RESEARCH PROTOCOL

FH-Risk 2.0: Updating breast cancer risk estimates

Recalculating breast cancer risk and exploring the experience of receiving updated breast cancer risk estimates in women with a family history of breast cancer

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Version Number	Author	Effective Date	Reason for Change
4.0	Victoria Woof, & Anthony Howell	18/08/2023	Change to add an additional participant procedures to the questionnaire arm (Part 4).

This protocol has regard for the HRA guidance

PROTOCOL VERSION 4.0, 18.08.2023 AUTHORISATION SIGNATURES

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Name & Role:	Signature:	Date authorised:
Prof Gareth Evans	----------	----------

For and on behalf of the study sponsor:

Name & Role:	Signature:	Date authorised:
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STUDY SUMMARY

Study Title	Recalculating breast cancer risk and exploring the experience of receiving updated breast cancer risk estimates in women with a family history of breast cancer
Short title	Updated breast cancer risk estimates
Study Design	Mixed methods, Quantitative/Qualitative
Study participants	Women who attend the Family History, Risk and Prevention Clinic (FHRPC) who were participants in the FH-Risk study (REC form 10/H1008/24) in 2010-2012
Planned size of sample	Part 1 (risk estimate recalculation on 954 women. All women (between the ages of 25 and 60) will be invited to receive updated risk feedback): Recalculation of breast cancer risk will be performed on 954 women's data from the FH-Risk study. Women in the FH-Risk study consented to: • All necessary genetic tests on a blood DNA sample • The measurement of mammographic density • That all information gathered can be stored by the custodians for possible use in future ethically approved research studies. Recalculation will be based on SNPs313, high and moderate risk gene analysis, mammographic density and updated risk prediction models (Tyrer-Cuzickv8, BOADICEAV [CanRisk]). FH-Risk women still in follow up and those who have been discharged from the FHRPC will be given the opportunity to learn of their recalculated risk via a clinic consultation. Part 2 (interviews with 20 women): Up to 20cross-sectional interviews across the following groups: • women who have received an increased breast cancer risk estimate (by at least one category) since their initial estimate • women who have received a decreased (by at least one category) breast cancer risk estimate since their initial estimate Part 3 (think-alouds with 30 women): Up to 30 cross-sectional 'think-aloud' interviews across the following groups: • women who have received an increased breast cancer risk estimate (by at least one category) since their initial estimate

	• woman who have received a breast cancer risk estimate that has not changed category since their initial estimate • women who have received a decreased (by at least one category) breast cancer risk estimate since their initial estimate. Part 4 (questionnaire study): Between 300 and 400 questionnaires sent to women who: • have had a consultation about their updated breast cancer risk from Part 1 of this study.
Study Period	3 years
Research Aims	i) To determine change in NICE categories of risk (average, moderate and high risk) when new risk factors are added to standard breast cancer risk models. ii) To explore how much new risk models (including MD, SNP313 and mutation testing) change risk estimates previously communicated to women as part of the FH-Risk study. iii) To explore whether a change in breast cancer risk affects credibility of how risk is calculated and communicated to women, including trust in its use iv) To use the findings to understand how and in what format(s) changes to breast cancer risk estimates should be communicated in the future to enable women to properly understand change in risk, potential change in management and manage emotional sequelae v) To use the findings to create information materials to communicate changes in breast cancer risk and assess their usability vi) To use the findings to develop a questionnaire to be given to women who previously took part in the FH-Risk study and assess the impact of changed risk in a definitive study
Funders & contact details	NIHR Manchester Biomedical Research Centre Cancer Prevention and Early Detection Theme; Professor Gareth Evans, University of Manchester, Manchester Cancer Research Centre, 555 Wilmslow Road, Manchester M20 4GJ Email address: gareth.evans@mft.nhs.uk Tel: 0161 701 5104
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1.0 STUDY PROTOCOL

1.1 Research abstract

Estimation of breast cancer risk is important since it enables selection of a high and moderate risk population who benefit from more frequent breast screening and the introduction of targeted measures to reduce risk such as lifestyle change, chemoprevention and risk reducing surgery. Traditionally, risk is estimated by combining information concerning family history and non-familial factors, such as age of menarche and first pregnancy. Subsequent management is related to the degree of risk (high, moderate or average) according to NICE guidelines. Members of the research team and others have added mammographic density (MD) and breast cancer risk associated single nucleotide polymorphisms (SNPs) to risk models which improves the accuracy of risk estimation but which may change the original given risk and risk management given before the updated models became available. The objective of this study is to quantify change in risk and risk management when MD and SNPs are incorporated into two standard models (Tyrer-Cuzick v8 & BOADACEA V). A second objective of the study is to determine the psychological effects of change of risk and management. This study will use participant data from the Family History Risk (FH-Risk) study to recalculate risk. The FH-Risk study population consists of 954 women referred to the Family History Risk and Prevention Clinic (FHRPC) between 2000 and 2012 who gave informed consent for DNA testing and estimation of MD as part of the FH-Risk study which recruited between 2010 and 2012. Change in risk and management will be calculated by comparing given risk at the time of clinic entry compared with re-estimated risk when MD and SNPs are added to the risk models according to NICE guidelines. Risk will be estimated retrospectively at the time of entry to the clinic and the time of latest follow up. All of those who took part in the FH-Risk study) will be given the opportunity to discuss their updated risk.

Following the risk update consultation a sample of women will be asked whether they would like to take part in an interview to assess the psychological effects of the change, as well as their views and perceptions of the change. These interviews will inform the development of information materials for communicating recalculated risk. These materials will be appraised via 'think aloud' interviews with women from the FH-Risk study who have received their recalculated risk. The results of this study are likely to inform the next iteration of NICE management guidelines for Family History Clinics, as well as inform the creation of patient facing information materials to aid patient - healthcare professional communication. The findings will also be used to develop a questionnaire to be given to women who

previously took part in the FH-Risk study (and who have been discharged from the clinic) to assess the psychological impact of changed risk in a definitive study.

1.2 Research background

Management of breast cancer risk: Family History Clinics

In the 1980's publicity concerning the rise in the incidence of breast cancer and the introduction of breast screening programmes increasingly led women with a family history of the disease, to seek advice concerning management of their personal risk of breast cancer. In response to primary care physicians and colleagues within our breast oncology service, we set up a referral Family History Risk & Prevention Clinic (FHRPC) Manchester, UK in 1987 with a cancer genetics component initiated in 1990. The clinic serves the catchment population of a National Health Service Breast Screening Centre (the Nightingale Centre) which covers a total population of 1.8m, (just over half the population of Greater Manchester) although women at high risk may be specially referred from a population of approximately 5 million in the Northwest Region of England.

During clinic appointments risk was explained, annual breast screening initiated and advice given concerning diet and lifestyle factors which might affect risk. Later genetic testing (1994), chemoprevention (1992) as part of the IBIS I clinical trial) and risk reducing surgery (1994) were introduced. Local (Evans 1994) and, later, national guidelines for management of women with a family history were published for the UK (Eccles 2000, NICE McIntosh 2004), the USA (Hoskins 1995, NCCN Merajver 2003). In the UK NICE guidelines indicate management should be stratified in the clinic. Women estimated to be at high risk (≥ 30% lifetime risk) are offered annual mammographic screening until 60, and chemoprevention or risk reducing surgery. Women at moderate risk (17-20% lifetime risk) are offered mammographic screening until 50 and are 'considered' (rather than 'offered' chemoprevention (Table 1)) but not considered for risk reducing surgery. Thus precise estimation of risk is important for management. Since the inception of the FHRPC in 1987, 49.7% of women were at high risk (n=5390) whereas 50.3% were at moderate risk (Howell 2020).

Table 1. Nice categories of lifetime BC risk and subsequent management dependant on risk

	Moderate risk (17-29%)	High risk (>30%)
Yearly screening	up to age 50	up to age 60
Chemoprevention	'consider'	'offer'
Risk reducing surgery	none	offer

*Many referrals will be assessed at 'average' risk and returned to primary care

Models for assessment of breast cancer risk.

Early observations on the greater incidence of breast cancer in nuns and the increased effect on risk of older age of first birth (Ramazzini 1713, MacMahon 1970) and family history (Broca 1866, Lynch & Krush 1966) suggested that both reproductive/lifestyle and familial factors were related to risk of breast cancer (Brinton 1982). Models combining these risk factors were developed to estimate overall breast cancer risk in individuals (Gail 1989).

The Gail (1989) model includes the risk factors shown in table 2 although only a limited first degree family history is used. In our clinic the expected number of cancers compared with the number observed was 0.48 using the Gail model (Amir 2003, Evans 2014). Before 2004, we used the Claus model modified by other risk factors which gave an E/O of 1.22. After 2004 the Tyrer -Cuzick model was used which includes a larger number of risk factors, including a more extensive family history and gave an E/O of 0.81 (Tyrer 2004). Recently even greater precision has been obtained by adding more risk factors including mammographic density and breast cancer risk associated single nucleotide polymorphisms (SNPs). (Tyrer-Cuzick model v8. 2017; http://www.ems-trials.org/riskevaluator/).

Some models assess only family history in order to help predict the probability of a gene mutation. (Mutations are now called pathological variants [PVs]). The most widely used model to predict PVsl is BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (see Table 2) (Antoniou 2004). Very recently the group in Cambridge, who developed the early BOADICEA models added hormonal/lifestyle factors and also mammographic density and SNPs to the model (Lee 2019).

Table 2: Known risk factors and their incorporation into existing risk models. The models which depend only on family history do not predict overall risk well.

	RR at extremes	Gail (1989)	Claus (1994)	BRCAPRO (1998)	Tyrer-Cuzick V6 (2017)	BOADICEA 1 (2004)	B0ADICEA V CanRisk (2019)
	Prediction						
Amir et al [validation study [E/O]		0.48	0.56	0.49	0.81		Not assessed
95% Confidence interval [30]		(0.54-0.90)	(0.59-0.99)	(0.52-0.80)	(0.85-1.41)		Not assessed
	Personal information						
Age (20-70)	30	Yes	Yes	Yes	Yes	Yes	Yes
Body mass index	2	No	No	No	Yes	No	Yes
Alcohol intake (0-4 units) daily	1.24	No	No	No	No	No	Yes
	Hormonal / reproductive factors						
Age of menarche	2	Yes	No	No	Yes	No	Yes
Age of first live birth	3	Yes	No	No	Yes	No	Yes
Age of menopause	4	No	No	No	Yes	No	Yes
HRT use	2	No	No	No	Yes	No	Yes
OCP use	1.24	No	No	No	No	No	Yes
Breast feeding	0.8	No	No	No	No	No	No
Plasma oestrogen	5	No	No	No	No	No	No
Personal breast disease							
Breast biopsies	2	Yes	No	No	Yes	No	No
Atypical ductal hyperplasia	3	Yes	No	No	Yes	No	No
Lobular carcinoma in-situ	4	No	No	No	Yes	No	No
Breast density	6	No	No	No	Yes	No	Yes
Family History							
First degree relatives	3	Yes	Yes	Yes	Yes	Yes	Yes
Second degree relatives	1.5	No	Yes	Yes	Yes	Yes	Yes
Third degree relatives		No	No	No	No	No	Yes
Age of onset of breast cancer	3	No	Yes	Yes	Yes	Yes	Yes
Bilateral breast cancer	3	No	No	Yes	Yes	Yes	Yes
Ovarian cancer	1.5	No	No	Yes	Yes	Yes	Yes
Male breast cancer	3-5	No	No	Yes	No	Yes	Yes

E/O Expected over observed cancer ratio (all models assessed underestimated cancer occurrence)
OCP- Oral Contraceptive.

