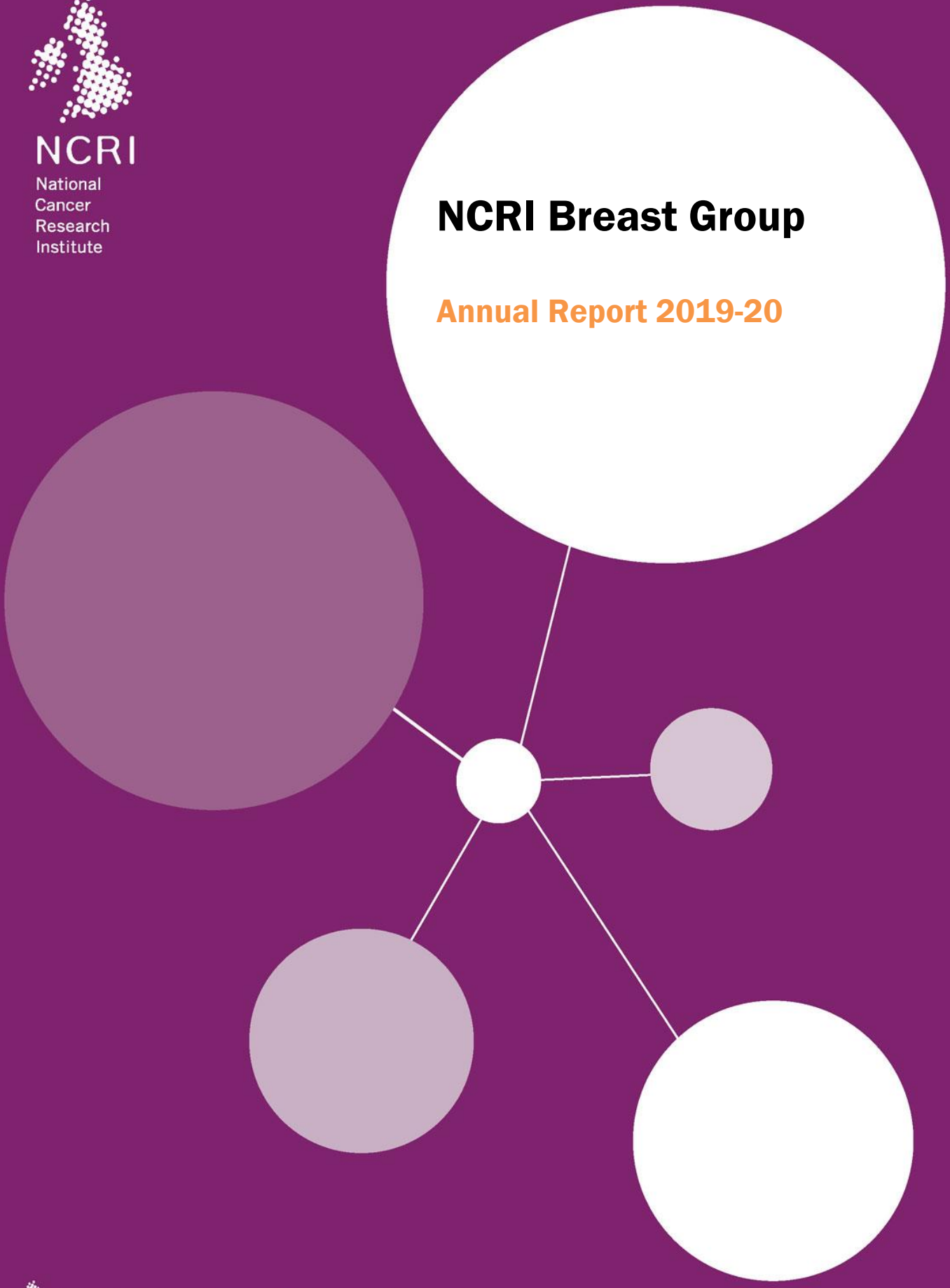
NCRI
National
Cancer
Research
Institute

NCRI Breast Group

Annual Report 2019-20



Partners in cancer research

The NCRI Group Annual Reports 2019/2020 span the time period April 2019 – March 2020. The reports were submitted during a challenging time for all in the healthcare sector due to the COVID-19 pandemic. This has had an unprecedented impact on the activity of both the Research Group itself and wider research activities, ranging from the time available for research work versus clinical commitments to the funding of new trials and the recruitment of existing trials. Due to this the NCRI significantly extended the deadline for submission of annual reports and allowed the Groups to submit reduced reports, if time permitted, with the following sections at a minimum:

- Achievements (section 1 of the report)
- Funding Submissions over the last 12 months (section 5)
- Priorities and Challenges (section 7)

In addition to this, Consumer representatives of each Group were asked to only complete their sections if they feel able to. Most of our Consumers have submitted reports, however where reports have *not* been submitted this was due to extended periods of ill health, or additional work/home life constraints, as a result of COVID-19.

NCRI Breast Cancer Group
Annual Report 2019-20

1. Top 3 achievements in the reporting year

Achievement 1

- High profile presentations at International meetings.
- World class NCRI supported studies presented by UK investigators continue to be a consistent feature at International scientific meetings.
- SABCS 2019. plasmaMATCH 2 oral and 4 posters presentation at international premier breast cancer meeting.
- ctDNA testing offers accurate, rapid genotyping that enables the selection of patients for mutation-directed therapies. Our results demonstrate clinically relevant activity of targeted therapies against rare HER2 and AKT1 mutations (NCT03182634. ISRCTN:16945804). 1051 patients were entered and ctDNA results available for 1034 patients. Our results demonstrate clinically relevant activity of targeted therapies against rare HER2 and AKT1 mutations). ctDNA testing had 93-98% sensitivity for mutations identified in tissue sequencing. In patients with HER2 mutations, response rate with neratinib, plus fulvestrant in ER-positive cancer, was 25.0% (5/20, 95%CI 8.7-49.1%). In patients with AKT1 mutations and ER-positive cancer, response rate with capivasertib plus fulvestrant was 22.2% (4/18, 95%CI 6.4-47.6%). In patients with AKT1 mutations and ER-negative cancer, 33.3% (2/6, 95%CI,4.3-77.7) responded to capivasertib.

Achievement 2

Team science has been particularly evident in early Breast Cancer Subgroup, resulting in successful funding of one major surgical study.

ATNEC – NIHR128311 - Axillary management in T1-3N1M0 breast cancer patients with needle biopsy proven nodal metastases at presentation after neoadjuvant chemotherapy and several other proposals in development invited to full applications (2 National Institute for Health Research (NIHR) Health Technology Assessment (HTA)):

1. The HER2-RADiCAL study (Response ADaptive CAre pLan) - tailoring treatment for HER2 positive early breast cancer,
2. EndoNET Neoadjuvant endocrine therapy for postmenopausal women with breast cancer.

PARABLE – proton beam therapy in patients with breast cancer: evaluating early and late effects.

POETIC-A funded by Lilly has been Cancer Research UK (CRUK) endorsed.

All developed through Subgroups, with Subgroup members as lead or co-applicants and all have integrated Public and Patient Involvement (PPI) within the study teams. We have responded rapidly and with some success to two NIHR calls.

Achievement 3

- Practise changing clinical trials
- Persephone:

Persephone randomised 4088 patients with HER-2 positive early breast cancer to 6 or 12 months of adjuvant/neoadjuvant trastuzumab. The primary endpoint of non-inferiority was met 4-year DFS rates were 89·4% (95%CI, 87·9-90·7) in the 6-month group and 89·8% (95%CI 88·3-91·1) in the 12-month group (Hazard Ratio 1·07; 90%CI 0·93–1·24, non-inferiority p=0·01), demonstrating non-inferiority of 6-months trastuzumab. Congruent results were found for overall survival (OS) (non-inferiority p=0·001). An NCRI/UK Breast Cancer Group (UKBCG) working group has written guidelines for patients with lower risk patients to stop trastuzumab after 6 months. These have been helpful during the COVID-19 situation. Now published Persephone, an HTA funded academic study developed within the NCRI Group, has been instrumental in our next trial in HER-2 positive early breast cancer.

2. Structure of the Group

- The group structure is largely unchanged, but the activity has shifted with subgroups playing a more substantial role in detailed trial development.
- Enormous thanks to our outgoing Chair Professor Dan Rea and Early Subgroup Chair Dr Charlotte Coles.
- Trainee members are attached to both main Group and to a Subgroup.
- Evaluation of new study proposals initially at the Breast Intergroup meeting continues to work smoothly. This single portal for investigator studies considered in open forum engages the wider research community and enables groups with similar ideas to work

together. This approach with a Red, Amber, Green (RAG) system has seen successful development of several funding applications as a reiterative process. The group has also responded to National Institute for Health Research (NIHR) calls with success. Proposals that require more detailed discussion are channelled to the main Group or to an appropriate Subgroup for more detailed review and refinement.

