Full Study Title

BRCA-DIRECT: randomised evaluation in women diagnosed with breast cancer of digitally-delivered pre-test information for BRCA-testing

Short Title: BRCA-DIRECT

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Study approvals

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Protocol Synopsis

Title	BRCA-DIRECT: randomised evaluation in women diagnosed with breast cancer of digitally-delivered pre-test information for BRCA-testing
Short Title	BRCA-DIRECT
Anticipated Study Start/End Dates	01/01/2021 – 31/12/2022
Number of participants	1000
Study objectives	**Primary Objective** To evaluate whether digital delivery of pre-test information for BRCA-testing in breast cancer patients is non-inferior to current standard practice of 1:1 delivery from a healthcare professional regarding uptake of genetic test. **Secondary Objectives** • To assess knowledge about genetic testing for BRCA genes, following delivery of pre-test information, in the two allocated groups • To assess anxiety following delivery of pre-test information, and test results, in the two allocated groups Additional secondary objectives: • To assess uptake of digital genetic testing • To compare 'Test-offer-to-results' time between BRCA-DIRECT digital model and contemporaneous clinical service • To evaluate uptake of telephone helpline • To evaluate Healthcare professional satisfaction with BRCA-DIRECT digital model • To evaluate Patient satisfaction with BRCA-DIRECT digital model
Centres	Royal Marsden NHS Foundation Trust (RMH) Manchester University Hospitals NHS Foundation Trust (MFT)
Study Endpoints	**Primary Outcome** Uptake of genetic testing for BRCA genes in women with a diagnosis of breast cancer **Secondary Outcomes** • Knowledge about genetic testing for BRCA genes (12-point knowledge test administered Day 1 following pre-test information) • Anxiety (Intolerance of Uncertainty and STAI Y-1/Y-2 state/trait anxiety) Additional secondary outcomes: • Potential participant decline on account of lack of digital access • 'Test-offer-to-results' time

	○ Study compared to audit of contemporaneous timings from referral to results at participating centres • Helpline usage ○ Evaluate proportion of patients receiving digital pre-test information who require 1:1 discussion via helpline • Healthcare professional satisfaction • Patient satisfaction
Inclusion criteria	• Diagnosis of invasive breast cancer or high-grade ductal carcinoma in situ (DCIS) • Female • Aged 18 years or over • Access to smartphone or email + internet • Good comprehension of the English Language
Exclusion criteria	Previous testing for BRCA1/2

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SUMMARY

BRCA-DIRECT is a pragmatic randomised non-inferiority evaluation.

Primary Objective

To evaluate whether digital delivery of pre-test information for BRCA-testing in breast cancer patients is non-inferior compared to current standard practice of 1:1 delivery from a healthcare professional regarding uptake of genetic test.

Participants

Women with a diagnosis of breast cancer or high-grade ductal carcinoma in situ, currently attending breast clinics at the Royal Marsden NHS Foundation Trust and Manchester University Hospitals NHS Foundation Trust, for management/follow up of their breast cancer.

Interventions

Current standard of care (500):
1:1 delivery via genetic counsellor of pre-test information and results for BRCA gene-testing (Standard of care is 1:1 delivery face-to-face, by telephone or by video-conference. In this study we shall use telephone only).

Intervention under test (500):
Digital delivery of pre-test information and results for BRCA gene-testing.

Primary Outcome

- Uptake of genetic testing (proportion of patients proceeding with BRCA-test following receipt of pre-test information)

Secondary Outcomes

- Knowledge about genetic testing for BRCA genes, following delivery of pre-test information
- Anxiety following delivery of pre-test information and test results

Additional secondary outcomes

- Study decline rates on account of lack of access to digital interface
- 'Test-offer-to-results' time (study compared to audit of timings under current pathways at participating centres)
- Helpline usage
- Healthcare professional satisfaction
- Patient satisfaction

Sample size

1000 participants

Internal Pilot

For the first 60 participants in each arm, pilot capture of outcome measures, including patient-reported, clinician and logistical outcome measures.

Study Duration

Two years total including development, set-up and shut-down

1 BACKGROUND AND RATIONALE

1.1 Targeting screening and prevention for those at a priori elevated risk of cancer

In the UK, there are >360,000 new presentations of cancer and >160,000 cancer deaths per year. More than half of cases present with advanced stage disease, for which outcomes typically remain poor. Near inevitable evolution of polyclonal drug resistance is casting increasingly long shadows over the anticipation that precision oncology might be the panacea by which we might reduce the bulk of cancer-related mortality from advanced presentation of solid tumours [1]. Accordingly, there has been renewed interest in programmes of cancer screening, early detection and/or prevention (SPED). Any SPED strategy is likely a priori to have significantly more impact if targeted at those individuals at highest risk of developing cancer, for example those who carry a mutation (pathogenic_variant) in a high risk cancer susceptibility gene [2]. For this high-risk population, we can offer interventions not clinically acceptable or economically feasible at population-level-risk, for example risk-reducing mastectomy for breast cancer patients or chemoprophylaxis.

1.2 g*BRCA1*/BRCA2 as a biomarker of cancer risk

Compared to the general female population, women who carry a pathogenic_variant in *BRCA1/BRCA2/PALB2* have a dramatically elevated lifetime risk of breast cancer (11% compared to 72%, 69%, 44% respectively) and ovarian cancer (1.5% compared to 44%, 17%, ~5%)(Figure 1) [3-5]. Pathogenic_variants in *BRCA2* also confer increased risk of prostate and pancreatic cancers [6-9]. *BRCA1* and *BRCA2* constitute far and away the most dramatic contribution to breast and ovarian cancer genetic susceptibility; pathogenic_variants in *PALB2* confer a risk of non-syndromic breast cancer that is well quantified and warrants equivalent clinical actions for *BRCA1*/*BRCA2*, but the frequency in the population of pathogenic_variants is much lower.

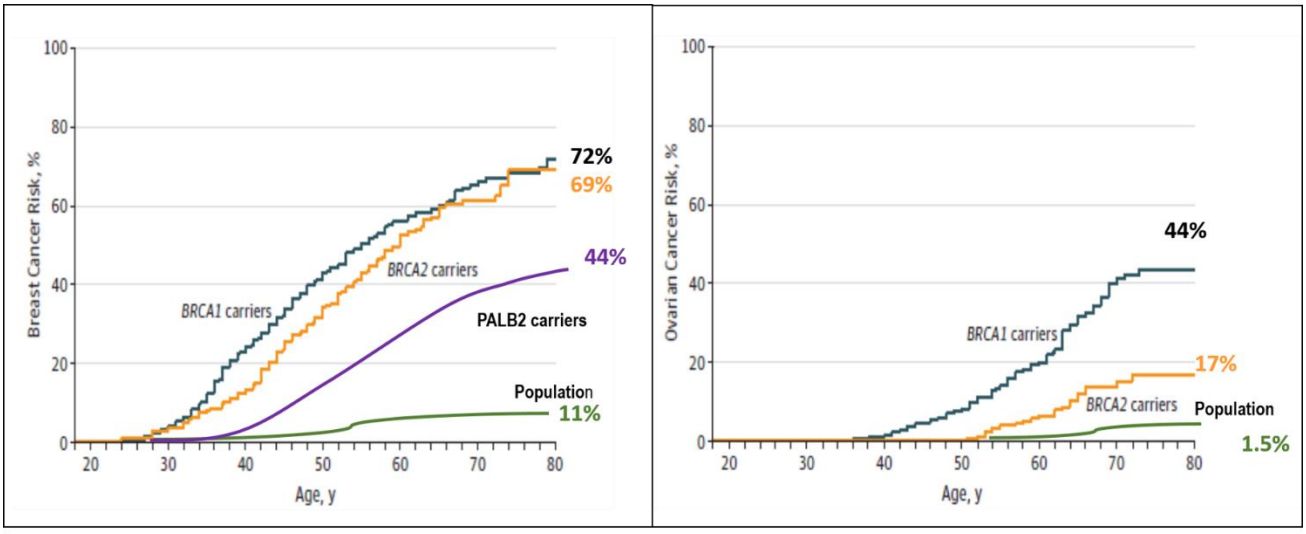


Figure 1: Age-related and lifetime risks of breast and ovarian cancer for women who carry a germline pathogenic mutation in BRCA1/BRCA2/PALB2 versus general female population (adapted from *Kuchenbaecker et al, JAMA 2017)*

Opportunities provided by identification of a pathogenic_variant in *BRCA1/BRCA2/PALB2* in a woman with breast cancer are as follows:

Secondary prevention in the woman herself

Serous ovarian cancers

On account of the poor prognosis and lack of effective screening, women typically opt for bilateral risk reducing salpingo-oophorectomy, which reduces their ovarian cancer risk by 80-95%[10].