Thus, since inception of the FHRPC, two major models have evolved. The Tyer-Cuzick model is widely used around the world. The CanRisk model evolved from the BOADICEA model (Antonionou 2004) was not published with the addition of non-family history risk factors until August 2019 but is already becoming widely used including in our own clinic (Lee 2019). In the clinics women are given their risks and are then followed up by annual mammography. The question we wish to ask in the study outlined here is how much these new models change previously given risk and should NICE guidelines be changed to include them? Most women in the clinic will have been given risk according to the early modified Claus and Tyer-Cuzick models. Our preliminary information indicates that using the new models risk can be different and thus potentially alter management according to NICE guidelines (Evans 2017. Figure 1). In addition to managing changes in NICE categories we wish to assess the psychological effects of change in risk.

The Tyrer-Cuzick model

The Tyrer-Cuzick model was first published in 2004 (Tyrer 2004) and updates were produced in 2013 (Version 7) and 2017 (Version 8). Statistically, the model is a combination of two approaches, 1) estimation from family pedigree data of the probability of carrying one or more high-risk mutations using segregation analysis, and then using the penetrance of a mutation to alter age-specific risk and, 2) regression analyses by combination of a regression model derived from case-control or cohort studies of specific relative risks combined with absolute population-based incidence rates from cancer registries (Brentnall & Cuzick 2020).

The model combines up to second degree family history and non-familial risk factors**.** These are family history, BRCA1 and BRCA2 in the family, age of menarche, age of first full term pregnancy, age of menopause, height, weight, use of HRT. Version 7 (2013) added Ashkenazi family history and V8 added polynomial risk scores (PRS) based on as many breast cancer risk associated SNPs that were available and mammographic density (measured either by visual analogue scale [VAS], Volpara or BIRADs). The model gives 10 year and lifetime risk until the age of 85. There is some evidence of a degree of under-prediction in women at low risk and over-prediction at high risk (Brentnall and Cuzick 2020). The risk prediction is stable for at least 19 years (Brentnall 2020). Our studies indicate the potential change in risk when adding mammographic density (Brentnall 2015, Warwick 2014), a PRS (Cuzick 2017, Evans 2017) and combining density and PRS (van Veen 2018, Brentnall 2020).

The BOADICEA V (CanRisk) model

The first BOADICEA model was published in 2004 based on family history alone (Antoniou 2004).

BOADICEA V extends the BOADICEA BC risk prediction model to allow for consistent prediction of personal BC for unaffected women on the basis of their rare (high risk and moderate risk) BC genetic

susceptibility variants, common genetic variants, explicit family history and other known risk factors. The model incorporates the effects of truncating variants in BRCA1, BRCA2, PALB2, CHEK2, ATM and a PRS based on 313 single-nucleotide polymorphisms (SNPs) The other risk factors included in the model are MD, age at menarche, age at menopause, parity, age at first live birth, oral contraceptive use, HRT use, height, BMI, and alcohol intake (Lee 2019). Among all factors considered, the predicted UK BC risk distribution is widest for the PRS, followed by mammographic density. The highest BC risk stratification is achieved when all genetic and lifestyle/hormonal/reproductive/anthropomorphic factors are considered jointly. With all factors, the predicted lifetime risks for women in the UK population vary from 2.8% for the 1st percentile to 30.6% for the 99th percentile, with 14.7% of women predicted to have a lifetime risk of ≥17–<30% (moderate risk according to National Institute for Health and Care Excellence [NICE] guidelines) and 1.1% a lifetime risk of ≥30% (high risk).

'New' risk factors incorporated into risk models – mammographic density & DNA tests

1. Measurement of mammographic density

The amount of dense tissue in proportion to the size of the breast, mammographic density is a strong breast cancer risk factor (figure 2). In the NIHR PROCAS (Predicting Risk of Cancer At Screening) study we assessed several methods for measuring the proportion of breast tissue in the breast in the NHS Breast Screening Programme. The importance of breast density for predicting risk is shown in figure 1. The risk of breast cancer (odds ratio) was 4 fold higher in the top quintile of density compared with the lowest. We compared five methods for density measurement: visual analogue scales (VAS), an AI method based on convolutional neural networks (CNN) and a commercial measure, Densitas. These three measures give density as an area of dense tissue compared with the area of the breast. Two other commercial measures were used which measure the volume of breast dense tissue and the volume of the breast Volpara and Quantra. The percent density assessed by our radiologists using a 0-100 visual analogue scale (VAS) was the optimal method but is cumbersome in practice. Our group has developed an automated method depending on convoluted neural networks (CNN. Ionescu 2017) which gives similar results to VAS and may be the method of choice in the future for estimating density for incorporating density into the risk models used in the clinic. The automated volumetric method, Volpara, performed well and we will also assess this method in the current study. The most widely used visual method for estimating density in breast radiology is the Breast Imaging-Reporting and Data System (BIRADs). It is a risk assessment and quality assurance tool developed by the American College of Radiology that provides a widely accepted lexicon and reporting schema for imaging of the breast. The BIRADs for density is shown in figure 3. The breast appearance is divided into four measures, (A) the breasts are almost entirely fatty, (B) there are scattered areas of fibroglandular density, (C) the breasts are heterogeneously dense, which may obscure small masses and (D) the breasts are

extremely dense, which lowers the sensitivity of the mammogram. The Tyrer-Cuzick model can use VAS, Volpara or BIRADs for risk calculation whereas BOADICEA V uses BIRADS only (T-C v8, BOADICEA V).

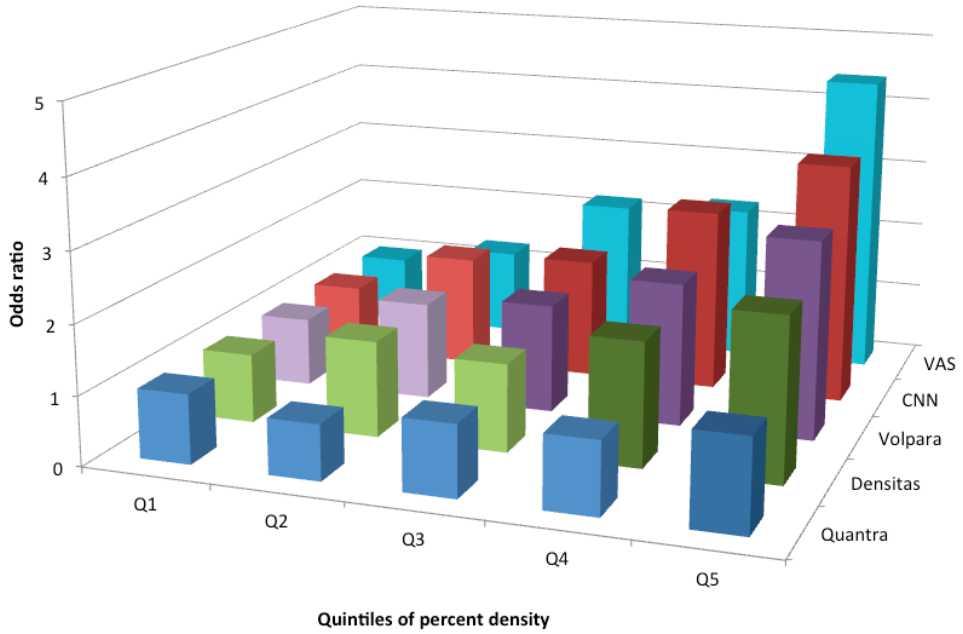
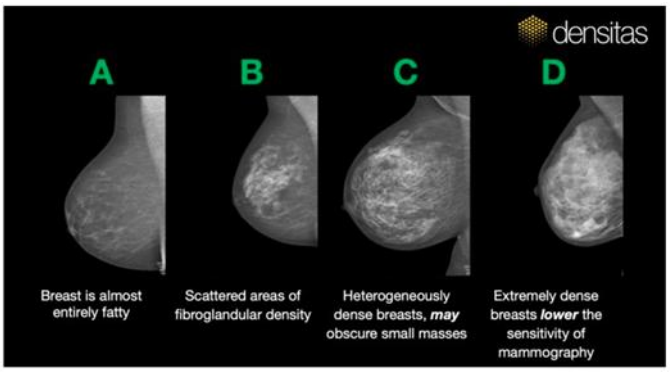


Figure 2 Odds ratio of developing breast cancer by quintiles of percent density and method (Astley 2018, Ionescu 2019) (VAS – visual analogue scale. CNN – convoluted neural networks)

Figure 3. BIRADs categories (see https://densitas.health/blog/breast-density-scales)



2. DNA measurements of risk of breast cancer

Genome wide association studies (GWAS) (Michailidou 2017, Turnbull 2010, Easton 2007, Mavaddat 2019) reported a series of common genetic variants (SNPs) each carried by 28-44% of the population associated with a 1.07-1.26 relative risk of BC. The first seven breast cancer risk associated variants where published in 2007 (Easton 2007). At the time of the initiation of the FH-Risk study (see below for explanation of FH-Risk study) in 2010, details of 18 variants were available. As a result of studies from the Breast Cancer Associated Consortium (which includes data from Manchester) a total of 313 variants are available and can be incorporated into the Tyrer-Cuzick v8 and BOADACEA V models (Mavaddat 2019). In an early report from the FH-Risk study we demonstrated that adding the results

of the 18 SNP score to the Tyrer-Cuzick model altered risk such that 25% of women increased risk and 25% decreased risk indicating the importance of SNPs in defining risk in women at moderate and high risk of breast cancer (Evans 2017).

PVs (mutations) in the TP53, BRCA1 and BRCA2 genes were shown to be associated with a high risk breast cancer in the 1990ies (Malkin 1990, Miki 1994, Wooster 1995). Since a number of potential breast cancer genes have been discovered. In order to delineate genes which are definitively related to breast cancer the Breast Cancer Association Consortium estimated the breast cancer risk association of 34 potentially important genes in 67,269 women diagnosed with breast cancer and 59,299 controls from a large number of study groups including PROCAS and FH-Risk studies from Manchester (Dorling 2020). The genes reported with PVs which were associate with a greater than twofold increase in breast cancer risk are *ATM*, *BRCA1*, *BRCA2*, *CHEK2, PALB2, BARD1*, *RAD51C, RAD51D* and *TP53.* **All women in the FH-Risk study have been tested for SNP313 and all potential breast cancer genes.**

Family History Risk study (FH-Risk)

The FH-Risk study aimed to assess, validate and improve breast cancer risk assessment models from the FHRPC at the Nightingale Centre in the North West of England (Evans et al., 2016). The FH-Risk study (funded by NIHR) recruited 954 women without a breast cancer diagnosis between November 2010 and November 2012 in a nested case control study who were age-matched to women who had been diagnosed with breast cancer (Evans 2017). The women in the control group, who form the basis of the study outlined in this protocol, had their first FHRPC visit between ~2000 and 2012. At their first visit if during the period 1993-2010, risk was assessed using Claus tables modified by hormonal risk factors as this is more accurate for predicting risk compared with family history alone (Amir 2003, Evans 2013). Later in this period, the TC V6 model (Tyrer, Duffy, & Cuzick, 2004) was validated to be the most accurate available model to predict individual breast cancer risk and was therefore subsequently used in the FHRP. Women received individual lifetime risk estimates and counselling when attending the FHRPC for the first time. Those with lifetime risks of 1 in 4-6 (moderate risk) or >1 in 3 (high risk) were included in the clinic annual screening programme according to NICE Guidelines. The women also provided blood samples to assess SNPs and other genetic information between 2010-2012. They received the results related to SNP risk via letter (as the SNPs had not been fully validated at time of sending letters this simply indicated whether risk had not changed substantially with odds ratios of 0.5-2 or if below or above that risk had decreased or increased as a result of the DNA tests. No personalized feedback was given). The results of estimated MD were not fed back at the time. The research group were later able to validate that the use of 18 SNPs accurately moved 50% of women a whole risk category upwards or downwards (Evans et al., 2017).