3. Breast Cancer Group & Subgroup strategies

Breast Cancer Group

Increase patient expectation of being involved in a clinical trial This is an on-going activity taken forward by our consumer members and the message cascaded through local patient support groups. Also discussed at length at professional meetings including Association of Breast Surgeons and our own Breast Trials Meeting.
Further the develop the Breast Cancer portfolio This very generic strategic goal is a persistent theme within the entire Group. The introduction of Subgroups and a more formal structure to the UK Breast Intergroup (UKBI) has facilitated better collaborative spirit, the bringing together of teams working on similar ideas, response to NIHR and other funding calls, and the systematic development of big picture ideas. One particular example of this is the HER2 Platform that we have been working on over 6 years, refining the concept as new data emerged. We have an HTA grant at 2nd stage as part of this programme and are working with international partners such as Breast International Group (BIG) on other aspects.
Collaborative approach to trial development & participation The Group operates an open-door approach to potential researchers wishing to develop a clinical study. We accept all proposals for initial presentation to the UKBI meeting. This is held 2 times per year and provides an open platform to bring new proposals to the Group and wider research community and patient advocates. The proposals are presented and discussed in open forum prior to a formal written feedback to investigators after discussion with the appropriate subgroup. This year at the biannual Breast Trials Meeting, the Chair (Professor Rea) presented an outline of the pathway for both established and emerging researchers to help them navigate the pathway through the various Group mechanisms of designing and successfully funding deliverable studies of the highest clinical and scientific value.
Improve trials methodology & clinical utility In addition to conventional trial designs we have an increasing number of novel design studies. Novel methodology, statistics and most efficient trial design is frequently discussed within the Group and with researchers presenting studies to the Group. The main Group has two senior trials unit methodologists who are very keen to advise and work with researchers in exploring the potential novel clinical trial designs. We try to maximise translational integration into most of the clinical trials we design.

Salient examples are the plasmaMATCH Umbrella platform of ctDNA screening with downstream treatment arms which was presented at San Antonio Breast Cancer Symposium 2019 and Phoenix: “A preoperative “window of opportunity” phase IIa biomarker endpoint trial of DNA damage response (DDR) inhibition or anti-PD-L1 immunotherapy in patients with post-neoadjuvant chemotherapy resistant residual triple negative breast cancer (TNBC)”

Our recent stage 2 HTA application HER2-RADiCAL uses a single cohort threshold design responding to recent opinion from leading clinicians and methodologists calling for more efficient study designs that:

(a) Maintain relevance and equipoise in a rapidly changing or variable clinical pathway
(b) Is adaptable to new medicines/molecular tests
(c) Uses real-world data for outcomes and value

Embed a research culture across the entire patient pathway within all healthcare

Clinical trials at the heart of clinical service is the Group’s approach to NHS practice within breast cancer services. This is reinforced through presentations at professional meetings. We are supporting regional clinical trial road shows the first of these held in Manchester hosted by the Association of Breast Surgeons. This first road show provided an educational forum for local research teams to learn about research activity and to meet Chief investigators (CI) in an interactive and constructive environment where locality issues can be explored.

Association of Breast Surgery (ABS) support and promotes The Royal College of Surgeons Academic and Research Committee badging and endorsing trials that have a significant surgical element https://associationofbreastsurgery.org.uk/professionals/research/trials/.

The ABS in collaboration with the Group have made considerable changes to ensure movement to a practice is defined by: “Every patient offered a clinical trial and a clinical trial for every patient” and “No innovation without evaluation”.

The ABS conference agenda has as a 'golden thread running through the whole conference' - so every session has a promotion of relevant national trials.

We have a very close relationship with UK Breast cancer group - the shareholder group for non-surgical oncologists.

Empower and educate patients and the public to drive research-oriented culture within the provision of routine care

Our consumer representatives are fully involved in all Group activity promoting a research ethos to the general public, existing patients and importantly health care professionals and organisations. The main Group has two consumer representatives, Mrs Lesley Stephen and Mrs Jan Rose. Mrs Lesley Turner co-chairs the Symptom Management Subgroup, with Dr Adrienne Morgan a member. Mrs Hilary Stobart and Ms Mairead McKenzie are members of the Early Disease subgroup. All are integrally involved in BG and sub-group strategies, trial development, funding applications and running of trials. All our trials are now developed with patient involvement from a growing number of patient representatives from concept to completion.

Breast Research Group patient representative link with national and international groups: National Audit for Breast Cancer in Older Patients Clinical Steering Group, Independent Cancer Patient Voice (ICPV) group, Breast International Group (BIG), the International Cancer Genomic Consortium – Accelerating Research into Genomic Oncology (ICGC-ARGO) project. They attend, speak at (ICGC-ARGO conference), and help to organise scientific meetings (including UKIBCS and the UK's first metastatic breast cancer (MBC) patient led conference), contribute to projects; and studies within and outside the NCRI, always with a clear focus on representing the needs of breast cancer patients.

Increase the number of local PIs participating in clinical trials

The open nature of our structure is intended to attract new investigators providing opportunities for networking at UK Breast Intergroup meetings.

We have in particular been making persistent efforts in collaboration with the Association of Breast Surgeons to encourage surgeons not previously active in research to become new Principal investigators and have been expanding the surgical research portfolio as part of the overall Breast Research Group strategy to increase interest and opportunities for surgeons to participate in multicentre studies. Nostra Feasibility determining the ability of protocolled radiologically guided biopsies to predict pathological complete response, the SMALL trial of radiological excision of small indolent cancers and the ATNEC study of post-neoadjuvant axillary management will maintain interest and momentum. The development within ABS of 'no innovation without evaluation' is bringing a variety of studies to evaluate new surgical techniques through the Breast Intergroup.

We have deliberately recruited basic scientists to improve the pull through from laboratory to clinic. Our success in biology driven studies will be an increasing focus of our work. We encourage team science the bringing together of individuals and groups to collaborate rather than compete in the same space. This, together with our trainees' collaborative will help foster and mentor new PIs.

Increase the level of access to and use of tissue from all patients throughout the patient pathway

The variability in willingness to release samples for research remains a challenge to some studies. The translational subgroup works with pathologists to encourage sharing of routinely collected tissue for research. We have encountered a trend towards a more restrictive approach in some hospitals as more indications for biomarker testing in breast cancer become routine, requiring tissue retention at site or provision of a trusted and robust real time service for tissue sample return from research collections. The Annual Birmingham pathology course organised by one of our group, Dr Abeer Shaaban, works to support pathologists in trial participation and translation into practice. The 2019 course included a talk on immunotherapy by Professor Rea which may be relevant for the report in view of the required PDL-1 testing, discussion on TILs assessment which are becoming increasingly important in breast cancer research and practice. Accessing tissue from an historic trial of duration of tamoxifen (aTTOM)

by communicating with UK pathologists in other sites has led to a test which may assist in deciding duration of treatment for patients.

Biological response to treatment is increasingly important for breast cancer treatment and we are leading this area in many respects such as ctDNA.

Understand the issues and pressures encountered at sites to inform researchers of potential challenges in local delivery

We have conducted a site questionnaire to explore barriers to research participation. The survey results have been shared at the Group/Clinical trials unit forum. They demonstrate patchy access to various elements of infrastructure to open and conduct clinical studies. Most notable is the difficulty in accessing pathology and imaging support to research.

Screening

A strategic goal of the Group has been to encourage collaboration and generation of studies to validate the utility of risk adapted breast screening and to evaluate new imaging modalities. This has resulted in successful funding and setting up of risk adapted screening study. Patients attending first round screening will be allocated to personalised screening, using a combination of genetic risk profiling breast density and lifestyle to determine individual risk and allocation to multiple imaging modalities and screening frequency.

Advanced Disease Subgroup (Chair, Professor Carlo Palmieri)

The Subgroup engages actively with the wider research community via the twice-yearly UK Breast Intergroup meeting. UKBI provides an opportunity for new trial proposal to be presented and receive structured feedback. The group encourages all new proposals, in the setting of advanced disease, to be presented at this meeting. This, along with the subgroup's own review and feedback, it is hoped, will provide only well worked up proposals moving forward to funding bodies.

The subgroup continues to deliver a broad trial portfolio, (based on both phase and disease Subgroup involved). There are currently: 20 trials open, in addition to 9 multi-Group Phase I studies and 14 in the process of opening (ref: portfolio map, May 2019). The portfolio had broad representation of trials in all disease subgroups (defined by ER, PgR and HER2 status), and maximises the likelihood that patients with advanced disease will be potentially eligible for a clinical trial. UK investigators continue to contribute at an international level to industry-sponsored studies.

Portfolio development

The Advanced Disease Subgroup has multi-disciplinary membership and aims to support the community in the development and delivery of studies in advanced disease. The group also takes a proactive approach in identifying areas where there are gaps or issues in relation to

the delivery of the portfolio. One recent example relates to the lack of studies for metastatic disease involving the central nervous system and the issues with delivering these studies when they are instigated. This is a current focus of the group.

