NCRI Breast Group

Annual Report 2020 - 2021

NCRI Partners

NCRI is a UK-wide partnership between research funders working together to maximise the value and benefits of cancer research for the benefit of patients and the public. A key strength of the NCRI is our broad membership with representation across both charity and government funders as well as across all four nations in the United Kingdom.

List of Appendices

NCRI Breast Group

Annual Report 2020-21

1. Top achievements in the reporting year (up to three)

Achievement 1

Continued Group activity throughout 2020 in the face of the COVID-19 pandemic represented a significant achievement both for the Group and the broader UK breast cancer research community. Despite the challenges of staff redeployment, and the competing challenges of clinical care and Urgent Public Health studies, recruitment to the majority of portfolio trials has continued throughout a challenging period for the community, with over 5000 patients being recruited to interventional cancer studies in 2020/21. In addition, Group activity has continued, with a rapid move to online meeting platforms enabling the main Group and Subgroups to continue to progress their objectives.

Achievement 2

Several studies developed through the Early Disease Subgroup and main Group have been funded by the NIHR over the last 12 months. These include:

HER2-RADiCAL: Response Adaptive Care pLan – tailoring treatment for HER2 positive early breast cancer

EndoNET: Neoadjuvant endocrine therapy for post-menopausal women with breast cancer

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

All these studies have been iteratively developed through the Group structures, with a highly collaborative approach incorporating our patient partners being integral to the success of these funding applications

Achievement 3

High quality, practice changing research outputs from world class NCRI supported and developed studies, including presentations at international scientific meetings (albeit virtual meetings in 2020) and publications in high impact journals.

These include:

FAST-FORWARD: hypofractionated radiotherapy for early breast cancer showing a 5-fraction treatment course to be non-inferior to standard 15 fraction treatment. This evidence was rapidly adopted into practice, with clear benefits for patients and the NHS, published in *The Lancet*

PALLAS: Palbociclib with endocrine therapy in early disease did not improve invasive disease-free survival in early disease compared with endocrine therapy alone, published in *Lancet Oncology*

MONARCH-E: showed a significant invasive disease-free survival benefit for adjuvant abemiciblib with endocrine therapy in HR+ HER2- node positive high risk early breast cancer presented at European Society of Medical Oncology and published in the *Journal of Clinical Oncology*

POETIC: this large UK study demonstrated the relationship between two-week Ki67 and long-term outcomes in patients treated with pre-operative endocrine therapy and has informed the design of the subsequent POETIC-A study (*Lancet Oncology*).

PRIME-II: presented at San Antonio Breast Cancer Symposium Virtual Meeting 2020 – 10 year follow up of this important trial of omission of radiotherapy in women over 65 with HR+ breast cancer showing increased local recurrence risk (9.8% vs 0.9%) with no impact on rates of distant metastases or overall survival.

2. Structure of the Group

- The group structure remains unchanged at present, although will evolve in 2021-22 as the NCRI Research Groups move to a new working model.
- Thanks are due to outgoing Chair Professor Andrew Wardley, who has moved from his NHS role to take up a new post within industry – we wish him well for the future.
- His role will be taken by an Interim Chair until the Group Structure changes later in 2021.
- Membership rotation for the Group and subgroups was suspended due to COVID-19.
- Trainee members remain attached to both the main Group and to one of the Subgroups.
- The model of new studies being proposed at the UK Breast Intergroup meeting before discussion at the appropriate subgroup remains in place, although the main focus of the November 2020 UK Breast Intergroup (UKBI) meeting was on the challenges associated with COVID-19 and there have been few new trial proposals presented latterly.

3. Breast Group & Subgroup strategies

Breast Group

The year 2020/21 has clearly been a challenging year for the Breast Group, as it has been for all the NCRI Research Groups. Nevertheless, activity has continued throughout the year, with the Group and Subgroups continuing to work virtually to make progress towards their objectives. Rapid adoption of virtual meetings has made this possible, and the use of such online platforms has also allowed us to continue to engage with the broader research community, including a well-attended online meeting of the UK Breast Intergroup (UKBI) in November 2021.