Pilot study. Currently, the FHRPC clinic follows up approximately 4,000 women per year for 12 monthly breast screening because of their risk. In a pilot study between September 2017 and August 2018, a sub-sample of women in the FH-Risk study who attend the FHRPC for screening had their risks re-evaluated using the updated TC Version 8 (V8). In 106 women whose SNPs and MD were added to the TC model, their lifetime risk estimate of breast cancer decreased by one or more categories (i.e. from high to moderate or moderate to low) in 53 (50%) women compared with TC alone (no MD or SNP included). Forty (38%) women did not change risk category whilst 13 (12%) women had an increased risk estimate by one or more category. See Figure 3 for changes in estimates according to TC model alone, TC model and MD TC model, SNPs and MD.

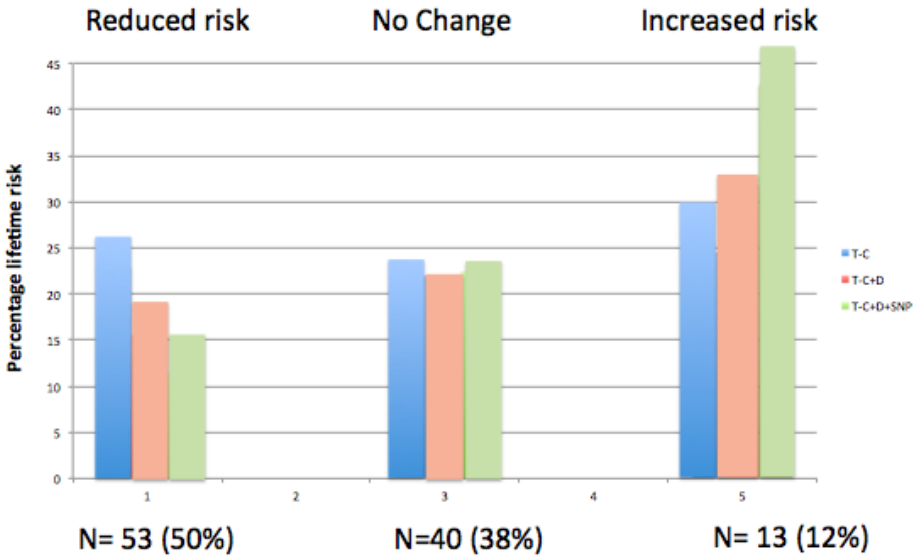


Figure 3 Change in risk in 106 women from the FH-Risk study when mammographic density (MD) and polygenic risk score derived from single nucleotide polymorphisms (SNP18) were used in the Tyrer-Cuzick (TC) model (blue – TC alone, red – TC+MD, green – TC+MD+SNPs).

These data highlight that substantial changes in risk can occur when MD and SNPs are added into the standard TC model. The women who participated in the study have not yet been offered the opportunity to receive their updated risk estimate. Similarly, the research team has the opportunity to provide women with feedback on a panel test of breast cancer related genes (for example, BRCA1, BRCA2, PALB2, CHECK2, ATM) that indicate mainly high lifetime risk of developing breast cancer.

Psychological, cognitive and behavioural effects of breast cancer risk communication

Risk prediction models have been found to support informed choices in women identified via FHRPCs as being at high risk of developing breast cancer in relation to aiding difficult decisions around risk reducing surgery (Evans, Baildam, et al., 2009; Evans, Lalloo, et al., 2009). One of the largest research

studies to explore the use of risk prediction in a population-level breast screening programme was conducted in Greater Manchester with over 56,000 women (Predicting Risk of Breast Cancer at Screening, PROCAS; Evans et al., 2016). One of the main reasons for the study was that only around 1 in 6 women in the population who would receive a high-risk estimate (and thus was eligible to receive more frequent screening or discuss preventative measures) have been identified. One might think that because this figure is low, women are not interested in knowing their breast cancer risk. However, a key finding from Evans and colleagues (2015) was that 96% of women (excluding those who received an 'average' risk estimate; 2-4.99%) wanted to receive their risk upon receipt of a risk appointment invite. Similarly, 70% opted to have a face to face appointment to discuss their risk. Interestingly, those who received high risk estimates were more likely to attend a review appointment (74%) compared to women who received moderate (73%) or low risk estimates (55%).

In a nested study, a sub-sample of women completed questionnaires assessing the psychological (anxiety, cancer worry, perceived risk of breast cancer) and behavioural (future screening intentions, lifestyle changes) effects of risk-stratification with or without a delay in receiving risk estimate feedback (French et al., 2018). There was no evidence that providing risk information influenced intentions to make lifestyle related changes although women who received a high-risk estimate were not included in this study. However, women were less anxious if they received their risk estimate compared to women in the control group who had not yet received their risk results. A UK survey also found that over two thirds of the sample (n=942 women) felt that genetic testing does more good than harm and that varying breast screening intervals is a good or very good idea (Meisel et al., 2015). However a recent review of qualitative research suggests that the acceptability of risk stratified screening depends on women's perceived risk of breast cancer (Rainey, van der Waal, Wengström, et al., 2018). Cancer worry and perceptions of being at risk are associated with uptake of breast cancer prevention medication and surgery in high risk women. Meanwhile low perceived risk has been linked to scepticism around preventative healthcare in women with high risk of breast cancer (Salant, Ganschow, Olopade, & Lauderdale, 2006). Further, poor understanding of genetic testing and heightened anxiety can be experienced during risk assessment in women with a family history of breast cancer (Phelps, Wood, Bennett, Brain, & Gray, 2007). This suggests that women can experience uncertainty and misunderstanding during risk communication which could undermine trust and credibility of its use to support healthcare decision making. Similarly, studies exploring risk information recall have shown that individuals tend to only remember the 'gist' of information about probabilities; this is therefore an important aspect to consider when communicating risk (Hopwood, Howell, Lalloo, & Evans, 2003). For example, a woman who received their risk of breast cancer may not recall what their risk was, particularly if a number of years have lapsed. Equally, a woman has to make an informed decision as to whether she would like to receive some or all risk estimate information for example,

genetic-related risk or risk information related to prevention of breast cancer (Kaphingst et al., 2016). Combined, these are important factors to consider regarding breast cancer risk communication in order to establish the likely harms and benefits of personalised breast cancer risk. However, there appears to be a paucity of research that has explored this.

1.3 Rationale

Women in the FHRPC were given partial or incomplete information about their breast cancer risk. We are now in a position to provide women in the FH-Risk study with a more accurate estimate of their risk due to use in the models of additional powerful risk factors. We can do this by using the updated Tyrer-Cuzick V8, MD (measured using Predictive VAS, BI-RADS and Volpara), SNP313 and genetic information for high and moderate risk genes. A recalculation of risk could result in women changing risk category, either up or down (some women will not have an altered risk estimate). The question we wish to ask in the study outlined here is how much these new models change previously given risk and should NICE guidelines be changed to include them? Most women in the clinic will have been given risk according to a modification of the Claus model (Amir 2003) and the early Tyer-Cuzick model. Our preliminary information indicated using the new models that risk can be different and thus may alter management according to NICE guidelines. As a result, women who still currently attend the FHRPC should be given the opportunity to learn of their revised risk estimate. This opportunity will be provided as part of this study.

Furthermore, conducting initial explorative research using qualitative methods can facilitate the development of appropriate risk materials and communication strategies that are acceptable to women. This is particularly important given that data on risk perception can be difficult to interpret. If the purpose of providing change in risk estimates is to inform healthcare decisions, framing the change in risk i.e. losses versus gains, will also have an effect on risk perceptions (and also may change subsequent clinical management). Importantly, there appears to be no published studies that have examined the effect of changes in breast cancer risk estimates during follow up with women, yet this is a vital aspect of risk communication. Likewise, qualitative research with a smaller sample of the FH-Risk case-control group can inform the development of definitive quantitative assessments to examine the psychological consequences of re-evaluated risk estimates in the remaining sample. This is crucial given that up to half of women may have a changed risk estimate higher or lower compared to the category that they initially received. Before any change in service that provides re-evaluated breast cancer risk estimates could be implemented, it is important to establish the likely harms and benefits of providing women with their personalized potential change in risk of breast cancer.

2.0 AIMS & OBJECTIVES OF THE STUDY

2.1 Aims

The aims of this study are:

i) To determine change in NICE categories of risk (average, moderate and high risk) when new risk factors are added to standard breast cancer risk models.

ii) To explore how much new risk models (including MD, SNP313 and mutation testing) change risk estimates previously communicated to women as part of their management plan at first attendance at the FHRPC.

iii) To explore the experiences of risk estimate changing over time in women with a family history of breast cancer. This will be assessed by using the re-evaluated risk estimates using the TC v8 and BOADICEA (with added MD, SNP313 and mutation testing) in a sub-sample of FH-Risk study participants and conducting qualitative interviews with women who choose to receive their re-evaluated breast cancer risk estimate.

iv) To determine whether change in management differs between the three density measures in the Tyrer-Cuzick model. (BIRADs, Predictive VAS AND Volpara).

v) To compare the degree of management change between the Tyrer-Cuzick (v8) and the BOADICEA model (v5) (Can-Risk).

vi) To create information materials informed by participant interviews to communicate and inform women of their breast cancer risk re-evaluation and have these materials appraised by a sample of the FH-Risk women who have received their recalculated risk.

2.2 Objectives

Specific objectives are:

i) To explore how much new risk models (including MD, SNP313 and mutation testing) change risk estimates, in women in the FH-Risk study, between their first referral and latest visit to the FHRPC.

ii) To compare the risk estimations given by Tyrer-Cuzick v8 and Can-Risk (BOADICEA).

iii) To compare the risk profiles given by TCv8 for different measures of mammographic density (BIRADS, Volpara and Predictive VAS) (BOADICEA V uses only the BIRADS to assess MD).

iv) To determine the reproducibility and validity of two readers of BIRADs

v) To explore how women recall being told about their initial personal breast cancer risk, including risk perceptions, psychological wellbeing and subsequent behaviour.

vi) To explore whether a change in breast cancer risk over time affects credibility of how risk is calculated and communicated to women, and trust in its use in the NHS.

vii) To use the findings to understand how and in what format(s) changes to breast cancer risk over time should be communicated in the future to enable women to properly understand change in risk, potential change in management and manage emotional sequelae.

viii) To develop information materials based on participant interviews and refine via further interviews with women.

ix) To use the findings to develop an understanding of the optimal way to communicate changes in breast cancer risk to women who were part of the FH-Risk study but discharged from the clinic.

x) To use the findings to develop a questionnaire to be given to women who previously took part in the FH-Risk study (who have been discharged from the clinic) to assess the psychological impact of changed risk.

3.0 STUDY DESIGN & PROTOCOL

3.1: Part 1: Re-evaluation of breast cancer risk in the FH-Risk study population.

Participants in the FH-Risk study

A total of 954 women were entered into the NIHR FH-Risk study which was designed to assess how standard breast cancer risk estimates based on familial and non-familial factors (components of the standard Tyrer-Cuzick risk model) might be altered by the addition of MD and the newly discovered (at the time) breast cancer SNPs. Women under follow up in the Manchester FHRPC were recruited between November 2010 and November 2012 to the FH-Risk study. Recruitment was from women who may have previously been referred (from approximately 2000 onward) or women newly referred to the clinic during the recruitment period between 2010 and 2012.

Feedback of the results of how SNP18 affected risk was given in 2013. The risk change was given in general terms since the precise importance of the risk change was only partially clear and the algorithm was not yet fully validated. Feedback on MD was not given as previously suggested because analysis was not possible to compare with cancers at the time as the raw mammogram images required for processing MD were not retained. In 2017 v8 of the Tyrer-Cuzick model and in 2019 v5 of the BOADICEA model (CanRisk) was introduced which incorporated density measures and the assessment of SNPs.