Current studies developed via Subgroup:

- Enhancement of immunotherapy combining avelumab and repeat doses of radium-223 in ER+ve, HER2-ve metastatic breast cancer '(NEPTUNE: Chief investigator (CI): Professor Janet Brown).
- Lifting Checkpoint Inhibitors with NSAIDs (LION; CI; Dr Anne Armstrong): Multi-tumour sites (Breast, Renal and Lung cancer).
- FAIM: Phase II study of induction Fulvestrant and CDK4/6 inhibition with the Addition of Ipatasertib in Metastatic ER+/HER2- breast cancer patients with PI3 Kinase pathway activation without ctDNA suppression' (FAIM: CI: Dr Alicia Okines).
- 'Impact of abemaciclib on patients' roles and responsibilities' (Impactor; CI Professor Lesley Fallowfield), this is a psychosocial 'real world' study to determine the impact of abemaciclib treatment outside of a clinical trial setting.

Collaborative approach to trial development and participation

A second cross Research Group brain metastasis in March 2020 (notes attached) was held to discuss the development of CNS studies. An early study idea that was discussed at the meeting was a randomised screening study for women with metastatic breast cancer at high risk of CNS metastasis.

Empower and educate patients and the public to drive research-oriented culture within the provision of routine care

A national patient questionnaire to understand the needs of the patients with metastatic breast cancer in the context of clinical studies has been finalised and is awaiting ethical approval from University of Warwick by Dr Janet Dunn.

Increase the number of Principal Investigators participating in clinical trials

Dr Indrani Bhattacharya (Clinical oncology) and Dr Adam Heetun (Breast surgery): a clinical gap analysis in metastatic breast cancer. An initial draft questionnaire has been developed and feedback is being sought and the process of how best to administer the questionnaire.

Breast Cancer Trainee Research Collaborative Group projects in area of advanced/recurrent disease:

1. Long term Herceptin use with no radiological evidence of disease.
2. Registry for CNS disease in breast cancer.
3. National investigation of tolerability of CDK4/6 inhibitors in the elderly population.

Early Disease Subgroup (Chair, Mr Stuart McIntosh)

Develop Early Disease Subgroup portfolio

The following areas for portfolio development have been identified:

1. Loco-regional therapy
    a. Can axillary treatment be safely de-escalated following complete pathological response to neoadjuvant systemic therapy?
    The subgroup has supported the development of this study (ATNEC); it has been funded by the NIHR HTA programme. Set-up has commenced but is currently on hold due to COVID-19.

    b. Is there an identifiable group of patients with early breast cancer gaining substantial benefit from proton beam therapy? This study (PARABLE) has been developed through the subgroup and UKBI, and an outline application successfully submitted to EME. A full application has been invited but submission deferred due to COVID-19.
2. Systemic therapy
    a. Can HER2-directed therapy be safely de-escalated in selected patients with a complete pathological response to neoadjvant therapy? This proposal (HER2-RADiCAL) has been developed by numerous key UK researchers, including subgroup members, and has been discussed several times at UKBI before submission to the NIHR HTA as an outline proposal in January 2020; a full application has been submitted.

    b. Can neoadjuvant endocrine therapy be used safely in post-menopausal women with breast cancer for surgical downstaging? This proposal (EndoNET) has been developed through the UKBI, Early Disease Subgroup and main Breast Research Group in response to an HTA commissioned call. A stage 1 application was submitted in January 2020 and a full application invited.
3. Translational studies/personalised medicine
    a. The subgroup, together with UKBI and the main research group, has supported the development of the POETIC-A study, looking at improving understanding of mechanisms of endocrine resistance. This study is now funded by Lilly and endorsed by CRUK; however, setup has been delayed due to COVID-19.

Adopt a collaborative approach to trial development

1. Engagement with the broader breast cancer community.

- UKBI continues to provide a forum for discussion of new trial proposals, allowing feedback from the research community broadly as well as key research leaders, providing written feedback to researchers. Work is currently ongoing to map the

outcomes of proposals presented to UKBI, to determine what proportion of studies go on to successful funding and delivery.

- Integration with Biomarkers and Imaging subgroup – deliberate overlap of subgroup memberships to allow closer working and integration of biomarker studies into clinical trials.

2. Integration of PPI into all stages of trial development

- Our PPI representatives continue to provide input into trial development from conception to delivery. There are numerous examples of this in funded trials where there is PPI representation on Trial Management Groups (e.g. SMALL, ATNEC, PRIMETIME), and also in trials in development where PPI has been integral to success in funding applications (e.g. EndoNET, HER2-RADICAL).

3. Engagement with Association of Breast Surgery (ABS)

- Closer working with the surgical community to develop engagement in neoadjuvant, window of opportunity and adjuvant studies continues. Portfolio trials such as SMALL, OPTIMA and PIONEER are now badged or endorsed by the ABS, with the intention of fostering surgical engagement with recruitment.
- Engagement with the ABS James Lind Alliance Research Priority Setting exercise to highlight key research priorities in loco-regional therapy – this is led by the subgroup chair, and builds on the ABS research gap analysis published in the Lancet Oncology in 2018.
- Breast Research Group chair and several members participated in ABS Clinical Trials Roadshow held in Manchester in May 2019 to raise awareness of clinical trials amongst breast surgeons.

Improve trials methodology & clinical utility

1. Ongoing collaboration with NIHR CRN Breast subspecialty group – the Breast Cancer Trainee Research Collaborative Group (BCTRCG) is a cross-specialty, multidisciplinary group which aims to develop and deliver pragmatic research proposals in breast cancer.
   - The group now has its own website (https://bctrcguk.wixsite.com/bctrcg), giving details of multiple ongoing projects including audits of the management of brain metastases, long-term trastuzumab use and pregnancy-associated breast cancer.
   - Editorial published in Clinical Oncology (2019;32:1,e16-e18).
   - Second national BCTRCG meeting in September 2019.

2. Collaboration with Biomarkers and Imaging Group to produce a manuscript on imaging and pathological correlation in HER2+ disease: this work is ongoing.

3. Engagement with NIHR Associate PI scheme. The SMALL trial will be the first breast cancer trial to register for the NIHR's Associate PI scheme, aiming to engage with trainees from surgery and radiology to develop the next generation of clinical researchers.

Symptom Management Subgroup (Co-Chairs, Anne Armstrong and Lesley Turner)

To identify gaps in current research in symptoms management in breast cancer

The Symptom Management Subgroup was established by patients to develop and promote research into symptoms after a diagnosis of breast cancer. The Subgroup achieved initial success by concentrating on single issues with work around hot flushes. This strategy of focusing on one key issue continues with more recent work looking at the management of urogenital atrophy and sexual health issues as a consequence of treatment for breast cancer. The Group has recently begun discussions on where future work should be directed. Consideration will be given to assessing the impact of COVID-19 on breast cancer patients and their treatment.

Support development of new research into identified gaps

To facilitate the development of research into sexual health issues after cancer we have:

- Surveyed health professionals and 300 patients have been undertaken and presented results at the UK Interdisciplinary Breast Cancer Symposium 2020 (manuscript in preparation).
- Worked with Ann Summers and Breast Cancer Now launching a partnership to raise the awareness (publication pending).
- Commenced work on body image and breast prostheses.
- Linked with Abertawe Bro Morgannwg University Health Board investigating the incidence and management of vulvo-vaginal atrophy utilizing the Welsh SAIL database (Professor Deborah Fenlon).
- Worked to develop a better tool to score urogenital atrophy symptoms (Dr Lyndsey Hughes, Professor Deborah Fenlon and Charity Knight); 2 interventional studies in development.

NIHR-funded SWEET programme (2018, Co-applicants Mrs Turner, Professor Andrew Wardley; £2,487,452) development supported by SCSG.

- Aims to develop aids to encourage adherence to adjuvant endocrine therapy.
- Work package on adherence related to side effects from therapy.
- Programme to commence 21 May 2020.

The group draws membership from a range of disciplines which allows a wide range of interventional methods to be explored. Dr Mel Flint (University of Brighton) continues to collaborate with the group in undertaking work on heat sensitivity in breast cancer survivors.

Support translation of research findings into practice

MENOS4 (CI Professor Fenlon) is a multi-centre phase II study which successfully demonstrated the use of breast care nurse delivered cognitive behavioural therapy to reduce the impact of hot flushes in women with breast cancer. The results were presented at Multinational Association for Supportive Care in Cancer (MASCC), June 2019 and a manuscript has been accepted for publication. Mechanisms to implement this practice as a standard of care were being explored with Maggie's Centres with plans delayed due to COVID-19.