Under the circumstances, the Breast Group's strategy review has been postponed until later in 2021; however, a strategy roundtable event followed by a larger Group strategy event is planned for this year. Pending this, the Group's overarching strategies retain broadly similar themes to previous years. The obvious exceptions are the need to support the restart and delivery of trial activity following the impact of the pandemic, and the implementation of lessons learned from our experiences during the pandemic.

1. **Support the development and delivery of the clinical trials portfolio following the impact of the COVID-19 pandemic**

Although the pandemic has had a clear impact on breast cancer clinical research activity during 2020-2021, we have managed to maintain a level of trial activity throughout this period. In addition, the Group and the breast cancer research community more broadly have demonstrated their engagement with several cancer/COVID-related activities, including the UK Coronavirus Cancer Monitoring Project and the B-MaP-C, study which assessed alterations to the breast cancer clinical management pathway during the pandemic.

Moving Group meetings to a virtual platform enabled us to continue to meet and discuss key issues relating to clinical research activity during the pandemic. Although the May 2020 UKBI meeting was cancelled, the Group held a successful meeting in November 2020 where we heard presentations from CIs across the portfolio, who spoke about the changes they had made to facilitate trial activity, allowing the sharing of good practice with respect to issues such as the use of remote consent, minimising hospital visits and virtual meetings, with the online format enabling broad representation from across the breast cancer research community. In addition, we were able to discuss and provide feedback to five new trial concepts presented by UK researchers, demonstrating that a pipeline of study development remains active in spite of COVID-19. For the future it is likely that we will retain the virtual format for at least some of our wider meetings as this facilitates attendance and engagement from a wide range of specialties and patient advocates without the need for or expense of travel.

2. **Increase patient expectation of being involved in a clinical trial**

This is a key part of our strategy and is integral to ensuring that clinical research participation is a vital part of the provision of high-quality cancer services. We continue to take this aim forward through the activities of our patient members, as outlined in the Consumer reports below, and as can be seen from their activity, this message is cascaded down through local patient support groups. Furthermore, this remains a key topic in our relationships with other professional groups such as the Association of Breast Surgery.

3. **Further develop the breast cancer portfolio, ensuring a collaborative, multidisciplinary approach to trial development and participation**

Developing and maintaining a broad portfolio of patient-centric and impactful trials remains a central theme for the whole Group, with risk-adapted treatment strategies at the core of this. The Subgroup structures and close relationships with UKBI are designed to facilitate improved

collaboration and bringing together multidisciplinary teams to develop key trial ideas and respond to appropriate funding calls from funders such as the NIHR. This has clearly been successful as evidenced by multiple successful funding applications in 2020 which were developed through the Group structures and UKBI, including the risk-adapted HER2 de-escalation study HER2-RADiCAL.

The Group continues to maintain an "open-door" approach for any researcher wishing to develop a clinical study, with proposal to the UKBI meeting being the initial platform for presentation to the Group and the wider research community including our patient advocates. Although the new NCRI Group structure will incorporate Proposal Guidance meetings, we wish to maintain the UKBI role in this setting as it provides a unique opportunity to gain broad input into proposals at an early stage of development and has been integral to the delivery of many successful breast cancer studies over the years.

In refining proposals brought to UKBI, subsequent involvement of the relevant subgroups has been key to the development of fundable studies. In addition, the Translational and Imaging Subgroup brings a breadth of radiological, pathological and translational expertise to studies in development, with the subgroup's virtual model (predating COVID-19) facilitating the input of acknowledged international experts to trial development. In addition, the inclusion of basic scientists in the Subgroup and the main Group ensures that there is a good scientific rationale underlying study design and translational components of the Group's studies. Furthermore, development of studies in both the management of symptoms and treatment-related adverse events remains an important aspect of the Group's strategy. The Symptom Management Subgroup remains a key driver of activity in this area, with ongoing work seeking to both identify knowledge gaps and develop appropriate studies to address these.

Finally, an important strategic aim for the next five-year cycle is to strengthen and build on our relationships with key international groups such as the Breast International Group, where established UK researchers (Cameron and Bliss) are members of the Executive Board, and our consumer members are members of the BIG patient partnership initiative. The NCRI Breast Group, in partnership with the ICR-CTSU have previously contributed to the successful delivery of BIG-led studies in the UK and we will seek to continue to do this, with the aim of commencing deliver of one new BIG-led study within the UK in 2021/22.