All women in the FH-Risk study were/are undergoing annual mammography. They were/are discharged to the NHSBSP at age 50 if moderate risk or at age 60 if high risk as per NICE clinical

guidelines. At present (October 2020) approx. 271 patients remain under annual follow up for mammography and should be given the opportunity to learn of their revised risk estimate, as this information could change their entitlement to risk reducing strategies. Women who have been discharged will also be given the opportunity to be informed on their updated breast cancer risk estimate.

All FH-Risk women had blood taken for genetic studies. A copy of the consent form and the participant information sheet for FH-Risk is given in appendix 1. The following statements on the consent form are of high importance since women indicated:

1. *I consent to the storage of my DNA sample for future research.*
2. *I consent to the gifting of my blood sample for future research.*
3. *I agree to my existing mammograms and information from my Family History questionnaire(s) being used in this research.*
4. *I consent to the transfer of coded data with no personal identifiers for the purpose of the current research study looking at common genetic changes associated with breast cancer risk to any sponsor of the research*
5. *I agree that the information gathered can be stored by the custodians, University Hospital of South Manchester Foundation Trust, for possible use in future ethically approved research studies as described in the information sheet.*
6. *Would you like to receive your updated breast cancer risk information? (Please tick one box below)*

Archived information that women consented to for the use in other ethically approved studies include: demographic details, family pedigree including any history of cancer (current age or age of death of any relative, type of cancer and age at diagnosis), reproductive history (age at menarche, age at first pregnancy, duration of episodes of lactation and age at menopause if applicable), history of benign breast disease (including number of benign biopsies), artificial oestrogen exposure (duration of oral contraceptive pill usage, hormone replacement or fertility drugs) and morphometric information (BMI is also assessable from self-reported height and weight estimates from the women). In addition, the database stores an absolute lifetime risk calculated using the modified Claus or Tyrer-Cuzick models. The database also contains information regarding breast cancer incidence until at least January 2015. This will be extended during the study to December 2020. Although MD was not included in the risk estimates provided as part of FH-Risk, women did consent to their MD being accessed, calculated and fed back to them and this data will be accessed under their original consent (See appendix 1).

Members of the research team who are consultants and who were also part of the FH-Risk research team have permission (as they are part of the clinical care team) to access the above data (including DNA data) which participants consented to in order to perform the recalculation of risk.

Eligibility criteria

Inclusion criteria for performing a recalculation of risk on the FH-Risk study population (approx.954) includes:

1. Completed entry risk form prior to first attendance at the clinic (clinic standard questionnaire).
2. Entry to the clinic between ~2000 and 2012.
3. DNA collected from a blood sample between November 2010 and November 2012 during the period of recruitment to the FH-Risk Study.
4. Signed informed consent to the FH-Risk study.
5. Signed informed consent for the use of genetic and MD data in future ethically approved studies.

Completions of a clinic standard questionnaire prior to the first visit to the FHRPC included details of family history, age of menarche and first full term pregnancy, number of children and their DoB, age of menopause, use of oral contraceptives and HRT, smoking history, self-reported weight, height, weight gain since the age of 20, alcohol intake, previous breast or ovary problems and breast biopsy results.

METHODS

Risk recalculation

Risk recalculation will be performed on all 954 consented FH-Risk women's data.

Risk estimation models to be used to recalculate risk

Calculation using Tyrer-Cuzick Version 8

Phenotypic risk will be assessed using predicted remaining 10-year and lifetime risks to age 85 from the TC model V8 (Tyrer 2004; http://www.ems-trials.org/riskevaluator/). The following information from the original risk questionnaire collected before 2012 will be incorporated: age at baseline; first and second-degree relatives (age affected by breast and ovarian cancer or current age or age at death); age at first child, menarche and menopause; height and weight; and history of prior benign breast disease. Changes in these risk parameters will be assessed at subsequent clinical appointments and incorporated into the model.

Version 8 of the TC Model differs from V6 in that risk is estimated until the age of 85 (from 73 or 80 years) and because breast cancer risks have generally increased since V6 was developed (Tyrer et al., 2004). Thus, women will have in any case somewhat higher risks than previously given at their initial

appointment. However they still may end up with a lower risk estimate than originally given when MD and SNPs are taken into account (Brentnall et al., 2015).

Calculation using BOADICEA V – Can-Risk

Collaborative work with the Cambridge team that have now produced a user-friendly risk algorithm called CanRisk from their BOADICEA programme, means we can now provide bespoke breast cancer 10-year and remaining lifetime risks especially for those who carry pathogenic variants in moderate risk genes CHEK2 and ATM that are not provided for in Tyrer-Cuzick model (Archer et al 2020). CanRisk includes the same inputs as Tyrer-Cuzick (above) but also includes additional genes. Women will be provided the CanRisk output instead of Tyrer-Cuzick when they carry a pathogenic variant in any of the high or moderate risk genes. Comparisons will also be made to identify discrepancies in 10-year risks that would mean women were in different risk categories.

Estimation of Mammographic Density

Mammograms will be assessed as near as possible to the time of first referral to the clinic and at the time of discharge (last clinic mammogram) or at the time of last visit if still under review. They will be assessed by the three methods used in the Tyrer-Cuzick model, (BIRADs, Volpara and an automated modification of the Visual Analogue Scale (Predictive VAS).

BI-RADS (Breast Imaging-Reporting and Data System) will be reported according the system developed by American College of Radiology (5th Version 2013). Breast density is reported on a four point scale, a. breast is almost entirely fatty, b. scattered areas of fibroglandular density, c. heterogeneously dense breast, may obscure small masses and d. extremely dense breasts, lower the sensitivity of mammography. All mammograms will be double read by two experienced readers and if there is disagreement between readers a consensus is then reached. Training for consistency of reading will be by assessment of a series of 100 pairs of mammograms taken less than two weeks apart as previously described (Astley 2020). A third reader will assess the images if there is a discrepancy in BIRADs category. The final result will be incorporated in the Tyrer-Cuzick and the CanRisk models together with additional data required for risk estimation for each model.

Volpara Volumetric Density (Volpara Health Tech- nologies, Wellington, New Zealand) is a fully-automated method to estimate percentage volumetric density that requires commercial software and digital mammography DICOM files ("FOR PROCESSING" type). VolparaTM from Matakina is able to process images from a range of manufacturers (Hologic, GE, Siemens and Fuji). The method, in which knowledge of tissue attenuation coefficients, the physics of the imaging process and information in the DICOM header, are used to compute glandular thickness at each pixel position. VolparaTM uses a

relative physics model which reduces the need for accurate imaging physics data, but depends on locating a suitable fatty reference area within the image. VolparaTM outputs the fibroglandular tissue volume, total breast tissue volume, percentage of density by volume, and a Volpara Density Grade. We will be using the most recent software.

The Volpara algorithm determines the X-ray attenuation between the image detector and the X-ray source, based on the pixel signals in the images. A pixel signal corresponding to purely adipose tissue is used as a reference to which all other pixels are compared, in order to calculate the thickness of adipose versus fibroglandular tissue that must have been present between the detector and the X-ray source. As the pixel dimensions are reported in the image, the volumes of adipose and fibroglandular tissue are then summed across the entire breast. VBD is calculated as the ratio of fibroglandular tissue volume to total breast volume, expressed as a percentage. This quantitative VBD value is then mapped to a FDA cleared VDG (i.e. an automated equivalent of the BI-RADS 5th edition density categories) using pre-set thresholds.

Predictive VAS – Members of the research team (Astley, Harkness) have built convolutional neural networks (CNN) to predict density VAS scores from full-field digital mammograms. The CNNs are trained using whole-image mammograms, each labelled with the average VAS score of two independent readers. Each CNN learns a mapping between mammographic appearance and VAS score so that at test time, they can predict VAS score for an unseen image. Networks were trained using 67,520 mammographic images from 16,968 women and for model selection we used a dataset of 73,128 images. There was no significant difference between reader VAS and predicted VAS for the prior test set (likelihood ratio chi square, p=0.134). The fully automated method shows promising results for cancer risk prediction and is comparable with human performance (Ionesco 2018).

Determination of Polygenic risk Scores and Gene Testing

Blood samples were taken from all women as part of the original FH-Risk study protocol, from which DNA was extracted, or pre-existing DNA samples (also previously extracted from blood) were used.

Single Nucleotide Polymorphisms & Polygenic risk scores

A polygenic risk score (PRS) will be used to provide an overall relative risk estimate. We calculate the odds ratios (OR) for each of the three SNP geno-types (no risk alleles, one risk allele and two risk alleles) from published per-allele ORs, assuming independence and normalizing by an assumed risk allele frequency 10 mL of extracted DNA 96-well plates. Two samples with known genotypes have been used as internal controls for each plate. Assays were carried out blindly at Genome Quebec (Montreal, Canada) and at the Sanger Centre (Cambridge). A PRS will be used to provide an overall

risk estimate based on 313 SNPs (Mavaddat et al 2019). Assay failures have been ignored in the SNP score by imputing a relative risk of 1.0 when they occurred. An overall SNP risk score for each woman in the original FH-Risk study was formed by multiplying the genotype ORs together for an overall PRS. **Results of SNP313 are available already for all participating women.**

Genetic testing - Assay methods

Blood samples were taken from all women as part of the original FH-Risk study protocol, from which DNA was extracted, or pre-existing DNA samples (also previously extracted from blood) were used. *BRCA1/2* mutation testing was carried out when clinically indicated (the prior probability of identifying a mutation must have met the threshold of *BRCA1/2* likelihood probability ≥10% in accordance with UK clinical guidance (NICE 2013), using the Manchester score, using DNA Sanger sequencing and multiple ligation-dependent probe amplification analysis of all exons and intronexon boundaries and more recently next generation sequencing). Relatives of those identified with *BRCA1/2* mutations were offered cascade screening for the family-specific genetic mutation. All women were genotyped for 18 SNPs that have been shown to be associated with breast cancer risk in general European populations (FGFR2, CASP8, TOX3, MAP3K, 2q,CDKN2A, 10q22,COX11,NOTCH, 11q13, 10q21,SLC4A7, 6q25.1, 8q24,RAD51L1,LSP1, 5p12, 10q). In brief, multiplex genotyping was performed using Sequenom iPlex Gold (Sequenom, San Diego, California, USA) and TaqMan assay (Life Technologies). Intra-plate duplicates and negative controls were included in all genotyping. Genotypes were verified by Scientific Data Systems (SDS) and MassARRAY TyperAnalyze. Since the study feedback in 2013-14 further analysis (see above) has been carried out to perform a SNP313 PRS. All samples have also been sequenced for mutations in a panel of 35 genes including 14 that confer at least a moderate risk of breast cancer (Dorling et al 2020). Results of gene mutations in a panel of 35 genes are already available for all women who took part in the FH-Risk study.

Statistical Analysis Plan

The baseline anthropometric, familial and hormonal information from the FHRPC questionnaires will be entered into the breast cancer risk prediction models under consideration (TCv8 and CanRisk) and estimates of absolute 10 year and lifetime risk to age 80 risk obtained for each woman. The performance of the models will be compared in two ways; differences in prediction of individual risk and the change in category of risk (average, moderate and high) according to NICE guidelines. The follow-up period will be taken to be the time from initial referral and first clinic assessment with risk assessment to the most recent assessment or December 1st 2020, whichever is later

1. Objectives

Primary

vii) To determine change in NICE categories of risk (average, moderate and high risk) when new risk factors are added to standard breast cancer risk models.

viii) To explore how much new risk models (including MD, SNP313 and mutation testing) change risk estimates previously communicated to women in the FH-Risk study, between their first referral and their latest visit to the FHRPC

ix) To compare 10-year and lifetime risk estimates given by Tyrer-Cuzick (v8) and the BOADICEA model (v5) (Can-Risk)

Secondary

i) To compare the risk profiles for TCv8 for different measures of mammographic density (BIRADS, Volpara and predicted VAS) (BOADICEA V5 – CanRisk uses only the BIRADS to assess MD).

ii) To determine the reproducibility and validity of two readers of BIRADs

2. Methods

Analysis will be based on those individuals who attend two risk appointments – at time of entry to the FHRPC clinic and at their latest FHRPC clinic appointment and who have corresponding risk scores.