Related Work

The Subgroup is proactive in raising awareness of symptom management issues. A successful workshop at the UK Interdisciplinary Breast Cancer Symposium 2020. Group members actively support on-going clinical research, such as PIONEER, a window of opportunity study to investigate the biological effects of the combination of letrozole and progesterone. Progesterone is an effective therapy for hot flushes and PIONEER was developed in part as the result of pressure from the members of this group and Independent Cancer Patient's Voice (ICPV). Additional projects include the analysis of quality of life differences with 6 or 12 months of adjuvant trastuzumab with the Persephone trial as well as related projects within the on-going OPTIMA trial. The group also supports SURECAN, investigating cognitive behavioural therapy to improve quality of life after cancer.

Translational & Imaging Subgroup (Chair, Professor Iain Lyburn)

The breast Group is unique within the NCRI in having a specific Translational & Imaging Subgroup as a 'separate' entity. The value of this role with utility across the group was specifically mentioned/highlighted as an area of strength of the Group as a whole in feedback from the Quinquennial Review Panel in October 2019.

Support the community in the development and delivery of studies across the portfolio

- The nature of the specialties and increasing intricacies of the translational and imaging components in medical care there is overlap and interfacing with all the other Subgroups/the main Group. The group rarely has face to face gatherings in the absence of tagging on to main Group meetings. The Subgroup is effectively a panel of experts with distinct niche areas of interest that can be called upon for expertise in specific projects.
- The Group provides informal advice for proposals and formal review of grant applications with translational or imaging components submitted to the Medical Research Council (MRC) and other bodies.
- Input to trials across the portfolio. E.g. 3 UK multi centre trials/projects within the NHS Breast Screening Programme:
    - Age Extension Trial assessing risk/benefits of an extra screen to women aged 47-49 (three years early) and, separately, offering additional screening to women after age 70.

- Breast Screening – Risk Adaptive Imaging for Density (BRAID), assessing a risk adaptive approach and various imaging tests in a screening, opened in September 2019.
- Prospective Randomized Trial of Digital Breast Tomosynthesis (DBT) Plus Standard 2D Digital Mammography (2DDM) or Synthetic 2D Digital Mammography (S 2D) Compared to Standard 2D Digital Mammography in Breast Cancer Screening (PROSPECTS).

Explore opportunities for identifying cross-cutting translational themes across the portfolio

- The Subgroup is continuing to build links with CM PATH.
- Mission papers on standardization may highlight areas of interest. The collaborative authorship for such manuscripts builds trial teams from multiple institutions. 2 areas are being worked on/considered at present with very valuable input from the Early Disease Subgroup:
  - Consensus of pathology reporting with a view to the potential of UK-wide validation of ki67 testing.
  - Imaging and pathological correlation in HER2+ disease: uniform acquisition/analysis protocols and consistent comparable reporting.
- Members of the translational and imaging Subgroup and Group were involved in setting up PRECISION – the CRUK Grand Challenge awarded for an international collaboration with teams from The Netherlands, USA and UK evaluating various aspects of Ductal carcinoma in situ (DCIS). As part of Work Package 4, samples from the USA are now being analysed (imaging characteristics, microstructure and fundamental chemistry of calcifications and adjacent tissues) at the University of Exeter and the University of Cranfield and Rutherford Centre. This led to the development of a successful grant application to the MRC –the CAPTURE (CAlicification Physicochemistry captures TUmour Remodelled Environment) study which is exploring the microchemical environment of breast calcifications – both benign and malignant from core biopsy samples. Tissue analysis began in February 2020.
- Discussion with industry partners about developing and validating artificial intelligence.

Identify future translational opportunities for inclusion within portfolio studies

- The Subgroup has continual liaison and discussion with the other subgroups to ensure that feasible opportunities for including translational and imaging elements are incorporated in to studies. Opportunities are explored for inclusion of specific parameters in to the trial design early in trial development and also to maximize data collection of any biomarkers which be acquired as part of routine care.
- Suggested standardization of breast MRI protocols – exploring utility in high-risk screening coordinated by the NHS Breast Screening Programme. As these are already in use in many centres, similar protocols could be embedded in trials facilitating more feasible role out and engagement from the imaging community less familiar with research.

- Digital diagnostic imaging (radiology) is effectively embedded in clinical medicine; digital pathology is rolling out. The benefits of digital systems enhancing collaboration are being explored. This will facilitate standardization, development and validation for artificial intelligence (AI).
- Continued participation in subspecialty meetings facilitating the cross fertilization of ideas/opportunities such as presentation of trials by oncologists and surgeons to the British Society of Breast Radiology research workshop.
- Active PPI involvement championing the cause of translational and imaging medicine.

4. Task groups/Working parties

UK Optimal Duration of Adjuvant Trastuzumab Working Group was established under the leadership of Professor Helena Earl to make recommendations for the implementation of the PERSEPHONE results into UK practice (Earl HM, 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. Lancet. 2019 Jun 29;393(10191):2599-2612. doi: 10.1016/S0140-6736(19)30650-6). These recommendations in consultation with UK Breast Cancer Group have been adopted by the group and have helped with systemic anti-cancer therapy delivery issues for NHSE during the COVID-19 pandemic.

5. Funding applications in last year

Table 2 Funding submissions in the reporting year

Study	Committee & application type	CI	Outcome	Level of Group input	Funding amount
Cancer Research UK					
May 2019					
EBCTCG programme grant funded April 2019-March 2024	Population research committee Programme grant	Richard Gray, Robert Hills, David Dodwell, Jeremy Braybrooke, Hongchao Pan, Isobel Barnes	Successful	Substantial informal input from individual members over the years. Programme presented to the CSG May 2018. Feedback used to improve application	~£5 million
November 2019					
MRC					
July 2019					
Breast Cancer: Early diagnosis using materials immortalization.	MRC	Keith Rogers		Conceived and developed in translational sub-group.	~£900K
NIHR					
Jan 2020					
ATNEC – NIHR128311 - Axillary management in T1-3N1M0 breast cancer patients with needle biopsy proven nodal metastases at	HTA	Amit Goyal	Successful	EARLY BREAST CANCER Subgroup extensively involved in development of	£2,998,853.43

presentation after neoadjuvant chemotherapy				application; current and past members of breast group are applicants.	
Tailoring treatment for HER2 positive early breast cancer – the HER2-RADiCAL study (Response ADaptive CAre pLan) HER2 RADiCAL	HTA	Andrew Wardley Judith Bliss Iain Macpherson David Cameron Stuart McIntosh Peter Hall Abeer Shaaban	Full application submitted	Conceived and developed in early breast cancer sub-group. Presented several times at UKBI. Feedback to improve application	£1,666,207.54
EndoNET – Neoadjuvant endocrine therapy for postmenopausal women with breast cancer	HTA	Michael Doueck Ramsey Cutress	Full application submitted	Developed through subgroup and main group; multiple group members as applicants.	£2,615,309
PARABLE – proton beam therapy in patients with breast cancer: evaluating early and late effects	EME	CI Charlotte Coles, , .	Full application submitted	Developed through subgroup; several members of subgroup applicants on proposal	£1,761,112.53

6. Consumer involvement

The UK breast cancer research community is recognised internationally for having been at the forefront of PPI involvement in trials with its close working partnership with patient advocacy groups, in particular Independent Cancer Patients Voice, NCRI PPI Group and NCRI Breast Group membership. The main Group has two consumer representatives, Ms Lesley Stephen and Mrs Janice Rose. With their input to the group in various ways they help support the group's overall strategy and the sub-groups' strategies in particular.

Janice Rose

Jan's focus is on Early Disease and Symptom Management and through those subgroups she has continued to contribute to a number of studies.

With POETIC-A, ATNEC and SWEET receiving funding, her involvement in these studies has continued and grown throughout the year. She is a co-applicant and member of the steering group on these studies. She is an equal and valued member alongside the researchers and is helping to guide the language used in patient materials for these studies as well as representing the patient voice as the studies progress. She makes sure that the research has relevance and benefit to patients and carers. She wants the research to support patients to live better with and beyond their cancer diagnosis and treatment, and be in line with the Living With and Beyond Cancer (LWBC) priorities supported by the NCRI.

Jan is a Patient Representative on the National Audit for Breast Cancer in Older Patients (NABCOP) Clinical Steering Group and the Independent Cancer Patient Voice (ICPV) group. Both groups have links with the NCRI Breast Group. Jan has attended the UK Breast Inter-Group (UKBI) meetings throughout the year, the UK Interdisciplinary Breast Cancer Symposium (UKIBCS) 2020 and the NCRI Cancer Conference 2019. This allows for her to network with various researchers and organisations and also supports her knowledge and development.

Lesley Stephen

Lesley's focus is on advanced breast cancer, which she has been living with for over 6 years. Metastatic Breast Cancer (MBC) patients often feel they are the 'invisible' ones in the breast cancer world, and Lesley hopes that by championing them on the Breast Group that she will give them a voice. Lesley has spoken about the need for brain metastases research, and now is a co-applicant on two innovative NCRI studies which will move forward our understanding of the disease and provide patients with more options – PRIMROSE and Radiant BC.