Second breast cancer

The ***average*** lifetime risk of a second breast cancer is 53% for *BRCA1*, 65% for *BRCA2* pathogenic_variant carriers [3]. Hence, if a *BRCA1/BRCA2/PALB2* pathogenic_variant is identified during breast cancer diagnostic work-up, instead of breast conserving surgery, women may elect upfront for bilateral mastectomy for treatment of the current cancer and prevention of future (ipsi- and contralateral) breast cancers. This treatment approach also potentially avoids need for breast radiotherapy.

Primary prevention in family members

Once a pathogenic_variant is identified in a family, cascade testing through the family is initiated, by which on average 3-5 unaffected carriers of the pathogenic_variant are identified [11].

Unaffected pathogenic_variant carriers may be offered risk-reducing breast and ovarian surgery, intensive breast cancer surveillance (annual MRI scans from age 30 years), chemoprophylaxis with drugs that reduce oestrogen signalling, prostate cancer surveillance and/or reproductive counselling (including preimplantation genetic diagnosis) [12].

Individuals not carrying the familial pathogenic_variant can be taken out of high-risk screening instigated on the basis of family history, and alleviated of the anxiety related to their cancer family history.

1.3 g*BRCA1*/*BRCA2* as a biomarker for predicting treatment response

More recently g*BRCA1/BRCA2* status has emerged as an important biomarker predicting treatment response in breast, ovarian and prostate cancers[13] [14]. *BRCA1/BRCA2* deficient tumours exhibit homologous recombination deficiency, resulting in dramatically enhanced response to platinum-based chemotherapy and PARP-inhibitors [13]. Rapid genetic testing at diagnosis of all individuals with these cancer types can ensure that people have access to the best treatment for their cancer.

1.4 Transformation in genetic technologies and its impact on the current landscape of g*BRCA1*/*BRCA2* biomarker testing

Genetic testing was previously restricted on account of the direct costs of genetic analysis however over the last ten years the technological step-change of so-called Next Generation Sequencing (NGS) has revolutionised this field, enabling massively parallelised sequencing of multiple genes/samples [15]. The throughput, turnaround time, accuracy and cost of genomic sequencing have been transformed by orders of magnitude but within the NHS, clinician time and administration are now cost- and capacity-limiting.

The current international standard for delivery of g*BRCA1*/*BRCA2* biomarker testing (Table 1) typically involves extensive "counselling", as per models first put in place for Huntington's disease. Because the volume of breast cancer cases is so huge, BRCA-testing has had to be restricted. The complex and restricted eligibility criteria regarding personal and family history and the much higher patient: clinician ratios in breast clinics, have meant that BRCA-testing for breast cancer patients is highly limited and inconsistently delivered. Less than 20% of breast cancer patients and very few prostate cancer patients are 'eligible' for testing [16]. In order to be equitable in allocation of BRCA-tests, the restricted resource of expert genetics manpower is further diverted towards complex evaluations of eligibility for each patient/family referred.

1.	Provisional evaluation and perception of eligibility by GP/oncologist
2.	Formal referral letter to Clinical Genetics from GP/oncologist
3.	Clinical Genetics sends family history questionnaire (FHQ) for patient to complete
4.	Patient completes FHQ and returns to Clinical Genetics Service by post
5.	Clinical Genetics professional draws up pedigree from completed FHQ and triages whether likely eligible for test
6.	Clinical Genetics issues appointment to patient (if eligible on family history).
7.	Patient has appointment with Clinical Genetics professional; family history reviewed
8.	Confirmation of reported family cancers via cancer registry/death certification
9.	Clinical Genetics professional gives pre-test counselling, blood draw and documentation of consent
10.	Patient appointment with Clinical Genetics professional for return of results
11.	If mutation positive, additional patient appointments for planning interventions and cascade testing of family

Table 1: Steps in current BRCA-testing protocol within Clinical Genetics

Patients are increasingly seeking to circumvent the limited availability of testing and lengthy delays for results by accessing direct to consumer (DTC) testing, which brings with it highly variable and poorly regulated levels of interpretation and accuracy [17-19]. Furthermore these results are wholly divorced from the NHS clinical infrastructure, NHS laboratory governance and NHS genetic data management.

1.5 Expansion of g*BRCA1*/*BRCA2* biomarker testing

Recent trials have shown significant clinical effects of PARP Inhibitors for pancreatic cancer and advanced castrate resistant prostate cancer. For both of these tumour types, it is challenging to procure tumour tissue. Hence, in both cases we are likely to see over the forthcoming 2-3 years, a dramatic surge in demand for germline genetic testing of genes associated with homologous recombination deficiency (i.e. *BRCA1/BRCA2/PALB2* +/- other genes).

Through national funding, simple eligibility, high detection rate and more modest patient volume significant progress has been made in delivery of BRCA-testing in serous ovarian cancer.

Breast cancers are less "enriched" than ovarian cancer for *BRCA1*/*BRCA2*/PALB2 pathogenic_variants with pick-up rates reported at 2.1% [20] to 3% (unpublished data, Fergus Couch, BRIDGES Study), (unpublished data, Doug Easton SEARCH study). On BRCA-testing of unselected breast cancer cases, in approximately 3% of women we would also detect a rare variant for which, due to lack of available evidence, the pathogenicity status is unclear: this is termed variant of uncertain significance (VUS).

There are 55,000 new cases of breast cancer per year and an estimated >800,000 prevalent cases alive in the UK. It is widely agreed across the UK clinical genetics community that transformation of

BRCA1/*BRCA2* testing in breast cancer patients is the most urgent priority on account of (i) clear opportunities for secondary prevention, in particular to mitigate unnecessary death from ovarian cancer in a woman who has survived her breast cancer, (ii) opportunities for precision oncology management of their current cancer, and (iii) primary prevention opportunities for the family [21-23].

The pick-up rate for *BRCA1*/*BRCA2*/PALB2 pathogenic_variants in the general population is ~ 1 in 200 [24 25] and in due course it is highly likely genetic susceptibility testing may be rolled out to the broader (unaffected) population.

1.6 Clinically-Integrated, Clinician-Independent, Rapid, Digital, Genetic Susceptibility Biomarker Testing (CICIRDGSBT) – why we need a trial now

Improvement in identification of carriers of BRCA pathogenic_variants has been cited as being a key priority in many public health systems. To date we have ascertained <5% of *BRCA1*/*BRCA2* carriers in the UK [26], and the targets for BRCA-testing in the 2015 UK Independent Cancer Task Force Report have not been met [27]. To redress this and avert further expansion of DTC testing, new approaches are urgently required to maintain robustness but enable dramatic expansion of volume.

Key features of any system of expanded testing must include:

Clinical integration within

- NHS genetic laboratory services, so that both positive and negative analyses are to the robust standard of a UKAS-approved NeQAS-accredited diagnostic laboratory
- NHS data systems, so that results are held within the NHS NGIS database, to ensure that patients benefit from reclassification of VUSs
- NHS cancer services, so that clinicians and the MDT receive the test results in real time to enable best management

Rapid turnaround

- To inform clinical decision-making at time of cancer diagnosis

Patient-centred and patient-managed

- To afford the patient choice regarding how, when and how much information they want about their genetic test and where, when and how soon they receive their results

'Clinician-lite' pathway

- To expand capacity for testing, improve turnaround time and reduce costs. In our pathway we propose that a hot-line is the most clinician-efficient patient-centred mechanism by which to enable access to experienced professionals for patients with specific queries/issues, and those who require more support

Flexibility

- Regarding bio-sampling (i.e. use of saliva rather than blood)

Digital platform to facilitate

- Delivery of high quality, standardised information
- Robust and rapid process management, sample-tracking, administration and communication

This paradigm shift in testing is essential to afford benefit to cancer patients. Clinically-Integrated, Clinician-Independent, Rapid, Digital, Genetic Susceptibility Biomarker Testing (CICIRDGSBT) aims to integrate all of these key features within a single web-based system. The BRCA-DIRECT study aims to test the feasibility and acceptability of this approach. It is hoped that the study will be a stepping stone in the transition to a new paradigm.

1.7 Prior relevant research

1.7.1 Moving genetic testing of cancer patients out of Clinical Genetics

The Wellcome-funded Mainstreaming Cancer Genetics Program (Deputy Directors: Turnbull, George), developed pathways, protocols and training materials to empower oncology professionals to undertake genetic testing and deliver pre-test counselling within the oncology clinic.