4. **Improve trials methodology and clinical utility**

Novel methodology and efficient trial designs remain key to the Group, and there are now three senior methodologists on the Group (including the Early Disease Subgroup Chair), ensuring there is expert methodological input into trial design and development. Input from the Translational and Imaging Subgroup ensures that opportunities for translational research are maximised in all trial designs.

An example of this is the successfully funded HER2-RADiCAL study developed by the group, evaluating risk-adapted de-escalation of therapy in HER2+ve breast cancer. HER2-RADiCAL has an efficient single arm cohort design in a setting where robust historical control data are available and where absolute disease-related event rates are low.

5. **Embed a research culture across all specialties within the patient care pathway**

Integration of clinical trials within clinical service is the Group's approach to breast cancer service provision. As part of this strategic aim, we ensure the promotion of this message through all appropriate opportunities; for example, the 2020 UK Interdisciplinary Breast Cancer Symposium incorporated a Clinical Trials Showcase with an emphasis on the multidisciplinary nature of clinical trials, featuring key portfolio trials such as SMALL, ATNEC, PRIMETIME and POETIC-A.

We have worked to foster links with professional bodies from across the disciplines involved in breast cancer care. We strongly support the Association of Breast Surgery's aims of "a clinical trial

for every patient" and will be working closely with the Association's Academic and Research Committee to ensure that the ABS Annual Conference (online in 2021) will ensure that relevant national trials are promoted to a surgical audience. These trials will also be promoted to the surgical community via the mechanism of ABS badging of studies. Additionally, the Group will support the ongoing James Lind Alliance Research Priority Setting Partnership in Breast Cancer Surgery, in which clinicians, researchers and patients in partnership will define and prioritise key research questions in breast cancer surgery, which will feed into the development of future studies.

The Chair of the Translational and Imaging Subgroup is research lead for the British Society of Breast Radiology (BSBR), and this has ensured high visibility for the breast cancer trials portfolio at recent BSBR meetings. We now have strong pathology expertise embedded both within the main Group and the Translational and Imaging Subgroup, and we seek to maintain our strong relationships with the UK Breast Cancer Group, the stakeholder group for non-surgical oncologists.

6. **Increase the number of local PIs participating in clinical trials and training the next generation of investigators**

As noted above, UKBI is intended to be open and welcoming to new investigators and provides excellent multidisciplinary network-building opportunities across the breast cancer research community. We have been working with the ABS to both support the development of the surgical research portfolio and now have multiple trials in early breast cancer with surgical leadership (ATNEC, EndoNET, SMALL). Consequently, these studies provide opportunities for surgeons, radiologists, and others not previously active in clinical research to engage with the trial portfolio.

Furthermore, training the next generation of investigators remains key to the Group's work and to this end we have ensure that new studies in development and set-up have trainee involvement and are active in the NIHR's Associate PI scheme.

7. **Educate and empower patients and the public to drive a research-orientated culture within clinical care**

Our Consumer representatives are fully engaged with all Group activities, and promote a research ethos to the general public, existing patients and health care professionals. The Group has two Consumer representatives (Mrs Lesley Stephen and Mrs Janice Rose), with Mrs Lesley Turner a co-chair of the Symptom Management Subgroup, which also lists Dr Adrienne Morgan among its members. Mrs Hilary Stobart and Ms Mairead McKenzie are members of the Early Disease Subgroup. All our trials are developed with patient involvement from a growing number of patient representatives from the stage of early concept through to completion, and this involvement has been integral to the success of multiple funding applications in the last year.

In addition to involvement with the activity of the Group and all Subgroups, our patient representatives provide links with both national and international groups, including being active on multiple Trial Management Groups, and being members of the BIG patient partnership initiative. Furthermore, they have led on the delivery of aspects of this strategic aim, with the development of the Patient Trial Advocate and the survey of metastatic breast cancer patients' clinical trial experience being key components of this workstream. They have also provided crucial support for the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), providing input to the successful EBCTCG application to the Confidentiality Advisory Group for long-term follow-up data from seven UK breast cancer randomised trials. The results of these trials (started between 1948-1982) continue to be important because these trials include standard therapies that are in use today and which may have effects still measurable decades after treatment. To date, this long term follow up has enabled results in 15 EBCTCG reports to be published, contributing to changing practice in surgery, radiotherapy, chemotherapy, hormonal therapy and ovarian ablation.