The consumer member of Advanced Disease Sub-group, Lesley, is passionate about raising increasing awareness of clinical trials amongst patients.

- Has helped to design a survey, for MBC patients' experiences of research and trials.
- Is involved in organising the UK's first MBC patient led conference.
- Is a Trustee of a fast-growing MBC charity, Make 2nds Count, helping to guide their research strategy.

- Has presented to the Executive Board of Breast International Group (BIG) on PPIE leading to greater PPIE across Europe.
- Provides the patient perspective on the International Cancer Genomic Consortium – Accelerating Research into Genomic Oncology (ICGC-ARGO) project. Invited to speak at their conference in S Korea in October 2020.
- Contributes to a Pfizer UK project which is gathering data on inequalities of access to treatment, and which will result in an action plan to address these issues.
- Works with the University of Glasgow's precision oncology team to raise awareness of their new genomic Glasgow Cancer test.

Other consumers involved on the Breast Group's Subgroups

A number of additional consumers are also involved in putting forward the views and needs of patients on each of its subgroups. Mrs Turner co-chairs the Symptom Management Subgroup, Dr Adrienne Morgan is also a member of this group. Mrs Hilary Stobart and Ms Mairead MacKenzie are members of the Early Disease subgroup. A number of these consumers are involved in studies including C-Trak TN, PRIMETIME, MENOS4, OPTIMA, PIONEER, ATNEC and SMALL that are on the Breast Group's portfolio. The members also helped to organise and chair sessions and talks and present posters at UKIBCS 2020, and have spoken on the importance of inclusive PPI at the Breast Cancer Trainees Research Collaborative Group.

All breast cancer consumers are involved in a wide variety of projects and studies within and outside the NCRI, always with a clear focus on representing the needs of breast cancer patients. All are members of Independent Cancer Patients' Voice
www.independentcancerpatientsvoice.org.uk

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7. Priorities and challenges for the forthcoming year

Priority 1

The development of a platform for HER-2 positive early breast cancer was one of the main strategic objectives for early breast cancer sub-group. The reduction of toxicity and treatment burden in patients for whom pathological complete response pCR after neoadjuvant therapy has been achieved has been submitted as the HER2-RADiCAL grant application.

The corollary to improve treatment in the non-pCR group who have a very poor outcome. We are exploring opportunities to work with pharmaceutical partners and also to build on the success of PHOENIX to develop HER2-PHOENIX. This will build on our novel trial and biological response expertise. We were involved in the KATHERINE trial which demonstrated that trastuzumab-emtansine rather than trastuzumab greatly improved overall survival in this group as well as new drugs tucatinib (Phase 3 improved overall survival) and trastuzumab-deruxtecan (phase 2 exceptional response rate and duration) both recently receiving FDA approval post trastuzumab-emtansine in metastatic breast cancer.

Priority 2

Complete a gap analysis working in metastatic breast cancer. This priority continues from last year. Following the gap analysis in breast surgery (Cutress et al Lancet Oncology 2018). A similar approach will be used in the planned metastatic gap analysis as previous gap analyses are now out of date. This new gap analysis will be spearheaded by our trainee representatives supported by the Metastatic Subgroup Chair and interdisciplinary group members. This exercise will identify areas of opportunity in metastatic breast cancer research. Whilst providing a comprehensive review of knowledge gaps and research opportunities and we anticipate that this will provide the background to new proposals in areas such as treatment sequencing and in the management of oligometastatic disease.

Priority 3

Further develop the Trainee collaborative recognised by the Association of Breast Physicians as an important component of research learning opportunities for trainees.

- Complete data collection on existing projects and publish within 18 months.
- Develop 2 new ‘real-world ’clinical research projects with potentially important clinical impact (surgical diathermy on axillary lymph nodes and tolerability of CDK4/6 inhibitors in an elderly population.
- Establish a network of mentors to embed research integrated into standard clinical practice culture and bring new young talent forward.
- Engage with underrepresented specialties, e.g. radiology to ensure membership is representative and inclusive of specialities involved in breast cancer.

NCRI Breast CSG Trainee Reps (Adam Heetun & Indrani Bhattacharya) lead the "Engagement with clinical trials" project received positively at NCRI meeting and by Breast Cancer Now. The next step is to refine the current questionnaire for re-distribution on a larger scale with input from Breast Cancer Now.

Challenge 1

Maintain levels of clinical trial recruitment in a challenging service environment faced with both funding shortages but also staffing shortages at multiple levels in the research team this is particularly acute in breast radiology and pathology. A UK-wide questionnaire regarding barriers to trial set-up/delivery has been circulated via UKBI– initial findings suggest consistent resource constraints for pathology and imaging and inconsistent access to support for setting up and conducting research in general but particular difficulty in accessing imaging and pathology.

Staffing constraints within Research & Innovation divisions has a performance impact on trial set up making the UK research environment increasingly challenging for commercial research partners. The impact of COVID-19 has had a major impact on recruitment, opening and delivery of all clinical trials as well as a huge impact on income for charities. These issues will need support from the wider NHS and government.

Challenge 2

Understanding the importance and benefits of research to patient care and service within a system focused on service. The current provision of breast cancer services is variable across the UK. Timely access to full pathology results at diagnosis, in particular HER2 status, compromises the ability to deliver systemic anti-cancer therapy before surgery (neoSACT) which is increasingly the international standard for aggressive breast cancer (HER2 positive and triple negative breast cancer (i.e. hormone receptor and HER-2 negative)) to all those who could benefit from it. The demands on the multidisciplinary team for undertaking neoSACT are greater than the conventional pathway of surgery first necessitating close working between radiology, surgical and non-surgical oncology. Provision of optimal imaging (MRI) is variable across the UK. Breast cancer services designed in the late 20th century may need review to facilitate better access to modern therapies, which is where clinical trials are focused.

Challenge 3

Ensuring that trials competing in the same population are managed appropriately. The demands on academics to lead trials sometimes sits at juxtaposition with the needs of the system and the ability to optimise trial design and recruitment. We will continue to pursue our recent success in team science approach across Breast Research Group. Better optimisation of the research environment would also facilitate the timing of trial opening and reduce cross trial competition. Predicting the life cycle of large trials is very difficult. Both set up recruitment and timely data return can be slowed due to resource issues at sites or regulatory funding or organisational barriers.

This requires close cooperation with individual trials management groups and is greatly aided by encouraging overlap of trial management groups and early engagement between these when potentially competing studies are being considered.

8. Collaborative partnership studies with industry

There are numerous studies within the portfolio that involve industry collaboration indeed the majority of metastatic studies are conducted in partnership with industry who provide novel agents and frequently full or partial funding to studies.

Recent examples of industrial collaboration for trials in set up phase include Radiant B, a trial of immunotherapy (durvalumab) in combination with stereotactic radiotherapy for breast cancer brain metastasis.

The POETIC-A study of adjuvant abemaciclib targeted to patients where window exposure to aromatase inhibition, demonstrates incomplete suppression of Ki67.

PHOENIX: “A preoperative “window of opportunity” phase IIa biomarker endpoint trial of DNA damage response (DDR) inhibition or anti-PD-L1 immunotherapy in patients with post-neoadjuvant chemotherapy resistant residual triple negative breast cancer (TNBC)”

9. Appendices

Appendix 1 – Breast Group and Subgroup strategies

- A – Breast Group Strategy
- B – Advanced Disease Subgroup Strategy
- C – Early Disease Subgroup Strategy
- D – Symptom Management Subgroup Strategy
- E – Translational & Imaging Subgroup Strategy

Appendix 2 – Top 5 publications in reporting year & Group involvement with NICE appraisals

Appendix 3 – Feedback from the QQR

Professor Andrew Wardley and Professor Daniel Rea (Breast Cancer Group Chair)

Appendix 1

Breast Cancer Group and Subgroup Strategies

A – Breast Group Strategy

Overall strategic aim

Improve the outcomes and experience of breast cancer patients and those at risk of developing breast cancer.

Aims

1. Ensure that all breast cancer patients have the opportunity to take part in research with access to a wide range of studies.
2. Increase patient expectation of being involved in a clinical trial.
3. Ensure equality of access for all patients through developing appropriate referral pathways and extended PIC sites for complex studies.
4. Embed a research culture across the entire patient pathway within all healthcare professionals and in all institutions providing breast cancer services.
5. Optimise trial design to adequately answer specific questions within the confines of the current and future health care environment.
6. Empower and educate patients and the public to drive a research oriented culture within the provision of routine care.
7. Increase the number of local PIs participating in clinical trials.
8. Increase the level of access to and use of tissue from all patients throughout the patient pathway.
9. Educate all healthcare professionals on the advantages of recruiting patients to trials.
10. Maintain international collaboration where appropriate and key to the success of a trial.
11. Strengthen links with other NCRI CSGs, HCIS and Advisory Groups.
12. Strengthen links with groups and alliances which impact on the ability to deliver trials.
13. Ensure a balanced portfolio of clinical trials with appropriate mix of complexity to allow full exploitation of clinical trial expertise and capacity.
14. Encourage the documentation of research initiatives, research competencies and achievements of all breast cancer clinicians.
15. Further develop the interaction with the CSG and the CLRN subspecialty research leads.
16. Extend trainee collaborative to oncologists, radiologists and pathologists.
17. Integrate Annual Trials day activities into the new multi-professional biannual breast cancer research meeting.
18. Deliver the commercial and non-commercial portfolio.

