which resulted in the model running faster. The following model parameters were updated: utility values for each stage of BC; cost of risk stratification; cost of treating different stages of cancer; cost of mammography; cost of biopsy; cost of ultrasound screening; cost of magnetic resonance imaging; survival for different stages of BC; all-cause mortality; Volpara breast density, 10-year risk and lifetime risk estimates for a simulated cohort of women; mammographic sensitivity by breast density; proportion of cancers detected by screening; recall rate; BC incidence by age; proportion of cancers that are ductal carcinoma in situ and likelihood a cancer is of a given stage based on its size.

Study 3: cost-effectiveness of a risk-based screening programme as part of the NBSP

Producing evidence of the cost-effectiveness of introducing risk stratification into a NBSP requires a validated decision-analytic model and relevant and good quality data.[36] An early economic analysis, such as the one produced by Gray *et al*.[37], provided evidence of which parameters affect the relative cost-effectiveness of a risk-stratified NBSP. Studies 1 and 2 produced an updated estimate for the cost of the risk-stratification process and validated an existing decision-analytic model structure, respectively. This study aimed to identify the incremental healthcare costs and health consequences of a risk-stratified NBSP compared with the current NBSP.

Method

A decision model-based cost-effectiveness analysis assumed the perspective of NHS England and lifetime horizon for a cohort of women eligible for a NBSP. The validated and updated model produced in study 2 was used. The following interventions were compared with the current NBSP: no screening, 2-yearly screening and risk-stratified screening, with women at high risk (≥ 8% 10-year risk) offered annual screening and women at moderate risk (> 3.5% and < 8% 10-year risk) offered 2-yearly screening. The expected quality-adjusted life-years (QALYs), costs and average number of screens per woman in the screening programme were compared for the four different strategies. Probabilistic sensitivity analysis is currently being conducted to understand the impact of parameter uncertainty on the results.

Results

The base-case analysis suggested that at a cost-effectiveness threshold of £20,000 per QALY, the risk-stratified approach to BC screening was the most cost-effective of the four strategies considered. This approach provided 0.004 incremental QALYs per woman screened at an additional cost of £42 when compared to 3-yearly screening. From the four strategies, the greatest potential health benefits were provided by 2-yearly screening, but the additional costs involved meant that this strategy was not cost-effective compared to the risk-stratified approach. At a cost-effectiveness threshold of £30,000 per QALY, risk-stratified screening and 2-yearly screening were equipoised as the most cost-effective strategies. However, 2-yearly screening was associated with a higher number of expected screens per woman (8.24) compared to risk-stratified screening (6.00) and 3-yearly screening (5.16).

Due to the equal cost-effectiveness of risk-stratified and 2-yearly screening at the higher cost-effectiveness threshold, understanding the impact of uncertainty on the results will be critical. Probabilistic sensitivity analysis is currently being undertaken for inclusion in a published paper.

Discussion

The economic WP4 produced evidence from three studies. A micro-costing study showed that using the Tyrer–Cuzick questionnaire alone, or in combination with information taking account of the Volpara breast density, was a relatively inexpensive strategy to identify a women's 10-year risk of developing BC. The main driver of these costs was clinician's time to consult with the women and feedback results. The addition of SNP testing substantially raised the cost of all of the stratification strategies even when optimising the batching of samples was taken into account. The increased cost will have implications for the budget impact of a risk-stratification process and also the potential cost-effectiveness of introducing a risk-based NBSP. However, evidence of the added predictive value of introducing genetic data into the risk-stratification process is needed to understand the cost-effectiveness. This evidence is not yet available for all women, taking into account ethnic background.

Work package 4 did produce evidence of the cost-effectiveness of introducing a risk-based NBSP using the Tyrer–Cuzick questionnaire by using a validated decision-analytic model structure with updated parameter estimates. The initial results of this analysis suggested that a risk-stratified approach to BC screening based on that used in the PROCAS2 study is likely to be the most cost-effective approach strategy compared to no screening, 3-yearly screening and 2-yearly screening. At higher cost-effectiveness thresholds, 2-yearly screening was equally as cost-effective as risk-stratified screening, but it was associated with a higher number of screens per woman (8.24 vs. 6.00). Given the existence of capacity constraints in the national BC screening programme, including in the number of available radiographers, the requirement for significantly more screening appointments in a 2-yearly approach may prove difficult to accommodate.

Further work is required to understand if, and how, starting medicines will reduce the risk of tumours developing in the breast of women found to be at high risk of BC.

Agenda-setting meeting for implementation

Research aims

The key aim of this WP was to involve external stakeholders to discuss the findings from PROCAS2 and to (1) identify whether risk-stratified breast screening should be implemented in the NHSBSP and to (2) determine the next steps for risk-stratified breast screening research/development work to ensure the feasibility of a risk-stratified programme being successfully implemented within the NHSBSP.

Methods

A 1-day hybrid meeting was held in Manchester, England, with 58 attendees.[53] Those who attended virtually (n = 20) joined via Microsoft Teams (Microsoft Corporation, Redmond, WA, USA). The hybrid format allowed individuals who may be unwilling or able to attend in person, for example due to COVID-19 or geographical constraints, to contribute to the meeting.

Possible attendees were invited via e-mail based on their professional role or involvement in the UK National Screening Committee (UKNSC) or related reference groups. A key focus was to aim to include all relevant disciplines related to breast screening consisting of those from radiology/breast imaging, breast screening service operations (both locally and nationally), breast surgery, primary care, behavioural science, epidemiology, health economics, BC prevention (including dietetics, medical oncology and genetics) statistics and public or patient contributors. Our patient co-applicant (Fiona Harrison) attended in person. In addition, representatives from the relevant BC charities, who both provide significant communication/support to the general public and lobby the government about improving outcomes for BC, including prevention and early diagnosis, were invited. All stakeholder groups were represented at the meeting.

During the meeting, presentations of the main findings from the programme (WP2, WP3 and WP4) took place. This was followed by seven discussion groups tasked with identifying uncertainties that need to be resolved prior to national implementation of risk-stratified breast screening. Indicative uncertainties were provided to each group, which were facilitated by a member of the research team and were audio-recorded. An audio-recorded plenary session then took place to identify the issues from each group. The plenary and discussion group recordings were used to produce a descriptive thematic analysis.