Early Disease Subgroup (Chair, Mr Stuart McIntosh)

1. Develop Early Disease Subgroup portfolio

Despite the challenges of COVID-19, 2020-2021 was a highly successful year for the Subgroup, with several large studies successfully funded by the NIHR. These studies all received extensive input from the Early Disease Subgroup and were developed iteratively through the Subgroup and the UKBI forum.

a. Loco-regional treatment

ATNEC: (de-escalation of axillary surgery following pathological complete response to neoadjuvant systemic therapy) has now commenced recruitment and has opened seven sites across the UK, with multiple additional sites in set-up.

PARABLE: (Proton beam theRapy in patients with Breast cancer: evaluating early and Late Effects) has been funded by the NIHR Efficiency and Mechanism Evaluation programme and is in protocol development

b. Systemic therapy

HER2-RADiCAL: (Response Adaptive Care pLan) – tailoring treatment for HER2 positive early breast cancer has been funded by the NIHR Health Technology Assessment programme and is in protocol development, aiming to open to recruitment later in 2021

EndoNET: (Neoadjuvant endocrine therapy for post-menopausal women with breast cancer) has also been funded by the NIHR Health Technology Assessment programme and is currently in protocol development.

c. Translational studies and personalised medicine

The POETIC-A study (funded by Lilley, endorsed by CRUK) has now started setup, having been previously delayed due to COVID-19.

The Subgroup continues to scan the portfolio to identify potential future gaps and to explore new opportunities for studies in loco-regional and systemic therapies, both by developing novel UK studies and engaging with studies at a global level through groups such as BIG to maximise opportunities for international collaboration. Future areas of interest include continued development of the risk-adapted portfolio and also non-IMP studies such as those involving exercise and prehabilitation.

2. Develop a collaborative approach to trial development

a. Engagement with the broader breast cancer community

Although at some levels COVID-19 made this objective challenging, particularly with the cancellation of many meetings and events in the first part of 2020, the increasing use of virtual platforms later in the year meant in some ways that we were able to extend our reach and perhaps engage with parts of the community which had previously been harder to reach. For example, the attendance of > 90 clinicians and researchers at the November 2020 UKBI meeting was higher than would generally be seen at face-to-face meetings. Similarly, many of the key clinical trials in our portfolio utilised this medium as a means of widely engaging with the community – for example, the SMALL trial held an online meeting for radiological PIs which was attended by over 50 clinicians, provide an excellent means of promoting the trial and raising research awareness,

and this model has been utilised by other studies such as OPTIMA. For these reasons it is likely that a proportion of this activity will continue to utilise an online platform for the future.

b. Integration of PPI into all stages of trial development

Our PPI representatives continue to input into trial development at all stages from concept to delivery, and this is key contribution is apparent through the successful funding of several trial applications in 2020/21, which have been commended for their PPI input. PPI representation also remains an integral part of many Trial Management Groups across the portfolio, and we will seek to maintain this for future studies.

c. Engagement with the Association of Breast Surgery

We continue to work closely with the surgical community to nurture surgical engagement with the portfolio, particularly with respect to neoadjuvant, peri-surgical and adjuvant studies in early breast cancer. Many of our portfolio studies are now badged by the ABS (SMALL, OPTIMA, PRIMETIME, ATNEC, POSNOC), with the aim of encouraging surgical engagement with recruitment, as this is key to the successful delivery of these studies. Additionally, active promotion of these trials through the ABS educational webinar series throughout 2020 provided a further key opportunity to engage with the ABS.

The ABS are conducting a James Lind Alliance Research Priority Setting Partnership exercise in Breast Cancer Surgery. The Group are highly supportive of this workstream, and JLA PSPs are a recognised means of informing both researchers and funders about key knowledge gaps which require to be addressed through research – the findings of this will inform future development of the early breast cancer portfolio through the subgroup.