B – Advanced Disease Subgroup Strategy

Strategic objective	Activity	CSG Lead	Date
1a. Portfolio development (general)	To horizon scan the portfolio to identify future gaps & to develop trial concepts for discussion within such areas To design and deliver trials embracing the concept of personalised medicine; explore targeted treatments in molecularly defined subgroups; modulate extent of treatment according to risk Explore opportunities for identifying cross cutting themes across the portfolio & for coupling / decoupling studies where appropriate	Subgroup	Ongoing
1b. Portfolio development (local therapy)	Explore opportunities for Surgery / RT technology evaluation • new technologies • extent of treatment • need for treatment • Refinement of screening	CC PB / AS / CK CH/DR /SM	Primtime open Nostra prelim Now open Risk adapted screening trial in set up
1c. Portfolio development (systemic therapies)	To promote concept of trial platforms / multi stage trials to test modulation of treatment according to risk & likely benefit To promote use of informative experimental models including focussing novel treatment evaluation to those with residual – assessable - disease • post neoadjuvant – macroscopic / microscopic (ctDNA) • adjuvant – microscopic (ctDNA) • window of opportunity – biological endpoints • Metastatic disease – plasma detectable ctDNA; disease accessible for biopsy To promote development of pragmatic trials to test residual unanswered treatment questions within context of contemporary trial design (exploring alternative routes for collecting follow up data – see below, incorporating PROMS collected digitally (e.g. via Web, App), serial monitoring for micrometastatic disease), e.g. • Choice of regimen (efficacy vs tolerability) • Duration • Sequencing of treatments	AT – PHOENIX – post neoadjuvant residual disease wop platform AW – her2+ modulating treatment according to risk JMB / DC / AR – pragmatic CT trials	HER-2 platform funding application now 2019/20 Phoenix open 2019 Ct-RACK In set up

Strategic objective	Activity	CSG Lead	Date
1d Portfolio development integrated (translational research)	Promote expectations for integrating translational research into all trials where possible (patient acceptability / cost considerations) • Biomarker evaluation to identify sensitive subgroups • Serial (plasma) monitoring for micrometastatic disease • Mutation testing in residual disease Develop virtual Biobank (guided by Translational subgroup) • cross talk between those holding samples • agreement about how material is collected, stored and shared • common expectations for generic consent, sharing etc. • SOPs for collections etc.	NT AT AW	HER-2 platform funding application 2018 Phoenix open 2018 Ct-RACK Funding application 2017
2 Collaborative approach to trial development & participation	Engage with breast cancer clinical research community to develop and deliver high quality internationally competitive studies • National Breast Trialists Day (now biannual) • National multiprofessional breast cancer reserach meeting • UK Breast Intergroup meetings 2x/year • UK Breast Intergroup Feasibility & interest surveys Harnessing expertise and linking people with related ideas (UKBI) – to maximise efficiency & quality to trials Promote integration of PPI involvement in discussions of both concepts and generic considerations (eg multiple biopsies) • Arrange forums for discussion • Ensure PPI representation at meetings • Aim to optimise efficiency in and minimise inconvenience to PPI representatives in relation to workload management Engage with Royal College of Surgeons and Association of Breast Surgery and to support initiatives to increase the number of surgical trainees involved in clinical trials research Link with CTRad to expand RT studies Maximise opportunities for international collaboration • BIG – UK a participant group • BIG – UK a lead group • Unilateral national collaborative groups (NSABP, NCIC, UNICANCER, ANZBCG)	All KR MM All CC JB DR DC	

Strategic objective	Activity	CSG Lead	Da
3. Improving trials methodology & clinical utility	Endeavour to identify new predictors of risk and outcome intermediate endpoints • aimed at being true surrogates of long term disease outcomes (DFS, OS) • able to identify/predict patients with residual disease risk Collaborate with NCIN (inc Breast SSCRG) and CRS to validate completeness and accuracy of data acquired from routine data sources with a view to replacing hospital based follow up for disease outcome Engage with trials methodologists for optimising trial designs efficiently – multiple questions within 1 trials (couple / decouple studies).	NT - Post neoadjuvant ctDNA mutation identification & monitoring for disease risk JB JD JD	CtTRA And su studie Ongoi Ongoi Ongoi

PB	Peter Barry
JB	Judith Bliss
DC	David Cameron
CC	Charlotte Coles
DF	Debbie Fenlon
CK	Cliona Kirwan
KR	Kat Randle
AR	Alistair Ring
AS	Anthony Skene
NT	Nick Turner
AT	Andrew Tutt
AW	Andrew Wardley

C – Early Disease Subgroup Strategy

Strategic objective	Activity	CSG Lead	Date
1a. Portfolio development (general)	To horizon scan the portfolio to identify future gaps & to develop trial concepts for discussion within such areas To design and deliver trials embracing the concept of personalised medicine; explore targeted treatments in molecularly defined subgroups; modulate extent of treatment according to risk Explore opportunities for identifying cross cutting themes across the portfolio & for coupling / decoupling studies where appropriate	Subgroup	Ongoing
1b. Portfolio development (local therapy)	Explore opportunities for Surgery / RT technology evaluation • new technologies • extent of treatment • need for treatment • Refinement of screening	Local therapy leads	Primetime open Nostra prelim to open 2017 SMALL proposal to apply for funding 2018
1c. Portfolio development (systemic therapies)	To promote concept of trial platforms / multi stage trials to test modulation of treatment according to risk & likely benefit To promote use of informative experimental models including focussing novel treatment evaluation to those with residual – assessable - disease • post neoadjuvant – macroscopic / microscopic (ctDNA) • adjuvant – microscopic (ctDNA) • window of opportunity – biological endpoints • Metastatic disease – plasma detectable ctDNA; disease accessible for biopsy To promote development of pragmatic trials to test residual unanswered treatment questions within context of contemporary trial design (exploring alternative routes for collecting follow up data – see below, incorporating PROMS collected digitally (e.g. via Web, App), serial monitoring for micrometastatic disease), e.g. • Choice of regimen (efficacy vs tolerability) • Duration • Sequencing of treatments	AT – PHOENIX – post neoadjuvant residual disease wop platform AW – her2+ modulating treatment according to risk JMB / DC / AR – pragmatic CT trials	HER-2 platform funding application 2018/19 Phoenix open 2018 Ct-RACK Funding application 2017 And Ongoing

Strategic objective	Activity	CSG Lead	Date
1d Portfolio development integrated (translational research)	Promote expectations for integrating translational research into all trials where possible (patient acceptability / cost considerations) • Biomarker evaluation to identify sensitive subgroups • Serial (plasma) monitoring for micrometastatic disease • Mutation testing in residual disease Develop virtual Biobank (guided by Translational subgroup) • cross talk between those holding samples • agreement about how material is collected, stored and shared • common expectations for generic consent, sharing etc. • SOPs for collections etc.	NT AT AW	HER-2 platform funding application 2018/9 Phoenix open 2018 Ct-RACK Funding application 2017
2 Collaborative approach to trial development & participation	Engage with breast cancer clinical research community to develop and deliver high quality internationally competitive studies • National Breast Trialists Day (now biannual) • National multiprofessional breast cancer reserach meeting • UK Breast Intergroup meetings 2x/year • UK Breast Intergroup Feasibility & interest surveys Harnessing expertise and linking people with related ideas (UKBI) – to maximise efficiency & quality to trials Promote integration of PPI involvement in discussions of both concepts and generic considerations (eg multiple biopsies) • Arrange forums for discussion • Ensure PPI representation at meetings • Aim to optimise efficiency in and minimise inconvenience to PPI representatives in relation to workload management Engage with Royal College of Surgeons and Association of Breast Surgery and to support initiatives to increase the number of surgical trainees involved in clinical trials research Link with CTRad to expand RT studies Maximise opportunities for international collaboration • BIG – UK a participant group • BIG – UK a lead group • Unilateral national collaborative groups (NSABP, NCIC, UNICANCER, ANZBCG)	All MM, HS All CC JB DR DC	

Strategic objective	Activity	CSG Lead	Date
3. Improving trials methodology & clinical utility	Endeavour to identify new predictors of risk and outcome intermediate endpoints • aimed at being true surrogates of long term disease outcomes (DFS, OS) • able to identify/predict patients with residual disease risk Collaborate with NCIN (inc Breast SSCRG) and CRS to validate completeness and accuracy of data acquired from routine data sources with a view to replacing hospital based follow up for disease outcome Engage with trials methodologists for optimising trial designs efficiently – multiple questions within 1 trials (couple / decouple studies).	NT - Post neoadjuvant ctDNA mutation identification & monitoring for disease risk JB JD JD	CtTRACK And successor studies Ongoing Ongoing Ongoing