Limitations

No external health economists attended the meeting; however, attendees who are members of or linked to the UKNSC regularly reviewed the cost-effectiveness evidence when considering changes to existing national screening programmes or introducing new ones. In addition, the health economists involved in this study have worked with other UK health economists evaluating risk-stratified BC screening outside of this project and presented the cost-effectiveness model to the UKNSC.[54] Although two women affected by BC represented the patient and public perspective at the meeting, there was a lack of ethnic diversity. Both cost-effectiveness and ensuring equality of access to risk-stratified screening were discussed at length during the meeting.

Key findings

Five themes were developed: (1) risk and health economic modelling; (2) health inequalities and communication with women; (3) extending screening intervals for low-risk women; (4) integration with existing NHSBSP and (5) potential new service models. Most attendees expected some form of risk-stratified breast screening to be implemented in England at some point and they collectively identified key issues to be resolved to facilitate this.

Breast cancer risk models were viewed as having good predictive utility, particularly when all known risk factors are included (mammographic breast density, hormonal/reproductive factors, family history and genetic information). However, a key issue identified with these current models highlighted the need for these to be validated across ethnic minority groups to ensure that they can accurately predict risk for all women in the English population. This related to ensuring that a risk-stratified screening programme would not exacerbate pre-existing health inequalities of access to breast screening. The workload capacity constraints that exist within the current NHSBSP were viewed as a key consideration that needs to be resolved prior to the implementation of a risk-stratified programme, especially the resource required to provide supportive risk communication to women. The inclusion of genetic information, including obtaining the samples and assessing them, may substantially increase the cost of risk assessment. Therefore, extending screening intervals for women at low risk of BC was considered as a possibility as long as evidence suggests it is safe to do so. That is, low-risk women are not likely to be diagnosed with higher-grade BCs during a longer interval than the current 3-yearly programme.

Approaches to ensure the equity of access to a risk-stratified programme were highlighted at the meeting, including the importance of engaging with local communities and that information about risk assessment across the pathway a women would experience must be carefully developed. It was also highlighted that women should be offered choice for communication preferences in a risk-stratified programme, which could facilitate engagement; for example, if support is required to provide self-report risk factor information, use of interpreters to discuss risk feedback or receiving information in a non-English language.

A key challenge with the current NHSBSP technology and community-based screening (via mobile vans) infrastructure was identified. It was clear that this must be resolved in order to successfully implement risk-stratified breast screening.

This issue was apparent both from the perspective of local screening sites, the primary care populations invited and the national operational team. An updated IT system is currently being developed, which should be able to accommodate risk-stratified screening intervals. Similarly, current workforce issues with mammography staff were highlighted, whereby screening sites already operate at capacity; therefore, approaches to increase the numbers in this staff group are essential. It remained unclear how best to include primary care in a risk-stratified programme, including how they might support women following receipt of BC risk estimates.

Attendees also considered how the aspects of the BC risk assessment may be embedded within healthcare services outwith the NHSBSP, including genetic services, primary care and other cancer screening programmes, such as cervical and bowel. However, this must be closely aligned with the NHSBSP to feasibly offer the appropriate screening regime for women, depending on their level of risk.

Inter-relation with other parts of the programme

This meeting brought together the findings from the earlier WPs and presented these to relevant stakeholders involved in deciding whether risk stratification such as BC-Predict should be implemented within the NHSBSP. The findings related to health inequalities echo the findings from the interviews with British-Pakistani women in WP2, and the workload and infrastructure concerns were identified in the post implementation of BC-Predict health professional interviews in WP4.

Equality, diversity and inclusion

There were several facets of this research that were not inclusive.

First, in the focus groups with the HCPs (Developing and refining the BC-Predict intervention), the sample was not diverse in terms of ethnicity. The research team is not clear if this was due to the composition of the healthcare teams or due to those from ethnic minority backgrounds being less likely to participate in the present research. Given that most staff of the NHS workforce are from an ethnic minority background, the latter explanation appears more likely. We are not sure how this lack of representation may have impacted on the research findings, although it was clear that inclusion was a clear consideration of those who did take part in focus groups (and later interviews in Main BC-Predict feasibility study).

We were able to assess the overall numbers of non-White British women who participated in the main BC-Predict trial. The proportion was higher than in PROCAS-1, although NE Lancashire has a higher rate of Asian women than Greater Manchester, which was only used for PROCAS-1.[10] Direct assessment of uptake was not possible as the NHSBSP does not have access to ethnicity data. Further, detailed investigation of uptake by ethnicity was hampered by the BC-Predict software not recording ethnicity data accurately. It is also important to note that the original research plans involved translation of the BC-Predict study website text into multiple key languages. However, the budget that was earmarked for this translation was instead spent on additional costs due to the delays entailed by the various factors, including the COVID pandemic.

We showed a clear decreasing trend for the uptake of both breast screening and BC-Predict, with increasing area of deprivation. However, in one of the highest areas of deprivation, we were able to show an increase in recruitment from only 9.1% to 63.2% at Withington Community, with a direct approach from a health practitioner on site with the offer of a paper questionnaire ($p < 0.0001$).

We would also like to note the lack of diversity in the composition of participants in the agenda-setting meeting (Agenda-setting meeting for implementation). As was the case with the HCPs included in focus groups, we are not sure how this lack of representation may have impacted on the findings of this meeting. Nevertheless, it was again clear that the inclusion was a clear consideration of those who did take part.

Patient and public involvement and engagement in the PROCAS2 programme

Introduction

As outlined in INVOLVE guidance, PPIE is a mandatory component of NIHR grant applications. To define this, we used the term ‘involvement’ to include any contribution to the PROCAS2 research programme made by members of the

public related to the conceptualisation, design and/or management of the research. We used the term 'engagement' for any activities used to disseminate findings from PROCAS2 beyond publication in peer-reviewed journals and presentations at academic conferences.

Involvement

Pre-grant award patient and public involvement and engagement

Fiona Harrison was involved as a PPIE representative on the steering committee in the preceding NIHR Programme Grant, PROCAS-1.[10] With this background, Fiona was involved in the conception and design of the studies within the PROCAS2 grant application. Fiona brought two perspectives with experience of being: (1) a research participant and (2) a patient accessing the local NHS BC risk service (family history clinic).

The PPIE panel established in 2013 was externally funded by the charity Prevent Breast Cancer. PPIE representation was present throughout the majority of working group meetings for the application. Once the design of the study had been agreed, the panel was sent a full application draft to review independently before meeting to discuss the proposed programme of research.