Subsequent surveys revealed that adoption of 'mainstreaming' was relatively popular amongst gynaecological surgeons/oncologists for ovarian cancer patients, but low in breast cancer services, especially outside of specialist centres [28-31]. Survey responses regarding the underlying reasons included (i) overwhelming patient volume (ii) lack of available time in breast cancer clinic appointments (iii) complexity in evaluating eligibility for BRCA-testing (iv) lack of expertise in genetic counselling [30 32].

1.7.2 Alternative methods to traditional 'genetic counselling' for genetic information-giving

A number of international studies have demonstrated non-inferiority in information uptake/recall and patient satisfaction of tele-counselling compared to in-person face-to-face counselling [33-35]. Tele-counselling is now standard of care in UK clinical genetics centres.

Studies of web-based information and aids as a supplement to 1:1 genetic counselling have been largely positive [36-39].

The Genetic Cancer Prediction through Population Screening (GCaPPS) trial compared web-based information vs 1:1 counselling in unaffected Ashkenazi Jewish individuals, demonstrating non-inferiority of cluster-randomised DVD-based pre-test counselling to traditional genetic-counselling [40 41].

1.7.3 Health economic analyses

Recent UK health economic analyses have demonstrated that testing for breast-ovarian cancer susceptibility genes as cost-effective at £20,000-30,000 per quality-adjusted life-year UK willingness-to-pay thresholds in (i) unselected breast cancer patients [42] (ii) unselected ovarian cancer patients [43] and (ii) in women in the general population [44].

1.7.4 Study recruitment through non-traditional mechanisms

Whilst standard practice in recruiting patients to CTIMPs studies is face-to-face explanation by a trained clinical professional in the clinical environment, recruitment to non-CTIMPS studies has been democratised and extended via a number of innovative non-face-to-face models of recruitment [45-53].

1.8 Rationale for the study design

This study aims to investigate the feasibility, acceptability and safety of CICIRDGSBT. In order to test whether patient-centred genetic testing for BRCA genes would be feasible within NHS breast cancer clinics, this study employs a number of patient-led procedures.

The patient pathway under test is:

- Digital delivery of information about genetic testing, followed by
- Patient-initiated consent for genetic testing to proceed, followed by
- Digital delivery of test results where no pathogenic_variant has been identified

The laboratory testing is a standard NHS genetic test. This is delivered for both the intervention arm and the stand-of-care arm.

Key features of the study design are:

- Patient-led saliva sample preparation
- Patient-led consent to join the study
- Remote access to the BRCA-DIRECT platform
- Digital delivery of pre-test information about genetic counselling
- Digital consent for genetic testing to proceed
- Digital delivery of genetic test results for patients with no pathogenic_variants identified

2 HYPOTHESIS AND STUDY OBJECTIVES

2.1. Hypothesis

Digital delivery of pre-test information for BRCA-testing in breast cancer patients is non-inferior to current standard practice of 1:1 delivery from a healthcare professional

2.2 Primary Objective

To evaluate whether digital delivery of pre-test information for BRCA-testing in breast cancer patients is non-inferior to current standard practice of 1:1 delivery from a healthcare professional as measured by rate of uptake of the genetic testing.

2.3 Secondary Objectives

- To assess knowledge about genetic testing for BRCA genes, following delivery of pre-test information, in the two allocated groups

- To assess anxiety following delivery of pre-test information, and test results, in the two allocated groups

This study will be conducted in compliance with the protocol, standard operating procedures, policies, local R&D management guidance, Good Clinical Practice including the Research Governance Framework 2005 (2nd edition) and other applicable regulatory requirements as amended from time to time.

3 STUDY DESIGN

BRCA-DIRECT is a pragmatic, randomised, non-inferiority evaluation. Estimated sample size is 1000 women.

3.1 Internal pilot

The first 60 women recruited to each arm will form an internal pilot sample from which recruitment rate, retention and data completeness will be assessed with a good level of precision and, if deemed necessary, changes will be made to the protocol to maximise chances of delivery of the study.

Detailed user feedback, via an optional telephone interview, will be available during this pilot phase – capped at 50 interviews.

4 PARTICIPANTS

Women with a diagnosis of breast cancer or high-grade ductal carcinoma in situ, currently attending breast clinics at the Royal Marsden NHS Foundation Trust and Manchester University Hospitals NHS Foundation Trust, for management/follow up of their breast cancer.

4.1 Inclusion criteria:

Women will be eligible if all of the criteria below are satisfied:

- Diagnosis of invasive breast cancer or high-grade ductal carcinoma in situ (DCIS)
- Aged 18 years or over
- Access to smartphone or email + internet
- Good comprehension of the English Language

4.2 Exclusion criteria:

- Previous testing for BRCA1, BRCA2, PALB2 genes

5 STUDY INTERVENTIONS

5.1 Pre-test information delivery about genetic testing for BRCA genes BRCA1/BRCA2/PALB2

Participants will be randomised 1:1 to receive either:

Telephone consultation with a genetic counsellor (standard of care)
The telephone consultations will be as per standard practice of the qualified genetic counsellor delivering the pre-test information.

Digital delivery of pre-test information via BRCA-DIRECT platform (intervention)
Participants will receive a link to the digital pre-test information. This will consist of text covering:

- Genetics and cancer risk
- Genetics testing
- What will happen if your test is positive
- What will happen if your test is negative
- Implications for insurance

Where relevant, parts of the text will be linked through to additional information, such as insurance advice from the ABI.

Participants in the intervention arm will be able to call a genetic counsellor on the hotline during weekday office hours, should they have any questions or require further information.

5.2 Delivery of genetic test results

It is predicted that 5-6% (3% VUSs and 2-3% pathogenic_variant) of individuals will have a positive result (pathogenic_variant or VUS detected). All participants whose test results indicate the presence of a pathogenic_variant or VUS will be informed of their result by telephone from a genetic counsellor. A priori, 2.5% participants will be selected at random to also receive their result (if negative) by telephone from a genetic counsellor.

97.5% of participants will be randomised to receive their result (if negative) digitally, however any individuals with a positive result will receive their result by telephone.

Telephone consultation with a genetic counsellor (current standard of care)
The telephone consultations will follow current practice.

Digital delivery of results (intervention)
Participants will receive a digital message that their results are available. When they click this, they will receive digital notification of their negative (normal) result in short form. Full details will be provided in an individualised letter.

6 OUTCOMES

6.1 Primary Outcome

- Uptake of genetic testing

6.2 Secondary Outcomes

- Knowledge about genetic testing for BRCA genes, following delivery of pre-test information
- Anxiety following delivery of pre-test information and test results

Additional secondary outcomes are the following:

- Potential participant decline on account of lack of digital access
- 'Test-offer-to-results' time
    - study compared to audit of contemporaneous timings from referral to results at participating centres
- Helpline usage
    - Evaluate proportion of patients receiving digital pre-test information who require 1:1 discussion via helpline
- Healthcare professional satisfaction
- Patient satisfaction

7 MEASUREMENT OF STUDY ENDPOINTS

Uptake of genetic testing will be measured as the proportion of participants proceeding to genetic testing following delivery of pre-test information either digitally, or via a telephone consultation with a genetic counsellor.

Knowledge will be assessed using a study-specific questionnaire, designed to test knowledge in key areas of genetic susceptibility awareness for breast/ovarian cancer. The questionnaire has been (i) developed using two previously published questionnaires developed to evaluate knowledge following delivery of genetic counselling information about increased risk for breast cancer, (ii) tested on 3 clinical genetics professionals, 3 oncologists, and (iii) reviewed by our PPI panel comprising patients with breast cancer and patients who have undergone BRCA-testing[40, 54].

Anxiety will be measured using the Spielberger state-trait anxiety inventory [55] and the short form Intolerance of Uncertainty scale [56].

The Spielberger state-trait anxiety inventory consists of two self-administered, 20-item questionnaires, with each item rated on a four-point Likert scale. It assesses anxiety proneness (trait) and the current state of anxiety change (state). The Trait anxiety is measured only once and the State at each time point. High STAI scores signify greater anxiety.

Research suggests that intolerance of uncertainty may be very important in understanding worry and may play a key role in the etiology and maintenance of worry. Evidence for the connection between intolerance of uncertainty and worry comes from studies that established that worriers possess a number of characteristics that set them apart from non-worriers. For example, worriers have been

shown to require more information before arriving at a decision [57]. The need for additional information may be a means for lowering the level of uncertainty.

Decline on account of lack of access to digital interface will be assessed from completed anonymous study summary forms posted into the secure study hub drop boxes.

'Test-offer-to-results' time (study compared to audit of timings under current pathways at participating centres)

Helpline usage will be assessed from a central log of the number, content and duration of calls made to the genetic counsellor telephone hot line.

Healthcare professional satisfaction will be assessed using a study specific survey

Patient satisfaction will be measured using a digital study specific survey.