3. <u>Improve trials methodology and clinical utility</u>

a. Ongoing collaboration with and support of the Breast Cancer Trainees Research Collaborative Group

Once again this was a challenging year, with the cancellation of the trainee collaborative annual meeting in 2020, and a likely virtual meeting in 2021. However, despite this, work continues with the group's ongoing projects which include audits of the management of brain metastases, long-term trastuzumab use and pregnancy-associated breast cancer.

b. Participation in the NIHR's Associate Principal Investigator scheme

SMALL, ATNEC, OPTIMA and Pre-BRA have all joined the scheme, with other studies to follow. This scheme aims to engage with trainees across all disciplines to develop the next generation of clinical researchers.

Advanced Disease Subgroup (Chair, Professor Carlo Palmieri)

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 Subgroup 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 CNS and the issues with delivering these studies when they are instigated. The Subgroup engages actively with the wider research community via the twice-yearly UKBI meeting. UKBI provides an opportunity for new trial proposals to be presented and receive structured feedback. The Subgroup 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 ensures only well worked up proposals move forward to funding bodies.

The Subgroup continues to deliver a broad trial portfolio with broad representation of trials in all disease subgroups (defined by ER, PgR and HER2 status). UK investigators continue to contribute at an international level to industry sponsored studies.

Translational & Imaging Subgroup (Chair, Professor Iain Lyburn)

As highlighted by the Quinquennial Review (QQR) Panel in October 2019, the Breast Research Group is unique within the NCRI in having a specific Translational & Imaging Subgroup. The Subgroup structure has evolved into a panel with a broad church of members with varied interests and specialisms, with the aim of providing access to this expertise for the wider Group. Members incorporate laboratory-based scientists and clinicians including oncologists, surgeons, pathologists and radiologists.

As previously, due to the ever-increasing complexities of the translational and imaging components in medical care, much of the Subgroup's activity takes the form of interfacing with the other Subgroups and the main Group to provide expertise to support study development. Like the wider research community, COVID-19 affected opportunities and patterns of work. Research and clinical resource in many centres were redeployed to directly address the clinical demands of COVID-19. Conditions of practice were affected markedly reducing the capacity of laboratories and imaging departments to provide clinical services with the knock-on effect of reducing research opportunity and capacity. Despite this, the Group has made progress against its strategic aims outlined in last year's report:

1. **Support the community in the development and delivery of studies across the portfolio**

Many trials with imaging and translational aspects ceased recruiting completely for a period, with the NHS Breast Screening Programme facing a large backlog of women requiring screening due to suspensions to the Programme last year. This affected a number of trials directly supported by the Subgroup:

a. **The Age Extension Trial** which was set up to determine whether extending the age bracket to include women aged 47-49 and 71-73 would reduce mortality will not restart randomisation after the COVID-19 pandemic. Follow up will be by electronic linkage to routine government records. Other trials after a gap last year have restarted. Members of the Subgroup are at many of the most active centres.
b. Breast Screening – Risk Adaptive Imaging for Density **(BRAID)**, assessing a risk adaptive approach and various imaging tests in screening in breasts of increased density has reopened and is recruiting well. Arms in this study include Contrast Enhanced Spectral Mammography (CESM) and Fast MRI (shorter protocols), with skills obtained imaging trial cases already being transferring to non-trial clinical cases (improved workflows and increased throughput) which is of net benefit to the screening community.
c. 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)** has also recommenced.
d. **SMALL** has been badly affected by the pandemic; both opening centres and recruiting patients was extremely challenging throughout 2020. Nonetheless, several Subgroup members have been pivotal in driving the study, and the Subgroup held a videoconferencing workshop for radiologists in February exchanging practical tips on sampling technique and post procedure image interpretation. This was a very successful example of collaborative remote working, with a large turnout (~50 participants) and generating substantial interest in the trial was generated, with tips about intervention in clinical practice in general exchanged with wider benefit for the

NHS and screening patients. The team leading this have been invited to repeat the message and present at the research session of the BSBR in November 2021, which will present a further opportunity to encourage centres to participate in this trial and engage with the imaging community more broadly.