Patient and public involvement and engagement involvement was vital in determining the importance of informing women of their BC risk and developing the most sensitive, accessible, acceptable yet cost-effective way to deliver risk information to women. The panel advised that risk information should not be complex, leading to a decision to use just four risk categories: high risk, above average, average and below average risk. The panel believed that many women in the NHSBSP were likely to want personalised BC risk information and that this could be delivered in a letter with a leaflet providing further information. They advised on the presentation of the advice and how it should be laid out as well as timing of the feedback. The letters and leaflet were developed in conjunction with nine PPIE representatives and then were co-redesigned in a separate research study for use in the think-aloud study in WP2.

As the main aim of PROCAS2 was to assess the feasibility of identifying women at higher risk of BC, but who may have never accessed a family history clinic, it was important to involve individuals who had previously or were currently accessing such a service. Therefore, Fiona was ideally suited to continue working with the research team and was subsequently named as the grant co-applicant. As such, Fiona committed to attend, wherever possible, wider PROCAS2 team meetings that were held approximately every 3 months and provide input to study materials and outputs.

Post grant award patient and public involvement: recruiting for involvement

Given that BC-Predict (WP3) involved inviting women around the time of their NHSBSP mammogram invite, the only criteria for PPIE involvement for the PROCAS2 Advisory Group was being a woman aged 50–70 years and not having had a diagnosis of BC. Importantly, since PROCAS2 would involve recruiting women from East Lancashire, a highly ethnically diverse region, the pre-existing PPIE panel would benefit from greater diversity. To establish a group of more than 12 women, several recruitment strategies were used:

- having a clear definition for this panel, that is the PROCAS2 Advisory Group
- a one-page poster was circulated to outline that researchers were considering whether to provide BC risk information as part of the NHSBSP and that we planned to interview women from different communities about these plans
- a two-page 'Further Information and Frequently Asked Questions' document outlining what PPIE is and the specific activities that the group may be asked to get involved with, for example, help work out the best ways to involve women in the study
- ensuring flexible involvement to review invite materials, that is, preference to interact using group meetings but indicating that documents could also be circulated via e-mail/post for review
- making it clear that women did not need any qualifications or specific experience and emphasising that every woman aged 50–70 years could contribute
- making contact with lay South East Asian Community Outreach Workers via St Mary's Genetic Counselling Service
- sending information to community organisations such as the North West League of Jewish Women, Lancashire Women's Centres and the AAWAZ Asian Women's Group.

This resulted in the addition of eight women: one from Eastern Europe and six South Asian women (four Outreach workers) to the group.

Methods of involvement

Meetings

Fiona provided input throughout PROCAS2 primarily by attending wider team meetings (virtual during COVID-19 pandemic). This was particularly helpful for identifying additional recruitment strategies for the BC-Predict study, having identified lower-than-anticipated participant recruitment figures. Fiona also attended the consensus meeting in March 2022 in person, as this was her preference rather than attending remotely so that support was readily available if required. Fiona contributed to the planning stages, including what topics were important to ensure that attendees discussed and contributed to one of seven discussion groups at the meeting.

As outlined in Developing and refining the BC-Predict intervention, in order to maximise engagement with women from ethnic minority groups, a face-to-face PPIE panel meeting was held to focus on developing the WP2 qualitative interview study with women from populations less likely to engage in breast screening. A key meeting aim was to identify how best to recruit people to interviews and ensure inclusivity from a socioeconomic and ethnicity perspective. The panel identified that sending invites via letter would not generate engagement in the study, nor would an event held in a hospital setting. Instead, an event promoted and held in the local community would likely be successful. Similarly, word of mouth from local community workers whom women trust would increase engagement in research. Additional insights gathered included ensuring cultural sensitivity, for example, providing samosas for event refreshments; having translators available to support communication with the English-speaking research team and providing local organisations with translated advertising materials based on the most common non-English languages spoken. The advertising materials also highlighted that women could attend with children to increase accessibility of the event.

Research materials input

Patient and public involvement (PPI) input was particularly helpful for reviewing participant-facing materials, including the dissent poster created for CAG approval. This ensured that the information displayed regarding BC-Predict in screening units about how women may choose to have their details removed was relevant to those who were likely to see it in that setting. Additionally, all other patient-facing materials, such as the participant information sheet, were reviewed by multiple women, primarily via electronic feedback. In addition to feedback on the self-report questions used in BC-Predict, a local PPIE organisation (VOCAL; www.wearevocal.org/) supported the testing of the online version of this questionnaire before the pilot BC-Predict study (WP1) commenced. Utilising the support from VOCAL allowed the research team to quickly access a group of people willing to provide input and ensure that it would be easy to complete for participants and that the time taken to complete the questionnaire was acceptable (approximately 20 minutes).

Research outputs

Fiona has been involved in contributing to all PROCAS2 manuscript drafts submitted to peer-reviewed journals. On reviewing the psychological impact manuscript draft (questionnaire study in WP4), Fiona stated that 'the results are fascinating and I am grateful for having the chance to be involved in this research'. Similarly, Fiona 'read through the document with interest' when reviewing the manuscript related to the consensus meeting (WP5).

Engagement

Public engagement event

As a result of the PPIE panel meeting for WP2, an engagement event was held in Blackburn Lancashire. The purpose was to explain the overarching BC-Predict study and to advertise recruitment to the interview study. The location chosen to recruit participants was a NHSBSP site for the BC-Predict study, and the venue was selected because women from the local community already used the centre for social activities. The event was widely advertised via local community organisations in North Manchester/East Lancashire. As part of this, the local breast screening patient navigator provided an information display on the day with culturally appropriate resources. For example, images of

lemons on a leaflet to demonstrate signs and symptoms. In addition, a radiographer from the South Asian community joined the event to discuss breast screening with women attending. A number of women who attended went on to join the study at a later date.