8 PARTICIPANT PATHWAY including COVID-19 pathway variation

8.1 Enrolment

- There will be a study hub in the breast clinic making available study summary sheets, study information packs and a locked drop-box (for submission of study paperwork and saliva samples). BRCA-DIRECT posters will be on display at breast clinics.
- The patient will be made aware of the BRCA-DIRECT study via:
    - Recommendation and sign-posting towards the study from their doctor/specialist breast care nurse
    - The study-hub/poster
- A BRCA-DIRECT research genetic counsellor or research nurse will be available in clinic to answer questions.

- ***COVID-19 addendum:*** All COVID-19 related government guidelines applicable during the recruitment period of the study will be followed, (e.g regarding the wearing of personal protective equipment and social distancing).

8.1.1 Study resources/paperwork

Study Summary sheet

Patients will be invited to read a study summary sheet which outlines the study and asks those interested in participating to collect a study information pack and saliva sample kit. A section at the bottom of the sheet invites patients not interested in participating in BRCA-DIRECT to complete it anonymously, providing their reason why from the categories listed, and post it in the secure study drop box.

Study Information pack

Patients interested in participating will be given a study information pack containing:

- A front sheet
- Patient information leaflet
- Saliva kit and Expression of Interest form
- Study consent form and pre-paid envelope

Saliva sample collection and Expression of Interest

- Patients interested in participating in BRCA-DIRECT will be encouraged to provide a saliva sample in clinic, before leaving hospital (this avoids delays in testing, the need for an additional visit to hospital and the possibility of saliva samples being spoiled in transit).
- The patient will be asked to produce their own labelled saliva sample (following the instructions provided in the saliva sample kit).
- Healthcare professionals will be available to assist, if required.
- Patients will be asked to complete an Expression of Interest form, located inside the saliva sample kit, to provide their name and preferred contact details (mobile phone, email) and permission for their saliva sample to be stored while they decide whether to participate in BRCA-DIRECT.
- This form will be placed together with the saliva sample inside the sample bag and placed in the secure study drop box.
- Expression of Interest details and receipt of sample will be entered onto the BRCA-DIRECT study databases.

- If there are any problems with the saliva sample e.g. tube not sealed properly, damage etc., the local site genetic counsellor will contact the potential participant and arrange for another sample to be collected.

- ***COVID-19 addendum:*** In the event of COVID-19 regulations disallowing generation of saliva samples in clinic, we will enable participation in the study via (a) a saliva sample generated at home and posted back to ICR (b) supply of a blood sample in clinic (if the patient is having routine bloods taken in clinic). Thus, we shall make available in clinic two types of study packs (a) "home-saliva study-pack", including tube for home saliva collection and secure sample postal kit and (b) "blood study-pack", including bottle and forms to be handed to phlebotomy. The "home-saliva study-pack" can also be posted out to potential participants undergoing telephone consultation. These pathways offer flexibility regarding (i) prohibition of saliva generation in hospital clinic setting (ii) discontinuation of laboratory analysis of saliva samples (iii) additional reduction in face-to-face appointments (see participant pathway flowchart COVID-19 contingency).

Patient information leaflet and consent to join BRCA-DIRECT

Potential participants can take home their patient information leaflet and study consent form. The telephone number of the local site research genetic counsellor is listed in the patient information leaflet. A study telephone hotline, manned by the local site research genetic counsellor, will be available to all participants ahead of recruitment to address any questions they have about the study. Those wishing to join the study are instructed to sign and return the study consent form in the pre-paid envelope provided. This form also contains a section for patients to complete and return if they don't want to participate in the study.

Some patients may choose to read the patient information leaflet and sign their study consent form whilst in clinic. This will be permitted because participants will not be contacted by the BRCA-DIRECT study databases for at least 24 hours. The study interface contains a link to take a participant to a study withdrawal screen, which will be available at all stages of participation.

All participants will receive a copy of their signed study consent form via a secure method (encrypted email or post).

If a signed study consent form is not received from a potential participant who provided a saliva/blood sample, the BRCA-DIRECT study system will send four consecutive reminders 1, 7, 12 and 17 days after the sample was deposited, using the patient's preferred contact (mobile phone/email). If signed consent is not received after six weeks, the temporarily stored sample and Expression of Interest form will be destroyed.

8.1.2 Baseline checks and 24 hour pause

On receipt of a signed study consent form, the local site will confirm the patient's eligibility and enter details required for study conduct onto the BRCA-DIRECT databases. If, in exceptional circumstances, a patient is found to be ineligible for the study, they will be telephoned by their consultant or the study genetic counsellor.

After 24 hours, the participant will be sent a link to the BRCA-DIRECT study platform interface. This link enables the participant to:

- Withdraw from the study if they have changed their mind
- Progress through the BRCA-DIRECT study

8.2 Commencing participation in BRCA-DIRECT

Participants will complete digitally:

- A cancer family history questionnaire
- Intolerance of Uncertainty questionnaire
- STAI Y-1/Y-2 state/trait anxiety questionnaires
- Knowledge questionnaire

If baseline questionnaires are not completed, an SMS/email reminder to complete them will be sent to the participant 1, 2 and 3 days after receiving the initial link to BRCA-DIRECT study interface.

8.3 Delivery of information about genetic testing for BRCA genes BRCA1, BRCA2, PALB2

Participants will be randomised 1:1 to:

(i) Receiving digital information about genetic testing for BRCA genes via the BRCA-DIRECT study interface

- Participants will be able to scroll forwards and backwards through the information visiting links etc.
- The BRCA-DIRECT study system will record participant activity to confirm that they have visited the information before proceeding to the next stage of the study.
- Participants will be able to call the telephone hotline with queries or if they would like further information.
- The final screen will provide a link to access the digital 'BRCA-test consent' form. Participants will be able to call the telephone hotline if they would like to be taken through the clauses on the form.

Or

(ii) **Receiving a current standard of care telephone consultation with a genetic counsellor**

- Participants will be instructed to book an appointment with a genetic counsellor via a digital calendar located on the BRCA-DIRECT interface. They will be asked to book an appointment within the next three working days, if possible.
- At the end of the consultation, the genetic counsellor will inform the participant that a digital 'BRCA-test consent' form is available to be completed and signed via the BRCA-DIRECT interface. An explanation of the individual clauses within the form will be given.
- The genetic counsellor will log the consultation as completed and enable the digital consent form.
- A standard summary of the consultation will be sent via post to the participant.

If a participant does not book a genetic counselling appointment or commence viewing the digital pre-test information, an SMS/email reminder will be sent 1, 2 and 3 days after notification of the randomised allocation was received.

If a participant is unavailable during the booked appointment time they will be invited to book another appointment three additional times by the BRCA-DIRECT study system.

8.4 Consent to proceed to genetic testing

- For both arms, if a participant decides to proceed with the genetic test they will sign a digital 'BRCA-test consent' form, which will be formatted to BSGM (British Society of Genomic Medicine) standards. All participants will receive a copy of their signed BRCA-test consent form via secure email/post.
- The participant will have two days following test-consent to reverse the decision to proceed with the BRCA-test. Beyond those two days, the test will proceed.
- If a signed 'BRCA-test consent' form is not received from a participant, the BRCA-DIRECT study system will send three reminders 1, 2 and 3 days after the participant viewed the digital pre-test information or had a telephone consultation with a genetic counsellor.
- If signed consent is not received after 8 weeks, the temporarily stored sample and Expression of Interest form will be destroyed and the participant will be withdrawn from the study.
- If a participant subsequently decides to proceed to genetic testing during the active period of the study, and is willing to provide another saliva/blood sample, this will be discussed with the patient and a test conducted if feasible.

8.5 Assessment of knowledge and anxiety following consent for genetic testing to proceed

24 hours after signing consent for the genetic test to proceed, participants will complete digitally:

- Knowledge questionnaire
- STAI Y-1 anxiety questionnaire

If these questionnaires are not completed, an SMS/email reminder to complete them will be sent to the participant 4, 5 and 6 days after signing consent for the genetic test to proceed.

8.6 Delivery of BRCA test result

The BRCA-DIRECT system will alert participants when their test result is ready. They will either receive their result digitally or via a telephone consultation with a genetic counsellor.

It is anticipated that 94-95% of the study cohort will have a negative (normal) result and 5-6% will have a positive result indicating the presence of a pathogenic_variant or a VUS.