JB	Judith Bliss
DC	David Cameron
CC	Charlotte Coles
CK	Cliona Kirwan
MM	Mairead MacKenzie
SM	Stuart McIntosh
AR	Alistair Ring
AS	Anthony Skene
HS	Hilary Stobart
NT	Nick Turner
AT	Andrew Tutt
AW	Andrew Wardley

D – Symptom Management Subgroup Strategy

Hot flush and night sweats workstream	Outputs
1. Raising awareness of the issue	• Undertaken rapid surveys into current knowledge and management of hot flushes with patients, primary and secondary care health professionals. • Acted as consultants to NICE guidance on menopause management, to ensure that management of menopause after breast cancer was included. • Presented eight posters and fifteen oral presentations at national and international conferences. • Presented a symposium on breast cancer at the European Menopause and Andropause Society conference 2015 and secured a further symposium for EMAS 2017. • Written five papers for publication. • Developing a brief guide for menopause management after breast cancer in conjunction with Macmillan.
2. Supporting the development of current interventions to manage hot flush related problems	• Currently have four funded studies (MENOS4, green pessaries, PIONEER, fMRI). • FOAM is also on the NCRI portfolio (folic acid for menopausal symptoms). • Two further studies currently shortlisted. • Two studies have been presented and supported at Group meetings. • Currently supporting the development of studies into acupuncture, CBT, adherence to hormone therapy and megace.
3. Supporting the development of new interventions.	• The group have identified researchers into the biology of oestrogen deprivation and new researchers in this area who will pursue this avenue for future research. A review of the current state of research has been undertaken and several studies are currently in development.

Our ongoing strategy is now to broaden out to include other symptoms. In the first instance we will focus on sexual difficulties as a consequence of treatment for breast cancer. The same strategy that was used for hot flushes and night sweats will be used to develop three streams of work: raising awareness of the issue, supporting the development of current interventions to manage hot flush related problems and supporting the development of new interventions. We will liaise with other CSGs where appropriate to ensure that research into other symptoms related to breast cancer is being supported in the most relevant CSG.

E – Translational & Imaging Subgroup Strategy

Strategic objective	Activity	CSG Lead	Date
1a. Portfolio development (general)	To identify future translational opportunities for inclusion within portfolio studies To work with the early and late subgroups to design and deliver trials embracing the concept of personalised medicine; explore targeted treatments in molecularly defined subgroups; modulate extent of treatment according to risk in early disease . Explore opportunities for identifying cross cutting translational themes across the portfolio & for coupling / decoupling studies where appropriate Encourage a uniform minimum standards across all MDTs for the extent and timing of pathological information including standard mutational analysis and biomarker evaluation through guideline and position paper publications Encourage uniform minimum standards for reporting and decision making within MDTs based on comprehensive and timely imaging and biomarker information including a requirement to identify and record potential trial eligibility	All AS SP	Ongoing
1b. Portfolio development imaging	Ensure /advise on appropriate protocols for imaging in portfolio studies identify opportunities for assessment of novel imaging research	IL/FG	PROSPECTS TRIAL now Ongoing
1c. Portfolio development (systemic therapies)	To promote concept of trial platforms / multi stage trials to test modulation of treatment according to risk & likely benefit To promote use of informative experimental models including focussing novel treatment evaluation to those with residual – assessable - disease • post neoadjuvant – macroscopic / microscopic (ctDNA) • adjuvant – microscopic (ctDNA) • window of opportunity – biological endpoints • Metastatic disease – plasma detectable ctDNA; disease accessible for biopsy		Plasma Match Almost complete cTRAC full now recruiting Phoenix First patient in 2019

Strategic objective	Activity	CSG Lead	Date
1d integrated Imaging and translational research within the breast portfolio	Promote and advise on the integration translational and imaging research into all trials where possible to include • Biomarker evaluation to identify sensitive subgroups • Serial (plasma) monitoring for micrometastatic disease • Mutation testing in residual disease • Appropriate imaging modalities for all trials • Novel imaging (as subprotocol if appropriate) in clinical trials Develop virtual Biobank through cross talk between those holding samples • agreement about how material is collected, stored and shared • common expectations for generic consent, sharing etc. • SOPs for collections etc	NT	
2 Collaborative approach to developmentt of translational research	Engage with breast cancer clinical research community to develop and deliver high quality internationally competitive translational elements to portfolio studies Harnessing expertise and linking people with related skills to maximise & quality of translational input to trials Promote integration of PPI involvement in discussions of both concepts and generic considerations (e.g. genomic information multiple biopsies data protection) • Arrange forums for discussion • Ensure PPI representation at meetings Engage with Royal College of Surgeons and Association of Breast Surgery (via Adele Francis) and to support initiatives to increase the number of surgical trainees involved in clinical trials research Maximise opportunities for international translational collaboration • BIG – UK a participant group • BIG – UK a lead group • Unilateral national collaborative groups (NSABP, NCIC, UNICANCER, ANZBCG)	All HS All AS DR DC JB	Ongoing

Strategic objective	Activity	CSG Lead	Date
3. Improving trials methodology & clinical utility	Endeavour to identify new predictors of risk and outcome. • able to identify/predict patients with residual disease risk • Able to predict sensitivity/insensitivity to therapeutic intervention Engage with trials methodologists and bioinformaticians to ensure trials are designed so that translational data is exploited effectively and fully	NT AS/JB	Ongoing

PB	Rob Stein
JB	John Bartlett
FG	Fiona Gilbert
IL	Iain Lyburn
SP	Sarah Pinder
CP	Colin Purdie
ER	Emad Rakha
AS	Abeer Shaaban
VS	Val Spiers
JD	Janet Dunn
AT	Alistair Thompson
AF	Adele Francis
HS	Hillary Stobart

Appendix 2

Top 5 publications in the reporting year

Trial name & publication reference	Impact of the trial	Group involvement in the trial
1. PERSEPHONE 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (**PERSEPHONE**): 4-year disease-free survival results of a randomised phase 3 non-inferiority **trial.** Earl HM, Hiller L, Vallier AL, Loi S, McAdam K, Hughes-Davies L, Harnett AN, Ah-See ML, Simcock R, Rea D, Raj S, Woodings P, Harries M, Howe D, Raynes K, Higgins HB, Wilcox M, Plummer C, Mansi J, Gounaris I, Mahler-Araujo B, Provenzano E, Chhabra A, Abraham JE, Caldas C, Hall PS, McCabe C, Hulme C, Miles D, Wardley AM, Cameron DA, Dunn JA; PERSEPHONE Steering Committee and Trial Investigators.Earl HM, et al. Lancet. 2019 Jun 29;393(10191):2599-2612. doi: 10.1016/S0140-6736(19)30650-6. Epub 2019 Jun 6.Lancet. 2019. PMID: 31178152	NIHR HTA-funded PERSEPHONE study (NCT00712140) randomised demonstrated that 6 months of adjuvant trastuzumab was not inferior to 12 months (4-year DFS 89.4% compared to 89.8%, respectively) with considerably less toxicity and a cost-saving of £9,793 /patient. This has been adopted as a standard of care in UK by UKBCG.	Group developed
2. KEYNOTE_522 **Pembrolizumab** for Early Triple-Negative **Breast Cancer.** Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Foukakis T, Fasching PA, Cardoso F, Untch M, Jia L, Karantza V, Zhao J, Aktan G, Dent R,	The Chief Investigator Peter Schmid was a Group member during the conduct of this study which is an NCRI adopted study and has established UK investigators in the forefront of PDL-1 inhibitors in breast cancer participation has	The KEYNOTE-522 study is a NCRI badged industry sponsored International study. The chief Investigator Peter Schmidt is a recent Group member. This achievement demonstrates the ability of the UK academic