Dissemination activities

A PPIE newsletter was created and provided to the PPIE panel, providing an update on the progress of PROCAS2. In addition, as the findings of the qualitative study in WP2 were highly relevant for breast screening generally,[19] this resulted in inclusion within various NIHR Evidence publications and the production of the following blog posts or evidence alerts:

- Why we need more inclusive research: cultural and language barriers need to be addressed for British-Pakistani women to benefit fully from breast screening. NIHR Evidence Collection. 2021. https://evidence.nihr.ac.uk/collection/why-we-need-more-inclusive-research/
- Catching cancer early: how research could help us improve the cultural and language barriers need to be addressed for British-Pakistani women to benefit fully from breast screening. *NIHR Evidence*. https://evidence.nihr.ac.uk/collection/catching-cancer-early-how-research-could-help-us-improve/
- Health information: are you getting your message across? Cultural and language barriers need to be addressed for British-Pakistani women to benefit fully from breast screening. *NIHR Evidence*. 2022. https://evidence.nihr.ac.uk/collection/health-information-are-you-getting-your-message-across/
- Woof V. Making breast screening more accessible: views from British-Pakistani women. PHE Screening Blog 2020. https://phescreening.blog.gov.uk/2020/02/19/breast-screening-accessible-british-pakistani/
- Woof V. Addressing inequalities – personalised breast cancer screening and views from British-Pakistani women. NIHR Manchester Biomedical Research Centre (BRC) Blog 2020. www.manchesterbrc.nihr.ac.uk/news-and-events/breast-screening-british-pakistani-women/
- Cultural and language barriers need to be addressed for British-Pakistani women to benefit fully from breast screening. NIHR Evidence Alert 2020. https://evidence.nihr.ac.uk/alert/cultural-and-language-barriers-need-to-be-addressed-for-british-pakistani-women-to-benefit-fully-from-breast-screening/
- NIHR. Be part of research podcast where researcher Victoria Woof talks about the barriers British-Pakistani women face when attending for breast screening. This podcast is currently in production.

Lessons learnt and recommendations

The team had not anticipated that women attending the Blackburn engagement event would be willing to join the study. Therefore, we now know to include this option at future events. Gaining PPI input on the CAG poster for BC-Predict resulted in a fast approval process, as no further edits were required. On reflecting on the role of patient representative in PROCAS2, Fiona highlighted the importance of a central point of contact, which, at times, was challenging due to changes in members of the research team. However, Fiona feels very proud to have contributed to this research by providing a lay perspective within the main research team and is willing to remain involved in subsequent studies.

Conclusion

The important contribution PPI made to the PROCAS2 programme can not be underestimated. Without the valuable insight and perspectives offered by the PPI members, the research team were unlikely to have foreseen some of the potential barriers highlighted that ultimately saved valuable resources and time.

Impact and learning

The earlier WPs of this programme were carried out largely as intended, but with some obstacles requiring minor modifications.

Work package 1 encountered problems, as the General Data Protection Regulation (GDPR) legislation was adopted in England in 2016 and was formally implemented in 2018. The PROCAS2 study begin in the middle of these dates and required multiple partners to adapt their practices to comply with this legislation. A particular challenge was that

CRA Health, which was responsible for integrating risk information from self-reported risk factors and mammographic density, was based in USA, and GDPR regulations did not allow transfer of personally identifiable information out of the European Union. There were other challenges to do with integration of personal data from multiple sources, and with multiple NHS and university partners involved, but these were resolved by the Digital Health Software team at the University of Manchester, albeit with some delays and additional costs incurred.

The research in WP2 was carried out largely as intended. A particular success was the recruitment of the British-Pakistani women from East Lancashire, many of whom were interviewed via a translator. These women were recruited using strategies suggested by the ethnically diverse PPI group and with the help of people who were embedded in the relevant communities. This allowed us to build relationships and trust with the women who were interviewed, which yielded particularly useful data, as a number of misconceptions and concerns were identified from this group, which have not been identified from more acculturated groups that are more commonly included in research on screening. This particular piece of research has been used by NIHR as an exemplar piece of research with ethnically diverse groups through various blogs and recordings (as noted in the previous section).

The later WPs had larger deviations from the original plan, largely due to the effects of COVID-19, just as we were starting the main feasibility study (WP3). One impact of COVID-19 was that the operation of the NHSBSP was fully shut down from 21 March 2020 to 1 August 2020. Further, it was not fully operational after this due to the need for social distancing and cleaning of equipment after each woman was screened. Women were asked to contact the NHSBSP to make appointments rather than given appointment times, and uptake was consequently reduced. Accordingly, the screening centres and sites were consequently stretched by changes in the NHSBSP as were the FHPC services. Research on screening was made less of a priority as funds from the NIHR Clinical Research Network were diverted to support research related to COVID-19 rather than the present study, and there were consequent but understandable delays in getting regulatory approvals from NHS sites to begin recruitment, to avoid placing additional burdens on already overstretched services. One implication of these challenges was that the recruitment period was extended to allow the required number of women who were to be invited to be able to reliably estimate uptake to NHSBSP, BC-Predict and subsequent screening and prevention offers.

Not only was the main feasibility study delayed, but the COVID-19 challenges also resulted in the study team altering the design of this study. Our original plan was to employ a fully counterbalanced design, whereby in an initial 8-month period, women covered by one group of NHSBSP centres would be offered BC-Predict while women covered by a different group of NHSBSP centres would be offered standard NHSBSP.[1] We then planned that, in the following 8-month period, the NHSBSP centres would switch to offer the other intervention (NHSBSP rather than BC-Predict and vice versa). Due to challenges of initiating BC-Predict in collaborating centres, and the overall lower uptake of NHSBSP by eligible women, we instead changed the design, whereby the main comparison was between women invited to sites offering BC-Predict and women invited to sites offering standard NHSBSP during the same time period.

The new study design was weaker in terms of causal inference than the one originally planned, as it does not control for differences in demographic characteristics between study sites offering BC-Predict versus NHSBSP. However, we believe that this is not a fatal drawback, given our aims. For instance, the number of women in the standard NHSBSP group attending NHSBSP and taking up chemoprevention was virtually nil, so attributing take-up of these services to BC-Predict is straightforward. By contrast, this design made it very problematic to compare whether uptake rates of NHSBSP were affected by the offer of BC-Predict, given that there were large differences in NHSBSP uptake between screening sites. The change in study design was not particularly problematic for the nested questionnaire and qualitative studies.

A more problematic aspect of changes related to COVID-19 was that uptake rates were affected, so the overall uptake of BC-Predict was much lower than anticipated, and uptake of risk consultations was similarly lower than anticipated. We originally anticipated offering BC-Predict to 18,700 women, and on the basis of PROCAS-1 results, we anticipated that 8000 women would consent to BC-Predict, of whom 1169 would be seriously considered for chemoprevention and 117 women would take it up. The uptake figures were lower than was the case in the previous PROCAS study.[10] It may also be noteworthy that the earlier PROCAS study asked women to provide information on paper questionnaires rather than online, which may also have impacted on uptake rates. However, as uptake of chemoprevention was much

higher than anticipated, the anticipated benefits were approximately in line with those on which the study was design, suggesting that there were worthwhile benefits to women of BC-Predict.