- All participants with a positive result will receive their results via telephone consultation with a genetic counsellor **(estimate 5-6%of total cohort)**
- The majority of participants with a negative result indicating normal genes will receive their result digitally **(97.5%of total cohort)**
- An additional randomly selected 2.5% of participants with a negative result will receive their results via telephone consultation with a genetic counsellor **(2.5% of total cohort)**

8.6.1 Digital receipt of result (participants with no pathogenic_variant detected)

The participant will receive a message informing that their test results are available. The message will contain a link to digital notification of their negative (normal) result. A results letter and copy of the molecular genetics laboratory report will be sent to the participant via secure email/post.

8.6.2 Receipt of result via telephone consultation with a genetic counsellor (all participants with pathogenic_variant plus 2.5% with a normal result)

The participant will receive a message informing that their test results are available. The message will contain a link to the study digital calendar to book an appointment with a genetic counsellor. Following the appointment, a results letter and copy of the pathology report will be sent to the participant via secure email/post.

If a participant does not book a genetic counselling appointment, an SMS/email reminder will be sent 3,4 and 5 days after notification that test results are available.

8.7 Post-test result anxiety assessment

Seven days after notification that their test results are available, participants will be asked to complete digitally:

- STAI Y-1 anxiety questionnaire

If this questionnaire is not completed, an SMS/email reminder to complete it will be sent to the participant 10, 11 and 12 days after notification that test results are available.

8.8 Participant user feedback

Seven days after receiving their test results, participants will be invited to complete a digital user feedback survey exploring user experience of the BRCA-DIRECT platform and acceptability of the method for providing information about genetic testing and results.

During the internal pilot phase participants will also have the opportunity to register for an optional telephone interview with a BRCA-DIRECT researcher to explore their experience of participating in the study in more detail, to highlight any unanticipated logistical problems that require resolution. This will be capped at 50 participants.

Following the pilot phase participants will have the opportunity to register interest for an optional video (or telephone if required) interview with a BRCA-DIRECT researcher. The interviews will expand on data from the pilot phase interviews and will explore the participant's motivations for, and experiences of, BRCA-testing via the BRCA-DIRECT digital platform at an early stage in their breast cancer diagnosis and treatment. Information will inform future adaptations or considerations for implementation of the pathway more broadly.

We will be conducting interviews in participants who are newly diagnosed, pre-surgical at time of enrolment to the study AND randomised to the digital pre-test information arm. We aim to complete interviews with all eligible participants who register their interest OR a minimum of 50 eligible participants, whichever is lower. No retrospective invitations to participate will be sent to participants who have already completed their involvement in BRCA-DIRECT.

8.9 Final anxiety assessment

Twenty eight days after receiving their test results, participants will be asked to complete digitally:

- STAI Y-1 anxiety questionnaire
- Knowledge questionnaire

If this questionnaire is not completed, an SMS/email reminder to complete it will be sent to the participant 31, 32 and 33 days after notification that test results are available.

Participants will also be offered a second opportunity to provide user feedback if this was not done previously.

8.9.1 Schedule of patient reported outcome assessments

Time point	STAI Trait (Y-2)	STAI State (Y-1)	Intolerance of Uncertainty	Knowledge Score	Participant Satisfaction Survey (+ optional telephone interview)
T0 - Baseline	✓	✓	✓	✓	
T1 – 24 hours after giving consent for genetic test to proceed		✓		✓	
T2 – 7 days after notification that test results are available		✓			✓
T3 – 28 days after notification that test results are available		✓		✓	✓ (reminder if not done at T2)

All calls to the telephone hotline will be logged on BRCA-DIRECT system by the genetic counsellor who took the call (content and duration of call).

8.10 Additional notification of test results to the participant's health care team

For each participant, a copy of the genetic test results will also be sent securely to:

- The participant's oncology consultant and breast care nurse
- The local site molecular diagnostic laboratory
- The local clinical genetics service
- The participant's GP

Regular summaries of results and those in whom testing is underway will be sent securely to the breast MDT coordinators at a frequency according to local site preference.

8.11 Clinical Genetics referral

For all individuals in whom a BRCA1/BRCA2/ PALB2 pathogenic_variant is detected, clinical genetics referral will be advised on the report and patient letter. The results will also be sent to clinical genetics so they can ensure all positive participants are referred.

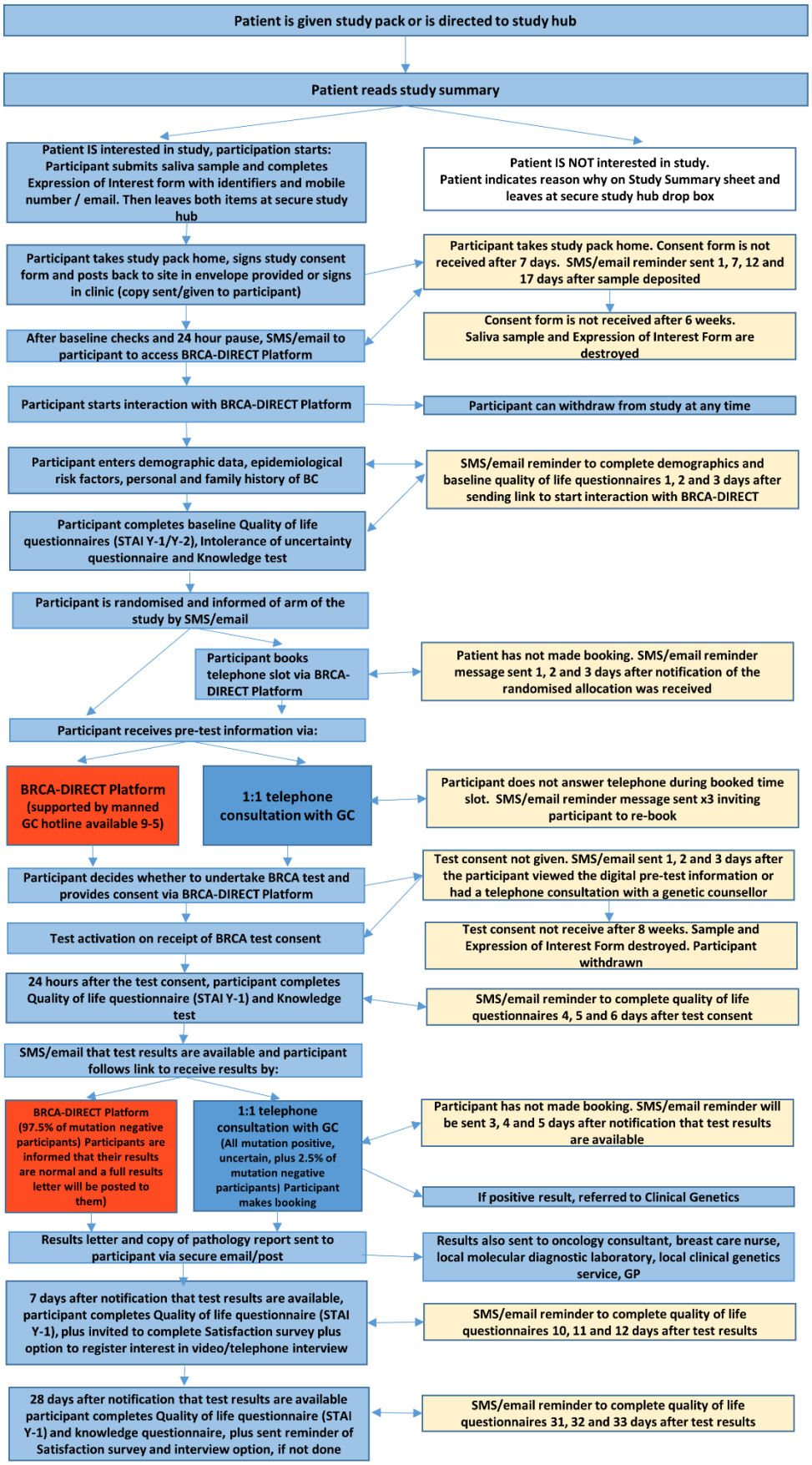
For all individuals with a significant family history of breast/ovarian cancer in whom no BRCA pathogenic_variant was detected, additional detailed evaluation of family history will be advised on the report and in an individualised standard patient letter.

8.12 Participant withdrawal

Participants may withdraw from the study at any time, if they so wish, without giving a reason. Information about withdrawal is included in the patient information leaflet, as well as on the BRCA-DIRECT platform. Participants can withdraw by contacting their clinical team, the study hotline or emailing BRCADirect@icr.ac.uk.

No further data will be collected about that individual. Study data collected up to that point will be retained for audit purposes. Samples derivatives (DNA) and data generated within the NHS diagnostic environment will be retained.

9 PARTICIPANT PATHWAY FLOWCHART (STANDARD CONDITIONS)



9.1 PARTICIPANT PATHWAY FLOWCHART (COVID-19 CONTINGENCY)

10 DEFINITION OF END OF STUDY

The end of the study is defined as the final data collection for the last participant. This will be the final STAI Y-1 questionnaire completed 28 days after receipt of genetic test results and collection of user feedback.