Primary endpoints:

- 10-year and lifetime breast cancer risk and the corresponding NICE risk categories for two risk prediction models: i) TCv8 and ii) BOADICEA v5.
- Risk scores from TCv8 and BOADICEA will be assessed using different model inputs: i) classical factors alone, ii) classical factors plus mammographic density (BIRADS) and iii) classical factors plus mammographic density plus SNPs.

Secondary endpoints:

- Differences in measures of mammographic density: i) visually assessed BIRADS, ii) Volpara and iii) predicted VAS using 'for presentation' and 'for processing' mammographic images and the relationship between these measures and 10-year and lifetime risk score in TCv8.

3. Analysis

The primary analysis will compare the risk categories and risk scores for the risk prediction models for women at entry to the clinic (or age 40) and at last follow-up in the clinic, and will compare the risk scores given by TCv8 and BOADICEA using different model inputs.

i) **Change in risk categories** – NICE risk categories (average, moderate and high) will be compared by creating cross tabulations of risk categories at entry and at last follow-up – the number (and percentage) of women moving up and down risk categories will be

reported and the McNemar-Bowker test will be used to determine whether the change in risk categories is statistically significant between the two time points.

ii) **Change in 10-year and lifetime risk scores** - change in continuous risk measures (10-year and lifetime risk estimates) will be estimated from TCv8 and BOADICEA risk prediction models. Normality and skewness of 10-year and lifetime breast cancer risk scores will be assessed. Where there is evidence of non-normality scores will be transformed. Scatterplots and correlation coefficients will be used to examine the relationship between 10-year and lifetime risk estimates at baseline and at latest follow-up.

Descriptive statistics will be used to report change in risk scores from time at entry to latest follow-up and will be compared using a paired t-test. Linear regression will be used to determine which risk factors (e.g. SNP313, MD) are associated with change in risk score.

iii) **Comparison between risk models** - descriptive statistics will be used to report risk scores from TCv8 and the BOADICEA models and differences in risk scores compared. Models will be compared using a) classical risk factors alone, b) classical risk factors plus mammographic density, as measured by BIRADS, which can be included in both models and c) classical risk factors plus mammographic density and SNPs. Scatterplots and correlation coefficients will be used to examine the relationships between models and Bland-Altman plots used to show the agreement between the models.

Secondary analysis will focus on the comparison between differences in mammographic density measures and the relationship with risk scores using TCv8.

iv) **Comparison of mammographic density methods and the relationship with TCv8 risk scores** – scatterplots, intraclass correlation coefficents and Bland-Altman plots will be used to look at the relationship between different mammographic density methods. Risk scores will also be compared for TCv8 using different methods for measuring mammographic density to determine the impact this has on overall risk score. Changes in NICE risk categories will be compared using the different methods using the McNemar-Bowker test and differences in the continuous risk measures will be compared using repeated measures analysis of variance (ANOVA).

v) **Reader reproducibility for BIRADS** - reproducibility for readers assessing BIRADS score will be determined using inter-reader and intra-reader statistics, using the McNemar-Bowker test to assess agreement within and between readers.

3.2 Part 1: Clinical consultations with FH-Risk women still in follow up at the FHRPC

As indicated above approx. 271 women from the FH-Risk study are still in follow up at the FHRPC. A re-evaluated risk can have implications for these FH-Risk women still in follow-up, i.e. it could affect their access to risk reducing strategies. Therefore the clinical team/research team have a duty of care to give these women who were part of the FH-Risk study and who still attend the FHRPC the opportunity to learn of their recalculated breast cancer risk. There is also a large sample from the original FH-Risk study have been discharged from the clinic. We also have a duty of care to invite these women to receive their updated breast cancer risk estimate regardless of whether they are still under follow-up.

Participants and recruitment

We expect to send invitation letters to up to 954 women who still attend or have been discharged from the FHRPC for check-ups (at the Nightingale Centre, Wythenshawe Hospital, Manchester University NHS Foundation Trust; MFT). Women still under follow-up will be invited after they have attended their annual mammogram and have received a clear result. Personal identifiable data will be accessed by the clinical care team who have legitimate access to patient information and the admin/research support office team based at MFT will send the invites out on behalf of the clinical team. As part of clinical follow-up these women have had their risk re-evaluated using the Tyrer-Cuzick Version 8. Women in the FH-Risk study who consented to the use of their data for future research purposes will be invited to consent to participate in a follow-up study and discuss their re-evaluated breast cancer risk at a clinic appointment (face to face or over the telephone).

Eligibility criteria

Inclusion criteria for invitation are:

- Previously given informed consent to participate in the FH-Risk study at the Nightingale Centre.
- Have an up to date clear mammogram.
- Who are still in follow-up at the FHRPC.
- Discharged from the family history clinic.
- Aged between 25 and 60.
- Have not developed breast cancer.
- Able to consent to participate in a research study.

Exclusion criteria are:

- Women who have received a diagnosis of breast cancer.

- Women who have not had a clear mammogram.
- Women who did not consent to their FH-Risk data to be used in other ethically approved studies.
- Women who lack the capacity to consent.

Procedure

Members of the clinical care team/authorised members of the research team with legitimate access to patient contact details will access contact details of eligible women in order to send invite letters out in the post to FH-Risk women to provide them with the opportunity to attend (in person or via the telephone) a clinic consultation to discuss their recalculated risk. The admin/research support office team based at MFT will send the invites out on behalf of the clinical team. Reminder invite letters will be sent out if deemed necessary (based on participant numbers). Women who are still under follow-up will be invited after they have attended their annual mammogram and have received a clear result. With this invite women will receive a participant information sheet an expression of interest and consent to contact form and three copies of a consent form (note: consent forms will be sent in the post to be signed and returned during the COVID19 pandemic as it may not be possible to complete the clinic consultation in person; consent forms can be signed in person if clinical appointments are to take place; one consent form to be retained by the participant and two to be sent back for the research file and medical records). Interested women will be able to indicate that they would like more information about their risk on the expression of interest and consent to contact form. On this form women will also be asked to provide their contact details so a member of the team can arrange their clinical consultation. A statement on this form will also ask women whether they are happy for their contact details to be retained for the purpose of inviting them to future research, including interviews in Part 2 and 3 of this protocol. Women will be asked to send the consent form and expression of interest and consent to contact form back to the team in the pre-paid envelope provided. A suitable time and date will be arranged for their clinical consultation which will either take place in person or over the phone (over the phone likely during the COVID19 pandemic).

On the consent form women will be indicate that they want their updated breast cancer risk estimate and their medical records can be accessed to calculate their risk. The clinical care team and the admin/research support office staff will provide the clinicians with the medical notes needed to calculate an updated risk before the appointment. Members of the research team required to calculate breast density will be provided with the appropriate data to do so.

Once women have consented and had their updated risk consultation the clinical care team will inform their GP of their updated risk estimate. The GP will only be informed when consent to do so has been gathered from the woman. Two GP letters will be in use, (1) one letter for those still under follow-up

and discharged and (2) one letter for those who have been discharged from the clinic and require a re-referral.

Following their consultation a summary letter will be sent to women, summarising the information that was spoken about in the appointment.

During the consultation the clinician will discuss any possible changes to risk management, i.e. a change to screening frequency or chemoprevention.

3.3 Part 1: Data Management (risk recalculation)

We are collecting and storing data in accordance with the General Data Protection Regulation (GDPR) and Data Protection Act 2018 which legislate to protect participants' personal information.

Current storage of data from the FH-Risk study:

All archived data from the FH-Risk study is stored on the MFT computer system by the FH-Risk study team (members of the present study team overlap with the FH-Risk study team). Clinical details are in the notes of each patient which are entered into the clinic database based in the clinical secretaries office. Consultants (who are members of the research team) currently have access to 271 women's information from the FH-Risk study as these women are still in follow up at the FHRPC and attend for annual mammograms as part of their ongoing care. An anonymised database of all the data obtained from women in the FH-Risk study (n=954) is stored at MFT on the hospital's computer system. SNP and genetic test results, Volpara and pVAS data will be/are stored on MFT computer databases. All these databases will be accessed to recalculate risk. All participants from the FH-Risk study have given informed consent for the use of their data in other ethically approved studies. The archived data from the FH-Risk study is stored in accordance with the FH-Risk study protocol, ethical approval and MFT sponsor conditions. UoM research team members will not have access to this data and archived data will remain at MFT.

Storage of recalculated risks:

Recalculated risk and risk information, i.e. SNP data and MD data are classed as clinical results and will be stored in patient FHRPC notes at the Nightingale Centre, stored on clinic computers on MFT's secure computer system. Images to calculate mammographic density will be used by UoM staff which honorary contracts with MFT. These images will be anonymised for the purpose of this analysis and will then be de-anonymised when being fed back to the patient. This is so UoM clinical staff with honorary contracts at MFT do not see any patient identifiable data. Images will not be retained on

UoM systems. Written clinic notes for women who consent to a consultation will be stored at the Nightingale Centre in the FHRPC in secure cabinets.

An anonymised database of all FH-Risk women's previous and updated breast cancer risk estimates will be stored on the MFT secure computer system. Only the clinical care team will be able to link this data back to women via a unique participant number.

A second anonymised database of women's previous and updated breast cancer risk estimates (who are still in follow up) will be stored on the MFT secure computer system. Only the clinical care team will be able to link this data back to women via a unique participant number.

Anonymised databases will be retained for at least 10 years after the study in accordance with UoM's retention policy.

Study databases/storage of consents/expression of interest and consent to contact details

A database of contact details of women who took part in the FH-Risk study and who are still in clinical follow up at the FHRPC will be created by the clinical care team/members of the research team who have legitimate access. This will be used to keep track of who has been invited to receive a consultation. This database will be stored on MFT computers by the clinical care team/authorised members of the study team and password protected. This database will be deleted securely following the completion of the study.

A separate database will be kept of women who have consented to taking part and information from their expression of interest and consent to contact form will be added to this database (i.e. level of feedback they require and consent to contact preferences for future research (interviews in part 2 and 3)). The physical copy of this form will be destroyed once information has been transferred to the database. This database will be stored on MFT computers by the clinical care team/authorised members of the study team and password protected. Entries on this database will be deleted at the end of the study if a woman did not consent to being contacted about future research. Those who consented to being contacted about future research, their details will be retained in this database.
All the above will be stored on the secure MFT computer network and will only be accessed by authorised members of the research team/clinical care staff.

Consent forms will be stored at MFT by the clinical care team in a folder in a locked cabinet in secure offices. A second consent form will be stored in women's medical notes. Consent forms will be stored for 2 years in accordance with UoM's retention period.

3.4 Part 2: Exploring the experience of receiving updated breast cancer risk estimates in women with a family history of breast cancer: an interview study

Participants and recruitment

Twenty women who have consented to discuss their re-evaluated risk estimate at the FHRPC (see part 1) and who have consented to be contacted about future research (namely the related interview studies in part 2 and 3) will be invited to participate in a semi-structured interview (over the telephone or via Zoom). Purposive sampling will be used to invite 20 women who have had their breast cancer risk estimate re-evaluated by the clinical team. The research team will invite 10 women who have a re-evaluated risk that has either increased by at least one category and 10 women who havedecreased by at least one category. Eligibility screening will be conducted before sending invitation letters by the breast cancer research team at MFT or by an eligible member of the research team with the requisite permissions. We estimate that a sample size of 20 will be sufficient to explore views around re-evaluated risk estimate experiences from the perspective of women who have received a range of risk estimate changes.