Thus, although the uptake of BC-Predict was lower than expected, risk-stratified screening also resulted in higher uptake of medicines to reduce the risk of BC than previously reported, so the number taking up medication in the present study (*n* = 105) was only slightly below the number (*n* = 117) originally expected. Given this, and as chemoprevention produces NHS cost savings, a validated decision-analytic model indicated that a risk-stratified approach to BC screening is likely to be the most cost-effective option or equally as cost-effective as a 2-yearly screening. However, current capacity constraints in the NHSBSP, including in the number of available radiographers, the requirement for significantly more screening appointments in a 2-yearly approach may prove to be difficult to accommodate.

Given the knock-on effects of GDPR and then COVID-19, WP4 had to be refocused because a substantial portion of the funding was diverted away from the economic WP. This repurposing of funding meant that the objectives delivered differed from those stated in the original proposal. The primary aim of the delivered economic analysis remained the same, which was to identify the key drivers of the relative cost-effectiveness of embedding BC-Predict in the national breast screening programme compared with the national breast screening programme. The original objectives were to: prospectively collect the healthcare resource use and health status (EuroQol-5 Dimensions) and capability (ICEpop CAPability measure for Adults) outcomes associated with BC-Predict, the model of service delivery and subsequent referral to management options; conduct a within-trial analysis to identify the key drivers of the relative cost-effectiveness of embedding BC-Predict in the NHSBSP compared with the current NHSBSP; conduct a decision-analytic model-based cost-effectiveness analysis of embedding BC-Predict in the NHSBSP compared with the current NHSBSP; and identify a primary outcome measure to quantify the value of information to quantify the extent of existing decision uncertainty in the evidence base, following completion of the early economic analysis to understand the potential value of future research. These objectives were reformulated into the three studies reported. Crucially, it was not feasible to evaluate the inclusion of risk-reducing medicines in the decision-analytic model-based cost-effectiveness of BC-Predict. However, this work is now being conducted by the research team as part of a different project.

Work package 5 was also reduced in scope. We originally planned three meetings to consider the way forward for risk-stratified screening in the NHSBSP. However, since the PROCAS2 programme was funded, the MyPeBS trial of the effectiveness of risk-stratified screening for BC has been set up and has recruited over 50,000 women.[31] Several of the PROCAS2 team are core members of the MyPeBS trial team, and many of the procedures used in PROCAS2 have been used in the MyPeBS trial.[31] Given this, we had a single more focused meeting to consider what needs to happen in the next few years, in anticipation of the results of the MyPeBS trial in 2027.

In addition to the work originally proposed, it is important to note that value was added to the present research by a complementary grant from Breast Cancer Now, concerning low risk women. The NIHR-funded PROCAS2 grant had a focus on whether providing more screening and prevention services to higher-risk women was feasible, increased balance of benefits to harms and was likely to be cost-effective. This additional grant considered the other side of risk stratification, which concerned reducing screening to women at lower risk. The published qualitative work from this additional work shows that reducing screening would be acceptable to key stakeholder groups[33,55–57] and identified uncertainties, some of which were discussed at the PROCAS2 stakeholder meeting in WP5. It also funded the epidemiological and health economic work on this issue, which supports the idea of reducing screening for women at very low levels of risk, as not only were they less likely to develop cancers, but any cancers would be much more likely to be slow-growing. Thus, low-risk women would not only would be much less likely to experience the benefits of screening but also more likely to experience harms such as false-positive screening test results. The health economic analysis also supports the case for reducing this screening.

Overall conclusions

Although there were several major changes to the present study, we believe that the programme met its central aim of resolving key uncertainties regarding the feasibility of integrating BC-Predict into the NHS. We have clarified many such uncertainties, notably by showing that risk-stratified screening is feasible, produces no major harms and is likely to be a good use of the NHS budget when compared with the current NHSBSP. The present study provides the necessary information on likely uptake rates for risk estimation, risk consultations and preventive options that are necessary to provide realistic estimates of costs and benefits of risk stratification.

We have helped catalyse conversations between academic, NHS and policy leaders around what next steps are needed. A meeting with 74 experts with a wealth of diverse but relevant experience identified a consensual view that risk-stratified screening would happen eventually and the need to develop plans to prepare for it. What will happen next will be informed by the results of the MyPeBS trial,[31] which has finished recruitment and is due to report in the near future.

The expert meeting identified remaining key uncertainties that need to be resolved to allow implementation, as follows:

1. identify procedures for how best to engage women
2. identify how best to promote uptake by women who are currently underserved by existing NHSBSP, notably women from minority ethnic populations and those living in more deprived areas
3. how to organise risk-stratified screening to avoid placing any additional burden on NHS staff and to consider further the role of general practice
4. consider feasibility of extending screening intervals of women at lower risk for new service to not require additional funding
5. validate risk prediction algorithms for other ethnic groups and over longer follow-up periods
6. consider whether risk assessments that consider other diseases alongside BC would be valuable to women.

Additional information

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. All available quantitative data that are in anonymised form can be obtained from the corresponding author on reasonable request. Requests to access some qualitative data should also be made to the corresponding authors. Please note that requests to access some qualitative data may be declined to protect the confidentiality of participants.

Ethics statement

NHS ethical approval for the PROCAS2 study was granted by Harrow Research Ethics Committee on 9 July 2018 (ref. 18/LO/0649)/ IRAS project ID 239199.

Information governance statement

The University of Manchester is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, the University of Manchester is the Data Processor; Manchester University NHS Foundation Trust is the Data Controller and we process personal data in accordance with their instructions. You can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for Manchester University NHS Foundation Trust's Data Protection Officer here: https://mft.nhs.uk/app/uploads/2021/12/Privacy-Notice-Apr-21-v0.7-Booklet.pdf

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/HGDW6751

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Anthony Howell received funding from Genesis Breast Cancer Prevention (GA15-003).

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Jack Cuzick receives royalties for commercial use of the Tyrer–Cuzick (IBIS) breast cancer risk evaluator.