11 STUDY DISCONTINUATION

The study may be stopped if the Sponsor or REC terminate it before the planned end date. The Sponsor and the Funder have the right to discontinue the study at any time for failure to meet recruitment goals, safety or other administrative reasons.

12 STATISTICS

We are seeking to evaluate whether digital delivery of pre-test information for BRCA-testing in breast cancer patients is non-inferior to current standard practice of 1:1 delivery from a healthcare professional regarding uptake of genetic test. Although the study is not primarily powered for these outcomes, data on measures relating to safety, effectiveness and clinician/patient acceptability will be collected.

12.1 Sample size and power calculation for measurement of study endpoints

Sample size

To ensure >95% likelihood of identifying ≥5 individuals with a pathogenic_variant at each of the two recruitment sites (prevalence in unselected breast cancer of BRCA pathogenic_variants is ~2-3%) and to test thoroughly the respective pathway logistics as shown below:

- Digital pre-test information – genetic test – digital notification of results
- Digital pre-test information - genetic test – notification of results from genetic counsellor
- Pre-test information from genetic counsellor – genetic test – digital notification of results
- Pre-test information from genetic counsellor – genetic test – notification of results from genetic counsellor

Recruiting 500 cases per site would give 97% probability to detect ≥5 individuals with a pathogenic_variant per site (assuming, conservatively, the frequency of BRCA pathogenicity is 2%).

Power calculation for measurement of study endpoints

The table below illustrates the non-inferiority margin in the patient reported outcome measures we would predict on one-sided analysis for non-inferiority of BRCA-DIRECT against standard pathway.

	Attrition	Predicted available participants (following attrition)	Assumptions (reference *)	Power	Sample size required for 80% power (digital: clinician = 1:1)	Significance level (one-sided)	Non-inferiority margin	Notes
Test uptake	0%	1000	90% test uptake in both groups	80-85% with 1000 participants	934	0.025	5.5%	Calculated using http://www.hwasoon.kim/NISSC/#!/binary
STAI state T1	0%	1000	Mean 43.2, SD 13.5 *(*58)*	90-95% with 1000 participants	636	0.025	3	Calculated using http://www.hwasoon.kim/NISSC/#!/continuous
STAI state T2	10%	900	Mean 43.2, SD 13.5 (*58)	90-95% with 900 participants	636	0.025	3	
STAI state T3	20%	800	Mean 43.2, SD 13.5 *(*58)*	85-90% with 800 participants	636	0.025	3	
Patient satisfaction	20%	800	Mean 3.75, SD 1 *(*59)*	90-95% with 800 participants	56	0.025	0.75	
Knowledge score T1	20%	800	Mean 5.71, SD 1.55 *(*36)*	>95% with 800 participants	38	0.025	1.40	

12.2 Randomisation

12.2.1 Randomisation to pre-test information delivery

- Participants will be randomised equally between standard care and digital delivery of pre-test information.
- Randomisation will be stratified by site and will use random block sizes up to 12.

12.2.2 Randomisation to receipt of genetic test results via telephone appointment with a genetic counsellor (participants with normal genes)

- We estimate that 94-95% (940-950) participants will have a negative (normal) test result
- Randomisation lists, stratified by site, will be produced to randomly pre-select 2.5% of this cohort to receive their test results via a telephone appointment with a genetic counsellor.

Randomisation lists will be generated by the study statisticians using Sealed Envelope's randomisation list generator: https://www.sealedenvelope.com/simple-randomiser/v1/lists.

12.3 Internal pilot

When 120 participants have been enrolled (60 participants in each arm), recruitment will pause and study data will be reviewed as follows:

Recruitment:

Actual recruitment will be compared with predicted recruitment. Any potential barriers to recruitment will be identified through liaison with local sites and information collected on Study Summary Sheets completed by patients who were not interested in taking part in BRCA-DIRECT.

Retention:

Retention will be evaluated by reviewing:

- Participant initiated withdrawal
- Drop out as a result of non-completion of study tasks

Where participants have provided a reason why they wished to withdraw, these will be examined for any consistent themes. Drop out time point will be examined to search for any problems within the BRCA-DIRECT study pathway.

Compliance:

Timeliness of completion of study tasks throughout the participant pathway will be compared to expected timelines, to identify any non-random delays at study timepoints. Data from the Participant Satisfaction Survey and telephone interviews (user feedback) will be examined to assist with identifying the cause of any such delays.

Completion of the full pathway will be compared to expected compliance. If compliance is less than expected, reasons why will be identified and resolved, where possible.

Preliminary review of participant knowledge following receipt of pre-test information and consent for genetic test:

We aim to provide participants with a clinician independent means of receiving information about genetic testing for BRCA genes that is not inferior to current practice. Review of Knowledge questionnaire data, user feedback and consent for genetic testing in 120 participants will highlight any major differences between the study arms that may require further investigation and resolution before recruitment recommences.

Data completeness:

Individual questionnaires will contain checks to prevent incomplete data. Non- completion of questionnaires will be examined at each study timepoint to search for any problematic timepoints. Reasons for non-completion of questionnaires will be identified and resolved, where possible.

Knowledge questionnaire and Participant Satisfaction Survey:

Pooled data will be examined to search for any consistent themes that may require resolution before recruitment recommences.

These study specific questionnaires are unvalidated. We will examine the pooled data for quality, and any deviations or exceptions to confirm that they are collecting secondary endpoint data robustly.

Referral to Independent Expert Group:

Any problems identified will be discussed by the BRCA-DIRECT Management Committee (MC) and local sites, as required, to resolve any issues. The progress of the study, including the internal pilot data, will be referred to the Independent Steering Advisory Group, along with any major problems identified that could affect the scientific integrity or quality of the study, including major barriers to recruitment.

The Independent Steering Advisory Group may seek further expert advice regarding continuation of the study, if required.

12.4 Statistical analysis

During this study and its internal pilot on the first 60 women randomised to each arm, we shall monitor closely and evaluate time taken for data collection, processing and analysis.

The progress of participants through the trial will be shown in a CONSORT[60] flowchart. Summary statistics will be calculated by trial group at baseline and at each follow-up time point. Normally distributed variables will be described by their means and standard deviations, skewed continuous variables by their medians and interquartile ranges and categorical variables by frequencies and percentages. The primary analysis will be on the per protocol population but we will also perform an analysis of complete cases following intention to treat principles. Further, we may use multiple imputation methods for quantitative outcome measures such as STAI, Patient satisfaction and Knowledge scores.

Continuous outcomes will be analysed using linear mixed effects models with fixed effects for baseline measure of outcome, randomisation arm, centre and time point, with a random effect for participant. Binary outcomes will be analysed using mixed effects logistic regression models with the same set of fixed/random effects. Other baseline covariates considered a priori to be prognostic of outcome may be included in these models. We will report two-sided 95% confidence intervals for each outcome comparison between the arms, with the main focus on comparison of the lower 95% confidence limit and the margin for non-inferiority. A full statistical analysis plan will be written and signed off prior to data analysis. Analyses will be conducted in Stata version 17.0[61] or higher.

13 DEVELOPMENT OF THE BRCA-DIRECT DIGITAL SYSTEM

The BRCA-DIRECT study databases and user-interface will be developed prior to recruitment with inbuilt user testing during development.