Eligibility criteria

Inclusion criteria for invitation are:

- Previously given informed consent to participate in the FH-Risk study at the Nightingale Centre.
- Consented to/have received their re-evaluated risk at a clinic appointment (see Part 1).
- Consented to be contacted about future research (namely interviews in Part 2 and 3).
- Aged between 25 and 60.
- Have not developed breast cancer.
- Able to consent to participate in a research study.

Exclusion criteria are:

- Women who have received a diagnosis of breast cancer
- Women who lack capacity to consent.

Part 2 Study Procedure - Interviews

Only women who consent to having a clinical appointment to discuss their re-evaluated risk estimate and consented to take part in future research will be invited to this interview study. The interview study will be mentioned to women at the end of their clinical appointment to assess their interest in taking part. As mentioned above women will complete an expression of interest and consent to contact form and a consent form prior to their clinical appointment. On these forms there is a statement which asks if the participant is happy for the research team to retain her contact details in

order to invite her to related future research and whether their contact details ONLY can be passed to a member of the research team based at UoM. Therefore information about this study will only be sent to women who consent to this statement.

Inviting women to interview

Part 1: Face to face consultation:

If a woman has indicated that she would be happy to be contacted about taking part in future research (via the expression of interest and consent to contact form) the consultant (and member of the research team) will provide them with information about the interview study. The consultant will introduce the study and answer any questions. Interested women will be given a participant information sheet (PIS) to take home. This will be provided at the end of the appointment. If a woman is interested in taking part they will be reminded that the contact details they provided on the expression of interest and consent to contact form will be passed to the UoM research team member who will be in touch (providing they have consented to this). Women may also call the research team directly using the contact details within the PIS if she wishes to take part.

Telephone consultation (and COVID):

For telephone consultations (and for during COVID-19) the consultant at the end of the appointment will explain the interview study to the women and ask whether they would be interested in receiving further information (providing they have consented to being contacted about future research and consented for their contact details to be passed to the researcher conducting the interviews (UoM based)). For women who have consented on their expression of interest and consent to contact form to being contacted via post, an invite letter and a PIS will be sent out from the research team at MFT/UoM. Women will then be asked to contact the researcher conducting the interviews if they would like to take part. Reminder invite letters will be sent out if deemed necessary (based on participant numbers). For women who consented to be contacted via email or telephone the researcher conducting the interviews (UoM based) will contact them via these methods prior to providing them with the PIS and arranging an interview.

Setting

Depending on the interviewees' preferences, interviews will either take place over the telephone or Zoom. Telephone and Zoom interviewing will be given as the only option during COVID-19. We may review whether it is possible to interview women face-to-face when COVID restrictions are lifted/less severe. Face to face interviewing is built in to this application.

Materials and Methods

Telephone and Zoom interviewing will be given as the only option during COVID-19 restrictions. Should restrictions change and allow for face to face interviewing, women can choose to be interviewed at the University of Manchester, their homes or a private location of their choosing. The participant information sheet has been created with additional information in relation to in person interviewing and Covid-19.

Audio recorded consent will be taken at the beginning of each interview. The researcher will read out the statements and ask whether the interviewee agrees. This will be recorded on an encrypted device separately from the study data. If interviews are able to take place in person the participant will be required to read and sign a physical copy of the consent form. With consent, interviews will be audio-recorded using an encrypted device. The researcher may take notes during the interview and this will be used as field notes only and will be destroyed at the end of the study data analysis. When zoom is used we will not video record the session. Instead the audio recorder will be placed next to the computer speaker. This has worked for colleagues and reduces the amount of identifiable data produce by the study.

A topic guide will be used to conduct the interviews to ensure that the same broad topics are covered, but leaving the participants free to talk about what is important to them and their own experiences. These may be iterative depending on on-going data collection. The main focus of the interviews however will be to gain an understanding of what the breast cancer risk estimates and possibly changed estimates mean to the women attending the FHRPC and how this may affect psychological wellbeing and future risk-related healthcare decisions. These will be piloted before use. Women may choose to bring notes to the interview in order to remember the risk estimate that they initially received and the re-evaluated risk. Interviews will be approximately 60 minutes in length. Non-mandatory demographic details will also be collected; which will be use to describe the sample when the findings are written up. Consent to use each participant's postcode to calculate an Index of Multiple Deprivation (IMD) will also be requested to use as a measure of deprivation when describing the study sample during write-up. Once this has been calculated the postcode will be destroyed.
With consent, medical data with be accessed after the interview including women's initial risk and re-evaluated risk estimates held within medical records at MFT (women will consent for the research team to access their medical records as indicated on the study consent form). Relevant medical data (for example, chemoprevention uptake, and frequency of mammogram attendance) will be extracted using a case report form (CRF). The CRF will be filled in by the consultant and will be provided to the researcher electronically without any personal identifiable data present. This will be provided as full data set for all the participants.

Analysis

Data will be analysed using Reflexive Thematic Analysis following the rigorous guidelines suggested by Braun and Clarke (Braun & Clarke, 2019). A reflexive thematic analysis aims to explore patterns that are inherent across the data and represent these patterns into a meaningful, in-depth, rich analysis; whilst acknowledging the role of the researcher in the final thematic structure. In this analysis, data will be analysed inductively at a manifest level. Analysing data inductively and at a manifest level means the researchers are able to remain close to the data and represent the interviewees' views and experiences, free from the influences of pre-existing theories and literature (Braun & Clarke, 2006). Additionally the theoretical position which will be used to inform this analysis will be essentialist. This approach will enable the researchers to report the experiences, meanings and realities of the participants as they appear in the data.

Data will be coded by experienced qualitative researchers and the emerging code framework will be developed with the guidance of qualitative and thematic analysis experts. Coding will be conducted systematically and interactively including double coding of initial transcripts. Negative cases will be sought to test the emerging code framework and highlight its limits. Regular coding meetings will be held to refine the coding structure. Coding will continue until the team are satisfied that codes and themes adequately describe and capture the data and that saturation has been achieved. Data with be analysed using NVivo, a qualitative analysis package.

The analysis from these interviews will be used to inform how best to assess the psychological and behavioural impact of receiving re-evaluated breast cancer risk estimates in the remaining FH-Risk sample in a prospective, longitudinal study. Additionally, the analysis will inform how best to communicate risk, discuss risk management (i.e. healthcare decisions) and manage emotional sequelae. Data from these interviews will also be used to inform the production of information materials related to breast cancer risk communication in the FHRPC (see part 2).

3.5 Part 3: Optimising and refining information materials for the communication of revised risk estimates: a 'think aloud' interview study

The findings from Part 2 will be used to develop information materials (i.e. letter and information leaflets) intended for women who have had their breast cancer risk re-calculated. Materials will be developed for the following groups: (i) women whose risk estimate has increased, (ii) women whose risk estimate has stayed the same and (iii) women whose risk estimate has decreased.

Once these materials have been developed and been through an ethical amendment we will invite women from the FH-Risk study who have had received a revised risk estimate to appraise these materials. We will invite women from the following groups, (i) women whose risk estimate has increased, (ii) women whose risk estimate has stayed the same and (iii) women whose risk estimate

has decreased. Each of these groups of women will appraise the materials applicable to their risk status. The interview method used will be 'think alouds'. 'Think aloud' interviews are a form of qualitative enquiry where the participant is required to read material out loud and provide their views and feedback as they naturally occur whilst reading. These interviews will be audio-recorded.

Women from each group will be required to read a suite of information materials out loud and will be asked to reflect on the following whilst doing so:

- The level of information, is there too little or too much
- The accessibility of the information
- The readability of the materials
- The appearance of the materials

A brief semi-structured element will end these interviews and will explore views on:

- Whether there is any additional information that should be added
- Whether the information aids women's understanding with regards their new estimated risk
- Whether the information provided would help women make a decision about risk reduction strategies and more frequent screening if moderate or high risk
- How women would feel about receiving this information

Participants and recruitment

Thirty women who have consented to discuss their re-evaluated risk estimate at the FHRPC (see part 1) and who have consented to be contacted about future research (namely the related interview studies in part 2and 3) will be invited to participate in a 'think-aloud' interview (over the telephone or via Zoom). Purposive sampling will be used to invite 30 women who have had their breast cancer risk estimate re-evaluated by the clinical team. The research team will invite 10 women who have a re-evaluated risk that has either increased by at least one category, decreased by at least one category or their risk category has remained the same. Eligibility screening will be conducted before sending invitation letters by the breast cancer research team at MFT or by an eligible member of the research team with the requisite permissions. We estimate that a sample size of 30 (10 women from each group) will enable a thorough appraisal of materials.

Eligibility criteria

Inclusion criteria for invitation are:

- Previously given informed consent to participate in the FH-Risk study at the Nightingale Centre.
- Consented to and have received their re-evaluated risk at a clinic appointment (see Part 1).
- Consented to be contacted about future research.

- Who are still in follow-up at the FHRPC.
- Aged between 25 and 60.
- Have not developed breast cancer.
- Able to consent to participate in a research study.

Exclusion criteria are:

- Women who have received a diagnosis of breast cancer.
- Women who lack the capacity to consent.

Part 3 Study Procedure

Only women who consent to having a clinical appointment to discuss their re-evaluated risk estimate and consented to take part in future research will be invited to this interview study. The interview study will be mentioned to the women at the end of their clinical appointment to assess their interest in taking part. As mentioned above women will complete an expression of interest and consent to contact form and a consent form prior to their clinical appointment. On these forms there is a statement which asks if the participant is happy for the research team to retain her contact details in order to invite her to related future research and whether their contact details ONLY can be passed a member of the research team based at UoM. Therefore information about this study will only be sent to women who consent to this statement. Reminder invite letters will be sent out if deemed necessary (based on participant numbers).

Inviting women to interview

Inviting women to interview in Part 3 will follow the same format as Part 2.

Setting

The same settings for part 2 apply for part 3.

Materials and Methods

Telephone and Zoom interviewing will be given as the only option during COVID-19 restrictions. Should restrictions change and allow for face to face interviewing, women can choose to be interviewed at the University of Manchester, their homes or a private location of their choosing. The participant information sheet has been created with additional information in relation to in person interviewing and Covid-19.

Audio recorded consent will be taken at the beginning of each interview. The researcher will read out the statements and ask whether the interviewee agrees. This will be recorded on an encrypted device separately from the study data. If interviews are able to take place in person the participant will be required to read and sign a physical copy of the consent form. With consent, interviews will be audio-

recorded using an encrypted device. The researcher may take notes during the interview and this will be used as field notes only and will be destroyed at the end of the study data analysis. When zoom is used we will not video record the session. Instead the audio recorder will be placed next to the computer speaker. This has worked for colleagues and reduces the amount of identifiable data produce by the study.

Women taking part in these interviews will be asked to read aloud the materials that are applicable to their risk status, i.e. risk has gone up, risk has stayed the same and risk has gone down. Materials could include letters and information leaflets. As interviews may take place over the telephone the researchers will post or email the materials to the participant prior to the interview taking place. If interviews take place over Zoom the researcher will either post or email the materials or share their screen with the participant so they are able to read the materials. Interviews will be approximately 60 minutes in length.

Following these interviews we will refine the materials based on the appraisals the women have provided. Once refined we will present the materials to a PPIE panel to request their feedback. Materials will be refined again following any PPIE feedback.

A topic guide will be used for the semi-structured component of the interviews and will be piloted before use. At the point of consent we will ask participants to provide some non-mandatory demographical information; which will be used to describe the sample when the findings are written up. Consent to use each participant's postcode to calculate an Index of Multiple Deprivation (IMD) will also be requested to use as a measure of deprivation when describing the study sample during write-up. Once the deprivation score has been obtained the postcode will be destroyed.