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Publications

French DP, Astley S, Brentnall AR, Cuzick J, Dobrashian R, Duffy SW, *et al.* What are the benefits and harms of risk stratified screening as part of the NHS Breast Screening Programme? Study protocol for a multi-site non-randomised comparison of BC-Predict versus usual screening (NCT04359420). *BMC Cancer* 2020;**20**:570. https://doi.org/10.1186/s12885-020-07054-2

Woof VG, Ruane H, Ulph F, French DP, Qureshi *N*, Khan *N*, *et al.* Engagement barriers and service inequities in the NHS breast screening programme: views from British-Pakistani women. *J Med Screen* 2020;**27**:130–37. https://doi.org/10.1177/0969141319887405

Woof VG, Ruane H, Ulph F, French DP, Qureshi *N*, Khan *N*, *et al.* The introduction of risk stratified screening into the NHS breast screening programme: views from British-Pakistani women. *BMC Cancer* 2020;**20**:1–9. https://doi.org/10.1186/s12885-020-06959-2

French DP, Woof VG, Ruane H, Evans DG, Ulph F, Donnelly LS. The feasibility of implementing risk stratification into a national breast cancer screening programme: perspectives of healthcare personnel responsible for delivery. *BMC Women Health* 2022;**22**:142. https://doi.org/10.1186/s12905-022-01730-0

McWilliams L, Evans DG, Payne K, Harrison F, Howell A, Howell SJ, *et al.*, on behalf of the Breast Screening Risk-Stratification Agenda Setting Group. Implementing risk stratified breast screening in England: an agenda setting meeting. *Cancers* 2022;**14**:4636. https://doi.org/10.3390/cancers14194636

Gorman LS, Ruane H, Woof V, Southworth J, Ulph F, DG Evans, *et al.* The co-development of personalized 10-year breast cancer risk communications: a 'think aloud' study. *BMC Cancer* 2022;**22**:1264. https://doi.org/10.1186/s12885-022-10347-3

Evans DG, McWilliams L, Astley S, Brentnall AR, Cuzick J, Dobrashian R, *et al.* Quantifying the effects of risk stratified breast cancer screening when delivered in real time as routine practice versus usual screening: the BC-Predict non-randomised controlled study *Br J Cancer* 2023;**128**:2063–71. https://doi.org/10.1038/s41416-023-02250-w

French DP, McWilliams L, Bowers S, Woof V, Harrison F, Ruane H, *et al.* Psychological impact of risk stratified screening as part of the NHS Breast Screening Programme: multi-site non-randomised comparison of BC-Predict versus usual screening (NCT04359420). *Br J Cancer* 2023;**128**:1548–58. https://doi.org/10.1038/s41416-023-02156-7

Hawkins R, McWilliams L, Ulph F, Evans DG, French DP. Healthcare professionals' views following implementation of risk stratification into a national breast cancer screening programme. *BMC Cancer* 2023;**22**:1058. https://doi.org/10.1186/s12885-022-10134-0

Khattak H, Woof V, French DP, Donnelly L, Ruane H, Ulph F, *et al.* The role of knowledge, primary care, and community engagement to improve breast screening access for Pakistani women in the UK: a secondary analysis of a qualitative study. *J Health Serv Res Policy* 2023;**28**;149–56. https://doi.org/10.1177/13558196231155824

McWilliams L, Ruane H, Ulph F, Woof VG, Harrison F, Evans DG, *et al.* What do women think about having received their breast cancer risk as part of a risk stratified NHS Breast Screening Programme? A qualitative study. *Br J Cancer* 2023;**129**:356–65. https://doi.org/10.1038/s41416-023-02268-0

Woof VG, McWilliams L, Howell A, Evans DG, French DP. How do women at increased risk of breast cancer make sense of their risk? An interpretative phenomenological analysis. *Br J Health Psychol* 2023;**28**;1169–84. https://doi.org/10.1111/bjhp.12678

Wright SJ, Eden M, Ruane H, Byers H, Evans DG, Harvie M, *et al.* Estimating the cost of 3 risk prediction strategies for potential use in the United Kingdom national Breast Screening Programme. *MDM Policy Pract* 2023;**8**:1171363. https://doi.org/10.1177/23814683231171363

Wright SJ, Gray E, Rogers G, Donten A, Payne K. A structured process for the validation of a decision-analytic model: application to a cost-effectiveness model for risk-stratified national breast screening. *Appl Health Econ Health Policy* 2024;**22**:527–42. https://doi.org/10.1007/s40258-024-00887-z

Wright SJ, Rogers G, Gray E, Donten A, McWilliams L, French DP, *et al.* Evaluation of a risk-stratified national breast screening programme in the United Kingdom: an updated cost-effectiveness analysis. *medRxiv* 2024. URL: www.medrxiv.org/content/10.1101/2024.04.16.24305897v1 (accessed 24 October 2024).

References

1. French DP, Astley S, Brentnall AR, Cuzick J, Dobrashian R, Duffy SW, *et al*. What are the benefits and harms of risk stratified screening as part of the NHS Breast Screening Programme? Study protocol for a multi-site non-randomised comparison of BC-Predict versus usual screening (NCT04359420). *BMC Cancer* 2020;**20**:570. https://doi.org/10.1186/s12885-020-07054-2
2. Evans DG, McWilliams L, Astley S, Brentnall AR, Cuzick J, Dobrashian R, *et al*. Quantifying the effects of risk stratified breast cancer screening when delivered in real time as routine practice versus usual screening: the BC-Predict non-randomised controlled study (NCT04359420). *Br J Cancer* 2023;**128**:2063–71. https://doi.org/10.1038/s41416-023-02250-w
3. French DP, McWilliams L, Bowers S, Woof V, Harrison F, Ruane H, *et al*. Psychological impact of risk stratified screening as part of the NHS Breast Screening Programme: multi-site non-randomised comparison of BC-Predict versus usual screening (NCT04359420). *Br J Cancer* 2023;**128**:1548–58. https://doi.org/10.1038/s41416-023-02156-7
4. Cancer Research UK. *Breast Cancer Diagnosis and Treatment Statistics*. 2022. URL: www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero (accessed 25 May 2022).
5. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012;**380**:1778–86. https://doi.org/10.1016/S0140-6736(12)61611-0
6. Evans DG, Warwick J, Astley SM, Stavrinos P, Sahin S, Ingham S, *et al*. Assessing individual breast cancer risk within the UK National Health Service Breast Screening Programme: a new paradigm for cancer prevention. *Cancer Prev Res* 2012;**5**:943–51. https://doi.org/10.1158/1940-6207.CAPR-11-0458
7. National Institute of Health and Care Excellence. *Familial Breast Cancer: Classification and Care of People at Risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer. Clinical Guideline 164*. London: National Institute for Health and Care Excellence; 2013.
8. Evans DG, Brentnall AR, Harvie M, Dawe S, Sergeant JC, Stavrinos P, *et al*. Breast cancer risk in young women in the National Breast Screening Programme: implications for applying NICE guidelines for additional screening and chemoprevention. *Cancer Prev Res* 2014;**7**:993–1001. https://doi.org/10.1158/1940-6207.CAPR-14-0037
9. Evans DG, Donnelly LS, Harkness EF, Astley SM, Stavrinos P, Dawe S, *et al*. Breast cancer risk feedback to women in the UK NHS breast screening population. *Br J Cancer* 2016;**114**:1045–52. https://doi.org/10.1038/bjc.2016.56
10. Evans DG, Astley SM, Stavrinos P, Harkness E, Donnelly LS, Dawe S, *et al*. Improvement in risk prediction, early detection and prevention of breast cancer in the NHS Breast Screening Programme and family history clinics: a dual cohort study. *Programme Grants Appl Res* 2016;**4**:1–210. https://doi.org/10.3310/pgfar04110
11. Pashayan N, Antoniou A, Ivanus U, Esserman L, Easton D, French DP, *et al*. (2020). Personalised early detection and prevention of breast cancer: ENVISION Consensus Statement. *Nat Rev Clin Oncol* 2020;**17**:687–705. https://doi.org/10.1038/s41571-020-0388-9
12. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, *et al*. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *BMJ* 2021;**374**:n2061. https://doi.org/10.1136/bmj.n2061
13. Gorman LS, Ruane H, Woof V, Southworth J, Ulph F, Evans DG, *et al*. The co-development of personalized 10-year breast cancer risk communications: a 'think aloud' study. *BMC Cancer* 2022;**22**:1264. https://doi.org/10.1186/s12885-022-10347-3
14. Forbes LJL, Ramirez AJ; Expert Group on Information about Breast Screening. The Expert group on Information about Breast Screening. Offering informed choice about breast screening. *J Med Screen* 2014;**21**:194–200. https://doi.org/10.1177/0969141314555350