O'Shaughnessy J; KEYNOTE-522 Investigators.Schmid P, et al. N Engl J Med. 2020 Feb 27;382(9):810-821. doi: 10.1056/NEJMoa1910549	been influential in placing the Group in the position to conduct the academically led CDK 4/6 inhibitor studies PALETT and POETIC-A	clinicians to work with industry to design and deliver practice changing clinical trials.
3. HER2CLIMB Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, Lin NU, Borges V, Abramson V, Anders C, Bedard PL, Oliveira M, Jakobsen E, Bachelot T, Shachar SS, Müller V, Braga S, Duhoux FP, Greil R, Cameron D, Carey LA, Curigliano G, Gelmon K, Hortobagyi G, Krop I, Loibl S, Pegram M, Slamon D, Palanca-Wessels MC, Walker L, Feng W, Winer EP.Murthy RK, et al. N Engl J Med. 2020 Feb 13;382(7):597-609. doi: 10.1056/NEJMoa1914609. Epub 2019 Dec 11.N Engl J Med. 2020. PMID: 31825569	Improved overall survival in patients post trastuzumab-emtansine with metastatic HER2 positive breast cancer including improved overall survival in patients with brain metastases a notoriously difficult problem in HER2 positive breast cancer. Licensed by FDA.	The HER2CLIMB study is a NCRI badged industry sponsored International study. The success of this study demonstrates the ability of the UK to work with international SMEs and recruit to international cutting edge research.
4. FAKTION Fulvestrant Plus Capivasertib Versus Placebo After Relapse or Progression on an Aromatase Inhibitor in Metastatic, Oestrogen Receptor-Positive Breast Cancer (FAKTION): A Multicentre, Randomised, Controlled, Phase 2 Trial Robert H Jones [1], Angela Casbard [2], Margherita Carucci [2], Catrin Cox [2], Rachel Butler [3], Fouad Alchami [4], Tracie-Ann Madden [2], Catherine Bale [5], Pavel Bezecny [6], Johnathan Joffe [7], Sarah Moon [8], Chris	Progression-free survival was significantly longer in participants who received capivasertib than in those who received placebo. The combination of capivasertib and fulvestrant has led to an international phase 3 trial	Developed by NCRI/AZ alliance by NCRI Breast Research Group researchers and delivered in UK. This shows the ability of the NCRI Breast Research Group to develop run and complete international cutting edge research.

Twelves [9], Ramachandran Venkitaraman [10], Simon Waters [11], Andrew Foxley [12], Sacha J Howell [13] Lancet Oncol . 2020 Mar;21(3):345-357. doi: 10.1016/S1470-2045(19)30817-4. Epub 2020 Feb 5.		
5.SOLAR1 Alpelisib for *PIK3CA*-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, Iwata H, Conte P, Mayer IA, Kaufman B, Yamashita T, Lu YS, Inoue K, Takahashi M, Pápai Z, Longin AS, Mills D, Wilke C, Hirawat S, Juric D; SOLAR-1 Study Group.André F, et al. N Engl J Med. 2019 May 16;380(20):1929-1940. doi: 10.1056/NEJMoa1813904	*PIK3CA* mutations occur in approximately 40% of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer and is associated with worse outcomes. This trial selected patients with *PIK3CA* mutations and has led to first in class licensed agent targeting *PIK3CA* mutations in breast cancer. Licensed by FDA	The SOLAR1 study is a NCRI badged industry sponsored International study. The success of this study demonstrates the ability of the UK compete in an international arena.

Group involvement with NICE appraisals

NICE appraisal	Appraisal outcome	Group involvement with NICE appraisal
Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer Technology appraisal guidance [TA619] Published date: 15 January 2020	CDF approved	NCRI Breast Research Group experts advised committee. Trial led by Prof N Turner of Breast Research Group

		Trial recruited in UK and NCRI badged
Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab Technology appraisal guidance [TA612] Published date: 20 November 2019	NICE approved	NCRI Breast Research Group experts advised committee. Trial recruited in UK and NCRI badged
Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer Technology appraisal guidance [TA593] Published date: 14 August 2019	CDF approved	NCRI Breast Research Group experts advised committee. Trial recruited in UK and NCRI badged
Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer. Technology appraisal guidance [TA569] Published date: 20 March 2019	NICE approved	NCRI Breast Research Group experts advised committee. Trial recruited in UK and NCRI badged

Appendix 3

Feedback from the Quinquennial Review Panel

Quinquennial Review Panel Feedback

Breast Cancer Research Group

Date of panel meeting 11 October 2019

Covering period from May 2014 – October 2019

Panel members

Professor Meriel Jenney (Paediatric Oncologist, Cardiff and Vale Health University Health Board)
Dr Ian Lewis (Head of Strategy and Initiatives, NCRI)
Dr Emma Pennery (Clinical Director, Breast Cancer Now)
Professor Hervé Bonnefoi (Medical Oncologist at the l'Université de Bordeaux, France)
Mr Michael Jenkinson (NCRI Brain Tumour Research Group Chair)
Dr Gillian Rosenberg (Head of Research Groups, NCRI)
Ms Andrea McConnell (Research Groups Manager, NCRI)
Miss Chantal Ball (Research Groups Coordinator, NCRI)

Presenting the report

Professor Daniel Rea, Breast Cancer Research Group Chair
Dr Charlotte Coles, Early Disease Subgroup Chair
Professor Carlo Palmieri, Advanced Disease Subgroup Chair
Dr Anne Armstrong, Symptom Management Subgroup Co-Chair
Professor Iain Lyburn, Translational and Imaging Subgroup Chair

The Panel thanked the Breast Cancer Research Group for the well written and clear documentation provided and the openness with which they had engaged in discussions.

The Panel identified a number of strengths of the Research Group and a number of areas for future consideration.

Comments and recommendations

Areas of strengths;

- The Panel acknowledged a sense of genuine collaboration and comradery of the Group. The Groups passion and compassion came across strongly during the review, as well as a strong sense of commitment amidst decreasingly available research time.
- Members congratulated the Groups activity, including its offline activity between meetings/subgroup meetings, its highly successful annual trials meeting, and its significant portfolio of flagship and patient directed trials.
- The Group was commended for it highly reputable multidisciplinary trainee scheme and was encouraged to identify ways to secure protected research time for trainees via research funding schemes.
- The Panel was impressed by the breadth and enthusiasm of the Subgroups, including the utility of the Translational and Imaging Subgroup across the Group's activities.
- Members thought that the Groups intention to initiate an NCRI badging system showed innovation and excellent leadership and noted that this could be applied to the wider NCRI Research Group community.
- The Panel highly commended the Groups exemplary patient and public involvement (PPI), with demonstrable equality embedded in the leadership with a Patient representative as the co-Chairmanship of the Symptom Management Subgroup.

Areas for the group to consider;

- In considering the collaborative strength of the Research Group, members noted that a large part of the Group's success is attributable to its strong leadership and people. Consideration should be given to how the infrastructure and framework of the Group will enable it to maintain its ongoing collaborative success, particularly after current members have rotated off.
- The Panel recommended that the Group would benefit from better defining, within its strategy, opportunities to work with international organisations (e.g. collaborating on rare subtypes). Members noted that the appointment of David Cameron to the Chairmanship of the Breast International Group (BIG) may help further support bringing a UK voice to international activities.
- Whilst noting that there are currently nurse members sitting on the Symptom Management Subgroup, the Panel recommended that the Group would benefit from wider professional multidisciplinary team involvement (e.g. Allied Health Professionals) to address supportive care issues in the survivorship community. It was also recommended

that the Group engage with the new NCRI Living With and Beyond Cancer (LWBC) Group to discuss how to improve integration of quality of life and patient reported outcome measures into future studies.

- The Group was asked to consider its future strategy around tissue collection, access to tissue, and how they plan to interface with pathology research. For example, it was discussed that the Group should give thought to what the research community needs (i.e. does a particular subtype need further banking), what are the practical next steps for getting access to tissue, how to address the challenge of banking outside a clinical trial, and how to work across genomic hubs and the Genomics England programme. Further engagement with the NCRI CMPath initiative was recommended to support these discussions.
- The Panel thought that the Groups strategy was strong but would benefit from defining some key deliverable objectives to enable the Group to review it progress and measure its future success.
- Consideration was given to the Groups industry engagement strategy, and in particular its intention to build an immunotherapy portfolio. The Panel was encouraged to hear that the Group are keen to do further work to understand the science of immune related toxicity in advanced disease, early disease and in younger patients. It was recommended that the Group should engage in the British Society of Immunology (BSI) and NCRI joint initiative to support future work.
- It was noted that the Group currently does not have a trial with a focus for geriatric patients. Whilst age should not be a barrier for access to clinical trials the Group was asked to give further thought to enhancing access to clinical trials for this patient population. Specifically, that consideration should be given to increasing the upper age range of trials whenever possible.
- The Panel noted that patient recruitment figures had decreased in recent years and encouraged the Group to keep a focus on recruitment.
- Members encouraged the Group to maintain its good geographical diversity of members across the UK, including trying to include representation from all the devolved nations.

Issues for the NCRI to consider;

- NCRI Executive and the Breast Cancer Group agreed to adopt a trial badging trials system to enable more accurate mapping of the Group's impact against grant funding success and changing practice.
- NCRI Executive is to review the structure of the QQR report to enable easier interpretation of the recruitment data. It was also recommended that the NCRI Executive should share the NIHR data with the Group at an earlier timepoint ahead of the report submission deadline.
- NCRI Exec should further consider if European representatives can sit on the Research Groups.
- NCRI Executive to further consider how to address consumer diversity.

In concluding the Review, Professor Jenney thanked the Panel and Group members for their participation. The business of the meeting took four hours. ***The Group will be reviewed in five years' time.***