With consent, medical data with be accessed after the interview including women's initial risk and re-evaluated risk estimates held within medical records at MFT (women will consent for the research team to access their medical records as indicated on the study consent form). Relevant medical data (for example, chemoprevention uptake, and frequency of mammogram attendance) will be extracted using a case report form (CRF). The CRF will be filled in by the consultant and will be provided to the researcher electronically without any personal identifiable data present. This will be provided as full data set for all the participants.

Analysis

A content analysis will be performed on the 'think aloud' data between each round of interviews. The conventional form of content analysis will be used where researchers explore the number of commonalities in the data. Thus, content analysis enables the researcher to systematically describe

the data by extracting the amount of times a point is raised by participants (Hsieh & Shannon 2005). Analysing in this way will allow the researcher to identify the commonalities and consistencies in participants' comments in order to refine materials in line with these views (Hsieh & Shannon 2005). For the brief semi-structured section of the interviews a manifest, inductive thematic analysis will be used as described in study 1. Findings from these interviews will be used to inform changes to information materials.

3.6 Data management for Part 2 and 3 (qualitative interviews)

We are collecting and storing data in accordance with the General Data Protection Regulation (GDPR) and Data Protection Act 2018 which legislate to protect participants' personal information.

The clinical care team/authorised members of the research team in Part 1 of this study will provide the UoM researcher with the contact details of women who indicated that they would be happy for their details to be shared with the UoM researcher in order for them to contact her about future related and ethically approved research. Their consent to be contacted will be recorded on the expression of interest and consent to contact form issued in Part 1. The clinical care team/authorised members of the research team in Part 1 will either enter women's details into an excel file and send the file password protected via secure email or will telephone the UoM researcher who will input the details into a password protected excel file stored on the University's Research Storage Service (Isilon). Each participant taking part in Part 2 and 3 of this study will be provided with a reference code used to label which interview they took part in. Participants will also be given pseudonyms in place of their real names in transcripts and publications. A password protected file containing the reference codes and pseudonyms for each participant will be kept on the University's secure server (p:drive) stored separately from study data. Study data (audio recordings and anonymised transcripts) will be kept on the University's Research Storage Service (Isilon). Audio recordings will be stored separately from other study data. Excel files containing participants' identifiable information will also be stored on Isilon. All files will be password protected. Only authorised members of the research team will be able to link this data together should participants want to withdraw their contribution. Files containing reference codes and pseudonyms will be deleted after a participants data has become part of the wider dataset, approximately 2 weeks after the interview. Contact details will only be retained if women consent to being contacted about future research. These details will be retained for up to 10 years after the study has ended. If and when women are contacted about future research they will be given the option to have their details deleted from the database. For those who do not consent for their details to be retained, their details will be deleted after results have been written up for publication and participants who requested it have received a summary of the results. After this point

the research team will not be able to identify participants from the data. Only authorised members of the research team will have access to this data. This data will be kept strictly confidential.

Forms containing demographical information will be added to a excel spreadsheet. Paper copies will be shredded by the University's service for disposing of sensitive documents. This excel file will be password protected and stored on Isilon and will be destroyed when findings have been written up for publication. With consent, medical data with be accessed after the interview including women's initial risk and re-evaluated risk estimates held within medical records at MFT (women will consent for the research team to access their medical records as indicated on the study consent form). Relevant medical data (for example, chemoprevention uptake, and frequency of mammogram attendance) will be extracted using a case report form (CRF). The CRF will be filled in by the consultant in part 1 and will be provided to the researcher electronically without any personal identifiable data present. This information will be added to the demographic information excel file. This excel file will be password protected and stored on Isilon and will be destroyed when findings have been written up for publication.

Audio recordings of all interviews will be recorded on an encrypted audio device. Video footage from zoom will not be recorded. Interviews will take place in a private location and where possible identifiable information which could be captured on the recording will be avoided. Any identifiable data captured will be replaced during transcription. Once an interview is complete the researcher will store the device securely until uploading to the University's secure server can be carried out (as soon as is feasible). The audio recording will then be uploaded to the University's Research Storage server, password protected and encrypted. The researcher will listen to the recording to check the upload and will then permanently delete the recording off the device. Transcription is to take place via a 3rd party service, approved by the University. Audio files will be uploaded via a secure file upload. Audio files will be stored separately from other study data on the Research Storage server until the final analysis of the results have taken place. After this point audio files will be permanently destroyed. Anonymised transcripts will be stored for up to 10 years following publication. The production and storage of audio files and transcripts will be carried out in accordance with the University's Standard Operating Procedure for secure handling of recordings and transcriptions. All audio recordings including audio recorded consent will be stored separately from other study data.

Should participants wish not to be recorded but would still like to be interviewed the researcher will take notes. These will be typed up, password protected and stored on Isilon. Quotes from these notes will not be used. Original hand written notes will be shredded via the University's shredding of confidential documents service

Recorded consent taken over the telephone/zoom will be stored securely, electronically and separate from the study data. These will be destroyed as per the policy for physical consent forms (for low risk studies: 2 years after the study has been completed) which is in line with University policy. Physical consent forms will be stored in a locked cabinet in the lead researchers locked office at the University for up to 2 years after the study has been completed. Consent forms will then be destroyed.

Anonymised quotes will be used in research conferences, presentations and publications. Pseudonyms will be used with each quote used. Anonymised transcripts may be shared with reputable researchers and organisations (NHS and healthcare organisations) who are required to handle data in the same way as the University. These organisations will have to request to see this anonymised data via a data sharing agreement. No personal information will be shared and participants will not be able to be identified.

In Parts 2 and 3, for the safety of the research staff, members of the study team who will be conducting the interviews will be required to fill out a lone working form detailing the address of the participant should they be interviewed at home. Only authorised members of the research team will have access to this information if needed. These forms will be destroyed when they are no longer required.

Managing distress and disclosure of bad practice:

We do not anticipate that the content of these interviews will cause any undue discomfort to participants. However, the discussion of a family history of breast cancer could potentially be distressing, as well as any changes to risk. We will follow the University's managing distress policy should participants become distressed or uncomfortable. In the unlikely event of a disclosure of malpractice or gross misconduct, the researcher may be obliged to report such a disclosure, breaking confidentiality.

3.7 Part 4: Communicating an updated breast cancer risk: A questionnaire study

Questionnaire rationale and objectives

It is well documented in the literature that women either under or over-estimate their risk of developing breast cancer even after the provision of a clinically-derived risk estimate. It is unknown however what women understand about their risk and how they describe their risk following an update which incorporates new strong independent risk factors.

In this questionnaire study we want to examine the relationship between objective risk (i.e. the updated clinical estimate) and women's subjective understanding of their risk following the provision of an updated clinically-derived breast cancer risk estimate. With this we also want to examine women's breast cancer risk knowledge, including whether they perceived a change to their risk and cancer worry.

Specific objectives include:

- To examine whether there is a difference between objective and subjective risk, looking at first risk given in the first FH-Risk study, updated risk (provided in Part 1 of this study) and women's perceived risk.
- To examine the predictors of subjective risk, including objective risk factors such as family history, PRS, breast density and weight.
- To examine whether women have perceived a change to their risk.
- To examine women's breast cancer risk knowledge, including factors which have contributed to their risk.

Participants and recruitment

Women who opted to have their updated breast cancer risk and attended a consultation in Part 1 will be approached for this part of the study. All these women will be eligible apart from those who took part in interviews in Part 2 and 3 and those who did not consent to hearing about future related studies. Approximately 330-350 women will be eligible from Part 1. Women will be invited to take part in this follow-on questionnaire study via post. They will receive an invite letter, PIS, consent form and paper questionnaire, together with a pre-paid returning envelope.

Sample size justification

The sample size calculation is based on detecting a weak positive correlation coefficient between variables (r=0.2). Assuming this, a sample size of at least n=194 will be required to have 80% power (β=0.2) at α=0.05 significance.

There are between 330 and 350 women eligible to complete this questionnaire from Part 1 of this study. We anticipate that asking 350 women to take part will result in responses from n=210 women, assuming a 60% response rate.

Procedure

Women will first be instructed to complete a copy of the consent form. They will receive two copies, one for their records and one for the study team. Following consent, women will be asked to complete the accompanying questionnaire. This should take no more than 10 minutes to complete. Once

complete women will be instructed to return their signed consent form and completed questionnaire in the pre-paid envelope provided. A reminder letter will be sent to women approximately 2 weeks after the first invite to gather additional questionnaires from those who may have forgotten to complete.

Once questionnaire responses have been received this information will be inputted onto a database and linked with women's data from Part 1 via their unique ID given to them in Part 1. This linkage will be carried out by members of the clinical care team at the hospital as they are the only ones who know how to link this data together. Once this data has been brought together their ID will be removed from the database and the dataset anonymised. This will happen approximately 2 weeks after receiving the questionnaire. All consent forms will be stored securely at UoM in a locked cabinet in a locked office.

Free text response box procedure: Since distributing questionnaires it has come to our attention that a minority of women are using the free text response box to pose questions to their clinician (who is the clinician on the study). Some of these questions require an answer and we would like to give these women the opportunity to speak with their clinician again as part of this study. We believe that we have a duty of care to provide this option. To do this, the researcher at the University who receives the completed questionnaires will provide women's study IDs and question response via a secure database to the research/clinical team at the hospital. As the hospital is able to link IDs to contact information, the clinician will identify these women and a member of the research team (on behalf of the clinician on this project) will contact those with questions and give them the opportunity to speak with their clinician further if they still want to. If women want a further conversation, an appointment will be arranged. A summary letter will be posted to women following their conversations, which will be copied to the GP is appropriate.

Materials and methods

An invite letter, PIS, consent form and paper questionnaire (and pre-paid envelope) have been developed to distribute to women from Part 1 who attended a consultation and consented to hearing about future related research. Data will be gathered by a short questionnaire. Data from women's involvement in Part 1 and the FH-Risk studies will also be gathered from those who consented for their data to be used in future related research.

The questionnaire will include the following measures:

- A measure of comparative risk using the measure proposed by Weinstein (1999; *What does it mean to understand a risk? Evaluating risk comprehension. J Natl Cancer I Monogr 1999; 25: 15-20).*
- A measure of absolute risk using lifetime risk thresholds for breast cancer as defined by NICE clinical guidelines.
- A measure developed by the research team assessing for a perceived change in breast cancer risk.
- A measure developed by the research team assessing for women's knowledge about breast cancer risk factors.
- A measure of satisfaction regarding receiving an updated breast cancer risk estimate proposed by French et al (2004; *The psychological costs of inadequate cervical smear test results. Br J Cancer. 2004;91:1887–1892).*
- One item from the Leman cancer worry scale (1991) about developing breast cancer (*Psychological side effects of breast cancer screening. Health psychology, 10(4), 259).*
- *A free text response option to allow participants to identify anything important to them that the questionnaire may not have asked.*

Analysis

Data will be analysed using correlational analysis and regression modelling. For example, correlational analysis will be used to assess the relationship between objective risk and women's subjective understanding of their risk, as well as the correlation between objective and subjective risk and cancer worry. Regression modelling will be used to explore which risk factors women attribute to their risk. Descriptive statistics will also be used for the satisfaction measure.

3.8 Data management for Part 4 (questionnaire study)

In accordance with data protection law, The University of Manchester is the Data Controller for this project. This means that we are responsible for making sure personal information is kept secure, confidential and used only in the way the participant has been told it will be used.

All data provided as part of the FH-Risk studies is stored on the secure NHS server on the hospital computer system by the study team. Notes from these studies are also stored in patient notes which are entered onto the clinic database based in the clinical secretary's office. An pseudonymised dataset is also stored at MFT and is linked to personal identifiable data via a study ID link. Only members of the research team can link this data to personal information. An anonymised database of all the data provided as part of the FH-Risk studies is also stored on the secure NHS server at the hospital, as well

as on secure servers at the University of Manchester. Women cannot be identified from this particular database.