15. Ramirez A, Forbes L. *Approach to Developing Information about NHS Cancer Screening Programmes*. London: King's Health Partners; 2012.
16. Spiegelhalter DJ, Short I, Pearson M. Visualizing uncertainty about the future. *Science* 2011;**333**:1393–400. https://doi.org/10.1126/science.1191181
17. French DP, Cooke R, McLean N, Williams M, Sutton S. What do people think about when they answer theory of planned behaviour questionnaires? A 'think aloud' study. *J Health Psychol* 2007;**12**:672–87. https://doi.org/10.1177/1359105307078174
18. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006;**3**:77–101. https://doi.org/10.1191/1478088706qp063oa
19. Woof VG, Ruane H, Ulph F, French DP, Qureshi N, Khan N, *et al*. Engagement barriers and service inequities in the NHS breast screening Programme: views from British-Pakistani women. *J Med Screen* 2020;**27**:130–7. https://doi.org/10.1177/0969141319887405
20. Woof VG, Ruane H, Ulph F, French DP, Qureshi N, Khan N, *et al*. The introduction of risk stratified screening into the NHS breast screening Programme: views from British-Pakistani women. *BMC Cancer* 2020;**20**:1–9. https://doi.org/10.1186/s12885-020-06959-2
21. Office for National Statistics. *KS201EW – 2011 Census: Ethnic Group, Local Authority in England and Wales*. 2012. URL: www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/2011censuskeystatisticsforlocalauthoritiesinenglandandwales (accessed 25 October 2019).
22. NHS Digital. *Breast Screening Programme, England – 2016–17 (PAS)*. 2018. URL: https://digital.nhs.uk/data-and-information/publications/statistical/breast-screening-programme/breast-screening-programme-england---2016-17 (accessed 25 October 2019).
23. French DP, Woof VG, Ruane H, Evans DG, Ulph F, Donnelly LS. The feasibility of implementing risk stratification into a national breast cancer screening programme: perspectives of healthcare personnel responsible for delivery. *BMC Womens Health* 2022;**22**:142. https://doi.org/10.1186/s12905-022-01730-0
24. Weinstein ND. What does it mean to understand a risk? Evaluating risk comprehension. *J Natl Cancer I Monogr* 1999;**25**:15–20. https://doi.org/10.1093/oxfordjournals.jncimonographs.a024192
25. Marteau TM, Becker H. The development of a six-item short-form of the state scale of the Spielberger state-trait anxiety inventory (STAI). *Br J Clin Psychol* 1992;**31**:301–06. https://doi.org/10.1111/j.2044-8260.1992.tb00997.x
26. Spielberger CD, Gorsuch RL, Luschen RE. *State Trait Anxiety Inventory Manual*. Palo Alto, CA: Consulting Psychologists Press; 1970.
27. Lerman C, Trock B, Rimer BK, Jepson C, Brody D, Boyce A. Psychological side effects of breast cancer screening. *Health Psychol* 1991;**10**:259–67. https://doi.org/10.1037//0278-6133.10.4.259
28. Department for Communities and Local Government. *The English Indices of Deprivation*. 2019. URL: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/835115/IoD2019_Statistical_Release.pdf (accessed 11 March 2022).
29. McWilliams L, Ruane H, Ulph F, Woof VG, Harrison F, Evans DG, French DP. What do women think about having received their breast cancer risk as part of a risk stratified NHS Breast Screening Programme? A qualitative study. *Br J Cancer* 2023;**129**:356–65. https://doi.org/10.1038/s41416-023-02268-0
30. Hawkins R, McWilliams L, Ulph F, Evans DG, French DP. Healthcare professionals' views following implementation of risk stratification into a national breast cancer screening programme. *BMC Cancer* 2023;**22**:1058. https://doi.org/10.1186/s12885-022-10134-0
31. UNICANCER. *My Personalised Breast Screening (MyPeBS)*. Clinicaltrials.gov; 2018. URL: https://clinicaltrials.gov/ct2/show/NCT03672331 (accessed 25 May 2022).