User interfaces required are:

- Participants
- Genetic counsellors
- Pathology lab
- Study coordination team

Functionality requirements are:

- Login/access at any time
- Withdrawal option available at any time
- Data entry
- Provision of digital pre-test information
- Digital consent form completion and signature
- Calendar management
- Saliva/blood sample management
- Automated reminders for uncompleted actions
- Automated messages linked to actions
- Production of test results letters
- Production of reports
- Participant pathway management to prevent deviations from protocol
- Notification/alerts of participant enrolment, non-compliance and withdrawals
- Communication between research team
- View and download key data including digital consent forms

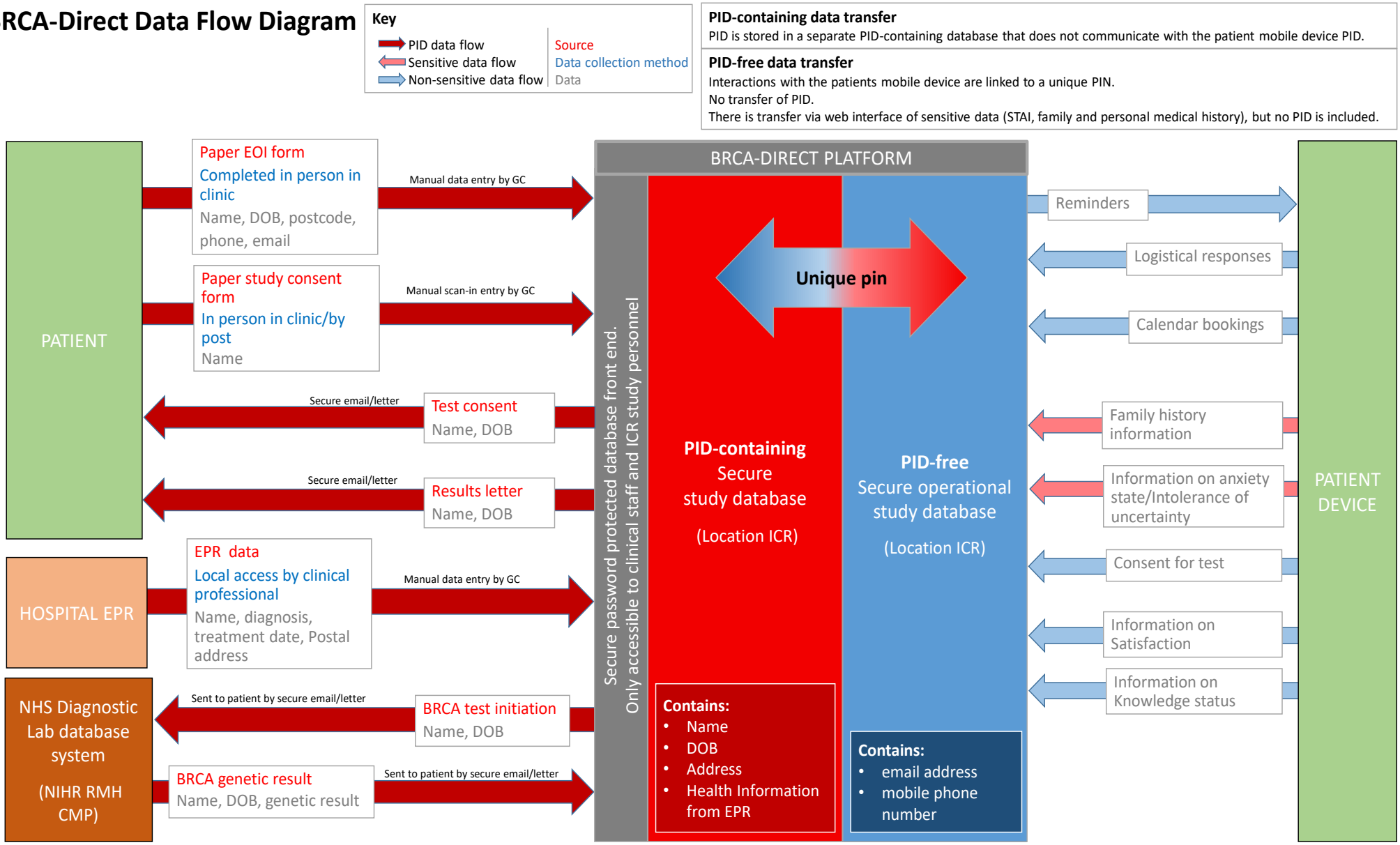
Additional requirements:

- 1:1 randomisation to pre-test information delivery method
- Selective randomisation of BRCA negative participants to receive results from a genetic counsellor

During development, the system will be user tested to ensure correct functionality. Previous breast cancer patients will provide PPI review of the ‘look and feel’ of the system, and its ease of use.

Further evaluation will take place during the ‘pause’ after 120 participants have been enrolled in case any major unanticipated user problems are identified. These will be resolved before recruitment re-commences.

BRCA-Direct Data Flow Diagram



14 STANDARD NHS GENETIC TEST FOR BRCA1/BRCA2/PALB2

Genetic Testing will be delivered by the NHS North Thames Genomic Laboratory Hub NIHR Biomedical Research Centre for Molecular Pathology **(ICR/RMH CMP),** located at the Royal Marsden Hospital, Surrey. The ICR/RMH CMP is a NeQAS-approved, ISO 15189 accredited medical diagnostic molecular genetics laboratory. Sample handling, sequencing and reporting will be performed to NHS diagnostic standard.

Saliva/blood samples will be supplied by participants at the Royal Marsden Hospitals (RMH) and Manchester Foundation Trust (MFT) NHS Hospitals, and will be identified via four patient identifiers marked on the tube (first name, surname, DOB, postcode). Samples collected at MFT will be transferred to the ICR/RMH CMP and will be stored and managed in accordance with established standards for NHS diagnostic patient samples. Transfer of saliva/blood samples will comply with biological sample transfer guidelines of the European Agreement concerning the International Carriage of Dangerous Goods by Road (ADR).

The request for a BRCA test will be initiated by the BRCA-DIRECT study databases 48 hours after a participant has given digital consent for genetic testing to proceed. The request will contain a unique study patient identifier (PIN), first name, surname, DOB, postcode and hospital number and will be transferred securely to the LIMS (Laboratory Information Management System) at ICR/RMH CMP. The genomic result and interpretation will then be returned from the CMP LIMS to the secure BRCA-DIRECT study databases via a secure upload.

DNA will be extracted from the saliva/blood samples and quantified via Qubit. Targeted libraries will be created via Qiaseq library preparation with DDR capture Panel hybridisation and enrichment comprising all coding exons and intron-exon boundaries of *BRCA1/BRCA2/PALB2*, and sequencing will be performed to NHS diagnostic test standards (minimum median coverage 50x, minimum per-base coverage 25x, with bidirectional reads). Data processing and calling of sequence variants and exon-level aberrations of dosage will be undertaken using established analytical pipelines and variant interpretation/classification using ACMG standards. The test results will be as valid as any other generated in the NHS and will therefore be valid for NHS clinical use.

Following the test, unused saliva/blood sample will be destroyed. Extracted DNA will be stored securely at the ICR/RMH CMP for an indefinite period of time.

If digital consent is not received from a participant, or a request to destroy a sample is made by the local site or participant, the sample will be destroyed in a manner appropriate for biological waste according to ICR guidelines and a record kept of this destruction.

15 DATA HANDLING AND RECORD KEEPING

15.1 Data acquisition

Data will be entered via the BRCA-DIRECT interface onto the BRCA-DIRECT data storage system.

Each participant will be assigned a unique participant identifier (PIN) and all of their data will be stored under this PIN.

Data will be entered by the following persons:

- Participant – family history, questionnaires, consent for genetic testing to proceed, user feedback survey
- Local site genetic counsellor – baseline data (including patient identifiable data), sample receipt, sample transfer, telephone hotline useage, record of consultations conducted
- ICR/RMH CMP - sample receipt, test results, record of destruction (unprocessed samples)

This data storage system will be comprised of two databases. The first database will handle PID. This will be partitioned and linked via PIN to the second, which will be PID-free, serving an operational purpose for the interface. These databases will meet all data security standards and be held within the ICR.

15.2 Data quality

Electronic participant questionnaires will be designed to constrain answers that can be supplied (range checks) and to prevent submission of incomplete forms. Computerised and manual consistency checks will be performed on a regular basis via downloads/reports from the study databases.

Newly entered family history questionnaires will be checked by the local site genetic counsellor and queries issued in case of inconsistencies.

The ICR/RMH CMP utilises a secure Line Information Management System (LIMS) by which the PID and genetic data generated are stored and QC (quality control) checks are implemented as routine. Sample handling, sequencing and reporting will be performed to NHS diagnostic standard.

15.3 Data access

Access to the central study databases will be limited according to user type. The restrictions will be built into the system as it is developed.

Access to the BRCA-DIRECT interface by the participant will require a login process. This will allow the participants journey through the study material to be mapped, and help authorise that all digital consenting and questionnaires are completed by the intended person.

15.4 Source data

Hardcopy source data will be filed at the local site. These will include current medical records, consent forms signed at enrolment, hardcopies of consent forms that were signed digitally and records of genetic counselling appointments and test results. The primary source of questionnaire and family history data will be electronic.

Source data regarding sample handling will be kept at the local site and the ICR/RMH CMP according to standard NHS procedures.

15.5 Data security

All data will be handled according to best practice principles and in compliance with the NHS Digital Data Security and Protection Toolkit.

Sensitive personal or medical data will be held in a partitioned, secure, firewalled database.

Recordings of telephone/video interviews will be stored at ICR on secure servers.

Participants will receive study notifications and reminders for uncompleted actions either by SMS or by email, using their study ID (PIN) only.

Data transferred or downloaded for quality checking, reports and analyses will be identified by PIN only.