Consent forms will be stored at the University of Manchester in the researchers locked office in a locked cabinet for up to 5 years following the end of the study and will then be destroyed. We will only retain participant contact details if they consent to being informed about future related research. If they do not consent to their contact details being retained we will destroy them once the findings have been written up for publication. Only authorised members of the research team will have access to this data. A database will kept at Manchester University NHS Foundation Trust electronically of contact details for those who have taken part and who wish to be contacted again.

Completed paper questionnaires will be securely destroyed once data has been inputted electronically. This data will be pseudonymised using the participant ID number assigned to women when they received their updated breast cancer risk estimate in Part 1. This participant ID is only known to authorised members of the research team. This ID number will be inserted on each questionnaire before dispatch. Once data from their involvement in the present questionnaire study has been added to the data from the FH-Risk studies women's participant ID will be deleted from this database and the dataset anonymised, meaning we will not be able to identify any woman from this data. This will happen approximately 2 weeks after receiving the completed questionnaire.

Electronic material including, the pseudonymised and eventual anonymised database with the FH-Risk study data and questionnaire responses will be stored at the University of Manchester and as well as at Manchester University NHS Foundation Trust (Nightingale Centre, Wythenshawe Hospital) on secure, password protected computers. Electronic files containing 'personal identifiable information' will be deleted when they are no longer needed. Files containing 'personal identifiable information' will not be linked to women's questionnaire data.

The study team at The University of Manchester will have access to personal information and they will anonymise this as soon as possible. Names and any other identifying information will be removed and replaced with the ID number assigned to women in Part 1. The research team will have access to the key that links this ID number to women's personal information. Should women wish to opt out of us retaining this information, they can email the research team to request their removal.

4.0 CONSENT

All potential participants in each part of this study will receive notification of the study either via invite letter (Part 1, 2,3 & 4), email or telephone (Part 2 & 3). With this invite participants will receive a PIS. This sheet will contain all the relevant information needed about the study to make an informed decision as to whether to take part. All participants in each part of this study will have at least 24 hours to consider whether they would like to take part. In Part 1 women will fill in an expression of interest and consent to contact form and post it back to the study team, together with their consent form (during COVID19) if they would like to have a clinical appointment to discuss their risk. The clinical care team/authorised members of the study team will then contact the women to make this appointment. If clinical appointments are able to take place face to face (due to COVID19 face to face consultations may not be available) women can sign the consent form and expression of interest and consent to contact form at the appointment. For interviews taking place over the phone or zoom (Part 2 and 3), the researcher will read out each statement of the consent form and ask the participant if they agree. This will be audio recorded on an encrypted device and kept separate from study data. In part 4 (questionnaire study) women will receive a copy of the consent form and will be asked to complete this and post back in the pre-paid envelope provided with the completed questionnaire. Women in all parts of the study can contact the study team to ask questions at any time using the details on the PIS.

5.0 ETHICAL AND REGULATORY APPROVAL

The study will be conducted in full conformance with all relevant legal requirements and the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and the UK Policy Framework for Health and Social Care Research 2017.

Research Ethics Committee (REC) and other Regulatory review & reports

The study will receive ethical review and approval from the necessary regulatory bodies. Before the start of the study, a favourable opinion will be sought from a NHS REC and Health Research Authority.

Amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site. All correspondence with the REC will be retained. The Chief Investigator will produce the annual report as required and notify the REC of the end of the study. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. If the study is ended prematurely, the Chief Investigator will notify the REC, including reasons for the premature termination. A final report will be submitted with the results to the REC within one year after the end of the study.

Sponsor approval will be sought prior to the study commencing.

Regulatory Review & Compliance

Before any enrolment of participants into the study, the Principal Investigator will ensure that appropriate approvals from participating organisations (in this instance, Manchester University Foundation Trust, Wythenshawe Hospital) are in place. For any amendments, these will be handled in line with the sponsors and site management organisational policies.

Peer review

Originally this study was under review for funding from Prevent Breast Cancer. A part of that funding application peer review was received using the internal peer review system within the Faculty of Biology, Medicine and Health at The University of Manchester and when the funding application went under review by Prevent Breast Cancer.

This study was also reviewed as PhD application by the MRC which was successfully funded and deemed scientific.

Patient & Public Involvement

The research team have strong links with a PPI group of women who have been involved in previous breast cancer risk-related studies that have taken place in recent years. This panel of women will be directly involved in the present research project and have contributed to the proposed design and reviewed this application. Co-applicant Dr McWilliams set up the PPI group and will support this aspect of the current application together with PhD student Miss Woof.

A woman who received her breast cancer risk estimate including SNPs in a previous research study (Predicting Risk of Breast Cancer; PROCAS) provided feedback on this proposal including our study objectives which have been incorporated into the final draft. Suggestions were also made and incorporated to improve the lay summary and lay overview in this application. This will include reviewing study information to recruit women into the study before the study begins during ethical approvals through to disseminating study findings. The research team also have close links with the Public Programmes Team which form part of the NIHR Manchester Biomedical Research Centre and will utilise their membership panel and advice, where appropriate. For example, the lead applicant has successfully received funding from this group (along with co-applicant Prof French) to conduct a community engagement project in cervical screening following completion of a research project and would reapply for the project outlined in this protocol. Costs for PPI involvement during the project have been established.

End of study

It is expected that the last participant to be recruited to all areas of this study will be by 1st June 2024. Before an end of study report is sent to HRA/REC participants will be provided with a summary of the results and dissemination of results via publications will be completed. If more time is needed for these activities an extension to the study end date will be applied for via an amendment.

6.0 STATEMENT OF INDEMNITY

The University has insurance available in respect of research involving human subjects that provides cover for legal liabilities arising from its actions or those of its staff or supervised students. The University also has insurance available that provides compensation for non-negligent harm to research subjects occasioned in circumstances that are under the control of the University.

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8.0 FUNDING

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9.0 PUBLICATION POLICY

Results will be written up in scientific journals and abstracts will be submitted for presentation of findings at national and international scientific meetings and conferences. A study of the main findings will be written with the PPI group and shared with participants who agreed to be contacted about this. The study contact should be contacted in the first instance regarding information about results and publication copies.

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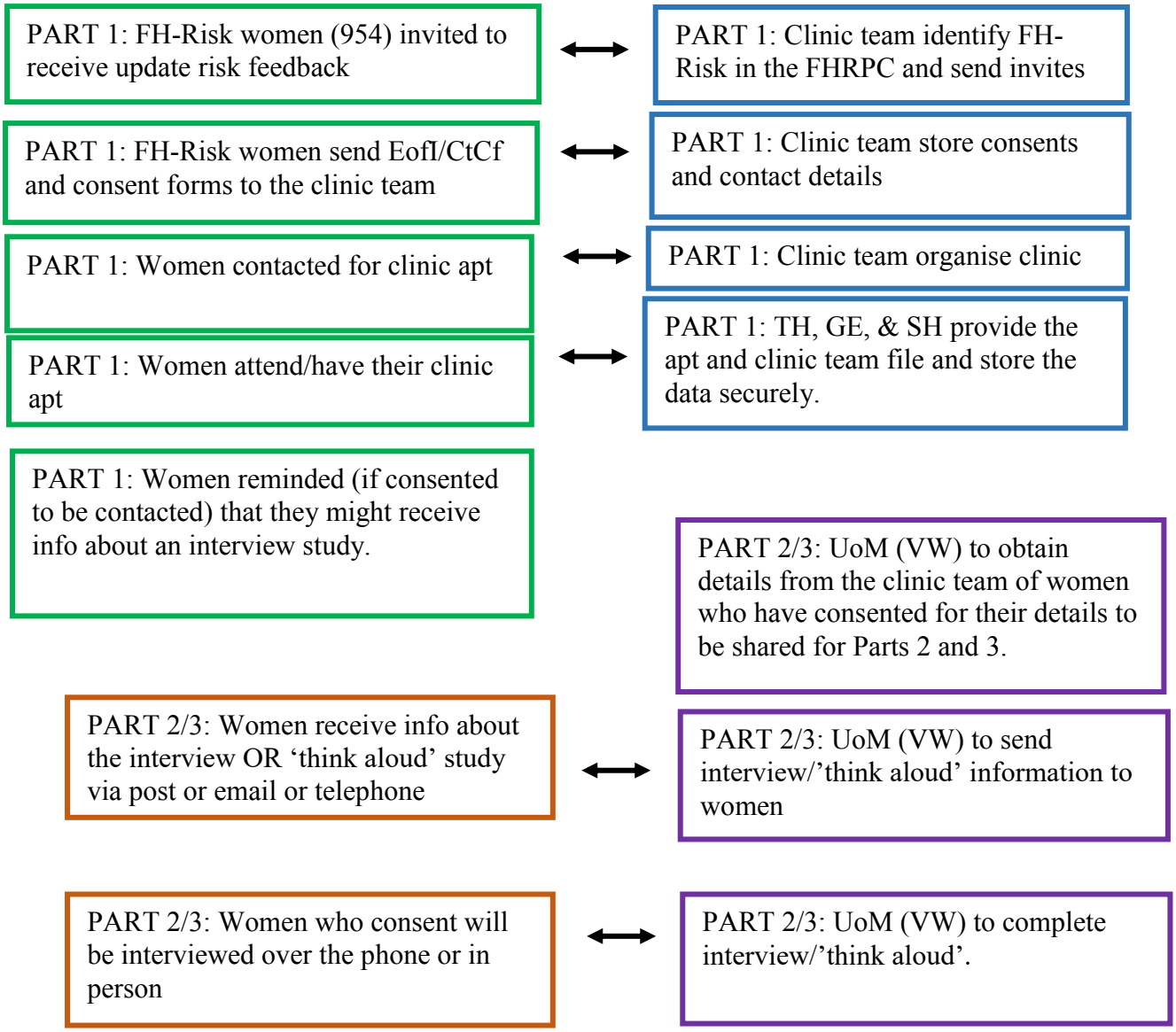
11.0 Participant pathway



Appendix 1: FH-Risk Original Consent Form (2012)

CONSENT FORM

FHRisk: Assessment, validation and improvement of breast cancer risk assessment models in the family history clinic

Please initial box

1	I have read and understand the Information Sheet dated 25th April 2012 (Version 1.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. I understand that withdrawal would not affect my medical care or my legal rights.	☐
3	I understand that relevant sections of my medical notes and data collected during the study may be looked at by researchers and individuals from University Hospital of South Manchester NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
4	I agree to my existing mammograms and information from my Family History questionnaire(s) being used in this research.	☐
5	I agree to give a sample of blood for research in this study. I understand how the sample will be collected and that giving a sample for this research is voluntary. I understand that I am free to withdraw my approval for use of the sample at any time, without giving any reason and without my medical care or legal rights being affected.	☐
6	I consent to the gifting of my blood sample for future research.	☐
7	I consent to the storage of my DNA sample for future research.	☐
8	I consent to the transfer of coded data with no personal identifiers for the purpose of the current research study looking at common genetic changes associated with breast cancer risk to any sponsor of the research	☐
9	I agree that the information gathered can be stored by the custodians, University Hospital of South Manchester Foundation Trust, for possible use in future ethically approved studies as described in the information sheet.	☐
10	I give consent for my GP to be informed of my participation.	☐
11	I agree to take part in the above study.	☐
12	I understand that if I choose to receive feedback, I will have an appointment to discuss this, and my GP will be given this information.	☐
13	Would you like to receive your updated breast cancer risk information? (Please tick one box below) **YES** ☐ **NO** ☐	

Name of Participant	Date	Signature
Witnessed by	**Date**	**Signature**