32. French DP, McWilliams L, Howell A, Evans G. Does receiving high or low breast cancer risk estimates produce a reduction in subsequent breast cancer screening attendance? Cohort study. *Breast* 2022;**64**:47–9.
33. Woof VG, McWilliams L, Donnelly LS, Howell A, Evans DG, Maxwell A, French DP. Introducing a low-risk breast screening pathway into the NHS Breast Screening Programme: views from healthcare professionals who are delivering risk-stratified screening. *Women's Health* 2021;**17**:1009746. https://doi.org/10.1177/17455065211009746.
34. Donnelly LS, Evans DG, Wiseman J, Fox J, Greenhalgh R, Affen J, *et al*. Uptake of tamoxifen in consecutive premenopausal women under surveillance in a high-risk breast cancer clinic. *Br J Cancer* 2014;**110**:1681–87. https://doi.org/10.1038%2Fbjc.2014.109
35. Howell A, Gandhi A, Howell S, Wilson M, Maxwell A, Astley S, *et al*. Long-term evaluation of women referred to a breast cancer family history clinic (Manchester UK 1987–2020). *Cancers* 2020;**12**:3697. https://doi.org/10.3390/cancers12123697
36. Wright SJ, Eden M, Ruane H, Byers H, Evans DG, Harvie M, *et al*. Estimating the cost of 3 risk prediction strategies for potential use in the United Kingdom National Breast Screening Programme. *MDM Policy Pract* 2023;**8**:171363. https://doi.org/10.1177/23814683231171363.
37. Gray E, Donten A, Karssemeijer N, van Gils C, Evans DG, Astley S, Payne K. Evaluation of a stratified National Breast Screening Program in the United Kingdom: an early model-based cost-effectiveness analysis. *Value Health* 2017;**20**:1100–9. https://doi.org/10.1016/j.jval.2017.04.012
38. Frick KD. Microcosting quantity data collection methods. *Med Care* 2009;**47**:S76–81. https://doi.org/10.1097/MLR.0B013E31819BC064
39. Jani M, Gavan S, Chinoy H, Dixon WG, Harrison B, Moran A, *et al*. A microcosting study of immunogenicity and tumour necrosis factor alpha inhibitor drug level tests for therapeutic drug monitoring in clinical practice. *Rheumatology* 2016;**55**:2131–7. https://doi.org/10.1093/RHEUMATOLOGY/KEW292
40. Wright SJ, Gray E, Rogers G, Hainsworth R, Donten A, Payne K. Validation of a decision-analytic model for the cost-effectiveness of a risk-stratified National Breast Screening Programme in the United Kingdom. *medRxiv* 2022. https://doi.org/10.1101/2022.12.05.22283099
41. Buxton MJ, Drummond MF, Van Hout BA, Prince RL, Sheldon TA, Szucs T, Vray M. Modelling in economic evaluation: an unavoidable fact of life. *Health Econ* 1997;**6**:217–27. https://doi.org/10.1002/(sici)1099-1050(199705)6:3%3C217::aid-hec267%3E3.0.co;2-w
42. Sculpher M, Drummond M, Buxton M. The iterative use of economic evaluation as part of the process of health technology assessment. *J Health Serv Res Policy* 1997;**2**:26–30. https://doi.org/10.1177/135581969700200107
43. Tappenden P, Chilcott JB. Avoiding and identifying errors and other threats to the credibility of health economic models. *PharmacoEcon* 2014;**32**:967–79. https://doi.org/10.1007/S40273-014-0186-2
44. Emerson J, Bacon R, Kent A, Neumann PJ, Cohen JT. Publication of decision model source code: attitudes of health economics authors. *PharmacoEcon* 2019;**37**:1409–10. https://doi.org/10.1007/S40273-019-00796-3
45. Jansen JP, Incerti D, Linthicum MT. Developing open-source models for the US health system: practical experiences and challenges to date with the open-source value project. *PharmacoEcon* 2019;**37**:1313–20. https://doi.org/10.1007/S40273-019-00827-Z
46. Büyükkaramikli NC, Rutten-van Mölken MP, Severens JL, Al M. TECH-VER: a verification checklist to reduce errors in models and improve their credibility. *PharmacoEcon* 2019;**37**:1391–408. https://doi.org/10.1007/s40273-019-00844-y
47. Hammerschmidt T, Goertz A, Wagenpfeil S, Neiss A, Wutzler P, Banz K. Validation of health economic models: the example of EVITA. *Value Health* 2003;**6**:551–9. https://doi.org/10.1046/J.1524-4733.2003.65241.X

48. Haji Ali Afzali H, Gray J, Karnon J. Model performance evaluation (validation and calibration) in model-based studies of therapeutic interventions for cardiovascular diseases. *Appl Heal Econ Heal Policy* 2013;**11**:85–93. https://doi.org/10.1007/S40258-013-0012-6

49. Ramer SL. Site-ation pearl growing: methods and librarianship history and theory. *J Med Libr Assoc* 2005;**93**:397–400. URL: https://pmc.ncbi.nlm.nih.gov/articles/PMC1175807/ (accessed 9 October 2025).

50. Schlosser RW, Wendt O, Bhavnani S, Nail-Chiwetalu B. Use of information-seeking strategies for developing systematic reviews and engaging in evidence-based practice: the application of traditional and comprehensive pearl growing. a review. *Int J Lang Commun Disord* 2006;**41**:567–82. https://doi.org/10.1080/13682820600742190

51. Hinde S, Spackman E. Bidirectional citation searching to completion: an exploration of literature searching methods. *PharmacoEcon* 2015;**33**:5–11. https://doi.org/10.1007/s40273-014-0205-3

52. Karnon J, Stahl S, Brennan A, Caro JJ, Mar J, Möller J. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force–4. *Value Health* 2012;**15**:821–27. https://doi.org/10.1016/J.JVAL.2012.04.013

53. McWilliams L, Evans DG, Payne K, Harrison F, Howell A, Howell SJ, French DP; Breast Screening Risk-Stratification Agenda Setting Group. Implementing risk stratified breast screening in England: an agenda setting meeting. *Cancers* 2022;**14**:4636. https://doi.org/10.3390/cancers14194636

54. Anderson A, Visintin C, Antoniou A, Pashayan N, Gilbert FJ, Hackshaw A, *et al*. Risk stratification in breast screening workshop. *BMC Proc* 2024;**18**:22. URL: https://link.springer.com/epdf/10.1186/s12919-024-00306-0 (accessed 25 October 2024).

55. McWilliams L, Woof VG, Donnelly LS, Howell A, Evans DG, French DP. Extending screening intervals for women at low risk of breast cancer: do they find it acceptable? *BMC Cancer* 2021;**21**:637. https://doi.org/10.1186/s12885-021-08347-w

56. McWilliams L, Woof VG, Donnelly LS, Howell A, Evans DG, French DP. Risk stratified breast cancer screening: UK healthcare policy decision-making stakeholders' views on a low-risk breast screening pathway. *BMC Cancer* 2020;**20**:680. https://doi.org/10.1186%2Fs12885-020-07158-9

57. Taylor G, McWilliams L, Woof VG, Howell A, Evans DG, French DP. What are the views of key stakeholders on extending the breast screening interval for low-risk women? *Health Expect* 2022;**25**:3287–96. https://doi.org/10.1111/hex.13637

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