NHS North Thames Genomic Laboratory Hub NIHR Biomedical Research Centre for Molecular Pathology is an established NHS molecular diagnostic laboratory undertaking routine analyses of cancer susceptibility genes. Divisional-level infrastructure and expertise are in place, with policies documenting systems for access, security and daily backup of the Divisional databases.

16 REGULATORY

16.1 Research Ethics approval

The Chief Investigator or their delegate will obtain approval from the Research Ethics Committee/Health Research Authority. The study will be submitted for local approval at each participating site and confirmation of Capacity and Capability will be obtained before participation commences.

The study will be conducted in accordance with the conditions of ethical approval.

The Chief Investigator will provide reports to the research Ethics Committee.

The protocol has been approved by the Committee for Clinical Research at the Royal Marsden NHS Foundation Trust and Institute for Cancer Research.

16.2 Ethical considerations and informed consent

This study will be carried out in accordance with the declaration of Helsinki (1996).

In order to avoid the need for patients to make extra visits to clinic, potential participants who are interested in participating in BRCA-DIRECT may be required to provide an ‘upfront’ saliva/blood sample before they have taken at least 24 hours to read the patient information leaflet and sign a consent form. To enable temporary storage of their saliva/blood sample, potential participants will be asked to complete and sign an Expression of Interest form, listing their email/mobile phone

contact details and giving the local site permission to store their sample while they decide whether to participate in the study.

Potential participants will be provided with a patient information leaflet and a study consent form that can be completed at home and returned in a pre-paid envelope. A telephone hot line to the local site genetic counsellor will be available during weekday office hours for patients to call if they require more information or have any queries.

In order to issue automated reminders to potential participants, their email/mobile phone details supplied on the EOI will be temporarily held on the BRCA-DIRECT study databases.

Upon receipt of a signed study consent form, the local site will enter a participant's baseline data onto the study databases to activate their account but the BRCA-DIRECT platform will not contact the participant for a further 24 hours. A link to a withdrawal screen will be available to participants immediately upon participation, so that they can withdraw at baseline.

If a potential participant decides not to participate in the study, or a signed study consent form is not received, their saliva/blood sample and Expression of Interest form will be destroyed and their contact details removed from the study databases.

Participants will not be able to sign digital BRCA-test consent for their saliva/blood sample to be tested until the BRCA-DIRECT system has recorded receipt of pre-test information, via data entry that a genetic counselling appointment has taken place, or electronic confirmation that the digital pre-test information has been visited.

There will be a 48 hour pause following receipt of digital consent for genetic testing to proceed before the instruction to process a sample is generated.

16.3 Confidentiality

Each participant will be assigned a unique participant identifier (PIN) and data will be stored under this number.

The study databases will hold all data securely. Patient identifiable data will be held in a partitioned firewalled database.

Information about participants will be kept confidential at the local sites. Access to data held at site will be restricted to members of the local study team as indicated on the delegation log. Hard copy data, for example paper copies of patient study-consent forms with identifiers, will be stored in locked, fireproof cabinets within the Division of Genetics and Epidemiology ICR, with access limited to staff working on the study who are trained in Data Protection policies and legislation.

Data downloaded for the creation of reports or analyses will be identified by PIN only. Any report data held at Sussex CTU/Sussex Health Outcomes Research & Education in Cancer (SHORE-C) will be held in password protected documents, with limited access.

17 TRIAL MANAGEMENT

17.1 Public and Patient Involvement

Initial expert patient input on the study design was provided by the founder of the 'BRCA journeys' patient support group, who reviewed the application submitted to the funder. All patient facing documents have been reviewed by members of our PPI group, comprising members of BRCA journeys and/ expert breast cancer patients.

The screen text to be used in the BRCA-DIRECT platform has been reviewed by these volunteers prior to its development. Further user testing by expert patients will be carried out during the development phase.

17.2 Trial management and oversight

The BRCA-DIRECT Management Committee (MC) (comprising PIs and study coordinator), will be responsible for the day-to-day management of the study and will meet regularly throughout recruitment. The Group will review recruitment, compliance and data quality.

An independent Steering Advisory Group, which will include expert patient representation, will be convened to provide independent trial oversight. It is not anticipated that there will be a need for a Data Monitoring Committee, however should any major problems be identified, the Independent Steering Advisory group may seek further expert advice regarding continuation of the study.

17.3 Trial monitoring

Site initiation visits will be conducted by the chief investigator and trial coordinator before recruitment commences. If recruitment does not proceed as anticipated, the chief investigator and trial coordinator will liaise with the site to identify and resolve any issues.

Monitoring of recruitment and data quality will be conducted by the BRCA-DIRECT Management Committee (MC) through regular reviews of data downloads and reports. The study has an inbuilt pause after 120 participants have been enrolled to enable any emerging problems to be identified.

During software development and the pilot phase, safety of the automated system will be closely monitored regarding system generated messages and reminders and provision of documents to participants. Following the pilot phase, safety will continue to be monitored as part of the regular data review.

17.4 End of study transfer of data

At the end of the study, the BRCA-DIRECT platform and study databases will be dismantled. All electronic data will be securely transferred to the Institute of Cancer Research for secure storage and archiving. A copy of the following raw data will also be transferred securely to Sussex Clinical Trial Unit (CTU)/ Sussex Health Outcomes Research & Education in Cancer (SHORE-C) for analysis.

- Intolerance of Uncertainty questionnaire data
- STAI Y-1/Y-2 state/trait anxiety questionnaires
- User feedback and telephone interview data

17.5 Archiving

All study data and documentation will be archived at the Institute of Cancer research for 5 years beyond the end of the study. Study data will be stored by PIN only. Following this period, data will be destroyed according to Institute of Cancer Research policy.

Following analysis and publication of main trial results, data analysis files created at Sussex Clinical Trial Unit (CTU)/ Sussex Health Outcomes Research & Education in Cancer (SHORE-C) will be transferred to ICR for archiving and all copies of raw data and analysis files at Sussex CTU/SHORE-C will be destroyed.

The genomic data (and related patient identifiers) will be retained within the NHS North Thames Genomic Laboratory Hub NIHR Biomedical Research Centre for Molecular Pathology at the Royal Marsden/ICR indefinitely, will form part of the NHS clinical record and will be held under the standards, terms and security processes employed for outputs of standard NHS diagnostic testing (under review by RMH Caldicott Guardian).The testing is being performed to NHS diagnostic standards and results will be utilised within the clinical care of the patient. Hence, the genetic result may be accessed and used for clinical care and also, potentially, may be referenced downstream (with procedural patient consents) when additional family members are requesting genetic testing, as is standard practice in clinical genetics.

17.6 Publication policy

The study results will be published in peer reviewed journals and presented at scientific conferences. It will not be possible to identify any individuals. Links to publications will also be available via the ICR and SHORE-C websites.

There is no plan to disseminate a summary of the results to participants because the study interventions (digital delivery of information about genetic testing for BRCA genes and digital delivery of test result for patients with negative (normal) results will have no impact on their subsequent clinical care. The results will be publicised through the BRCA Journeys support group.

17.7 Data sharing

Any requests from external parties for data collected for BRCA-DIRECT will be considered by the BRCA-DIRECT Management Committee (MC). The final decision will rest with the Custodian of the data.

Genetic data resulting from the standard NHS genetic tests will form part of the NHS clinical record. Summary data will be combined with other similar NHS genetic test data that is released back to the UK diagnostic laboratory community and made public by the CanVar UK website (http://www.canvar.org/). Individual level genetic data will be linked to NCRAS datasets in the section-251 compliant area of Public Health England/NHS Digital.

17.8 Indemnity

The study sponsor, the Institute of Cancer Research, has no special compensation arrangements for this study. The NHS Litigation Authority covers standard clinical negligence of NHS employees, staff and health professionals under its Clinical Negligence Scheme for Trusts.

Each participating site is responsible for ensuring insurance and indemnity arrangements are in place to cover the liability of the principal Investigator.

17.9 Funder

This study has received funding from Cancer Research UK via a Population Research Committee Award C61296/A29423.

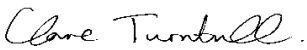
18 Protocol Signature Page

BRCA-DIRECT: development and piloting of a digital platform to deliver Clinically-Integrated, Clinician-Independent, Rapid, Digital, Genetic Susceptibility Biomarker Testing

BRCA-DIRECT-pilot

I have read this protocol and agree to conduct the study as outlined herein, in accordance with Good Clinical Practices (GCPs) and the Declaration of Helsinki, and complying with the obligations and requirements of the clinical investigators.

Site: Institute of Cancer Research and The Royal Marsden



Chief Investigator's Signature : **Date: 17/03/2023**

Chief Investigator's Name and Affiliation :

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19 References

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