2. **Explore opportunities for identifying cross-cutting translational and imaging themes across the portfolio**

The Subgroup is developing and supporting several substudies within existing portfolio trials to leverage translational and imaging opportunities afforded by these studies, including:

a. **NOSTRA** – the Subgroup have been involved in developing an MRI substudy for this trial, with a suggested protocol to facilitate standardization of MRI practice across the UK, as this is one of the long-term strategic aims of the Subgroup's.
b. **PHOENIX -** a pre-surgical window of opportunity and post-surgical adjuvant biomarker study of DNA damage response inhibition and/or anti-PD-L1 immunotherapy in patients with neoadjuvant chemotherapy resistant residual triple negative breast cancer has sought the expertise of the Subgroup in designing and amending parameters for inclusion and evaluation.
c. **PRECISION** – the CRUK Grand Challenge awarded for an international collaboration with teams from The Netherlands, USA and UK evaluating various aspects of DCIS involving several members of both the Subgroup and main Group, including our PPI members. As part of Work Package 4, international samples are being analyzed (imaging characteristics, microstructure and fundamental chemistry of calcifications and adjacent tissues) at the Universities of Exeter Cranfield and Rutherford Centre.
d. **CAPTURE** (CAlicification Physicochemistry captures TUmour Remodeled Environment) is exploring the microchemical environment of breast calcifications – both benign and malignant from core biopsy samples. Tissue analysis with electron microscopy and Rahman spectroscopy commenced in February 2020 and has been slightly curtailed in light of the COVID-19 pandemic, but full activity has commenced with > 90 samples now in preparation.

3. **Improving trials methodology and clinical utility from a translational and imaging perspective**

a. **Ki67:** One of the previous objectives for the Subgroup in conjunction with the Early Disease Group was to explore the analytic standardisation of and validation of Ki67 testing, both within clinical trials and in wider clinical practice. Both Subgroup Chairs met with NEQAS and other key stakeholders in early 2021 to move this issue forward and will support the rollout of a NEQAS programme for QA for this biomarker.
b. **Artificial Intelligence:** This is clearly going to play a greater role in medicine in general with many applications in the translational and imaging domains. The Subgroup is involved in **OPTIMAM**, an Image Database with nearly 3 million mammography images with associated clinical data collected from multiple NHS Breast Screening sites. The OPTIMAM project offers the opportunity for Virtual Clinical Trials, Computer Aided Detection, Artificial Intelligence, Image Perception Studies and Training and Quality Assurance.
c. **Digital pathology**: As pathology becomes increasingly digitised, there will be a focus on harnessing opportunities arising for the collation of large data sets within clinical trials, which due to their electronic nature can be shared more easily. An example of this will be the central pathology review component of the HER2-RADiCAL study which will both utilise digital pathology methodology to quality assure the trial and simultaneously develop a valuable electronic specimen collection to facilitate translational research.

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

1. **To identify gaps in current research in the symptom management after a diagnosis of breast cancer**

The Symptom Management Subgroup was established by patients to promote and develop research into symptoms after a diagnosis of breast cancer. To date the Subgroup has achieved success by concentrating on single issues with members from a wide range of disciplines. The current focus is on the management of urogenital atrophy (UA) and sexual health issues as a consequence of treatment. We are exploring future work on areas of unmet need and have concerns about restrictions on funding opportunities due to the COVID-19 pandemic.

2. **Support development of new research into identified gaps**

A study of the real-world experiences of over 2000 women on adjuvant endocrine therapy has been completed and a manuscript in preparation (CI L Hughes). It is anticipated that this will provide data to guide areas of future research into symptom management. A manuscript reporting on the psychometric properties of a sexual health quality of life measure led by the group is also in in preparation.
The e-PATH study led by L Hughes, consists of a randomised controlled trial of an mHealth intervention to support women prescribed adjuvant hormonal therapy. The trial is coming to an end in July 2021 and the results will be submitted for publication later in the year. Additional studies and grant applications are ongoing to understand the mechanism of action of the intervention and implementation, which is supported by the Subgroup.
Work on UA continues with an application for a trial to investigate the use of vaginal oestrogens in women on aromatase inhibitors.
The Subgroup continues to support the NIHR-funded SWEET programme (co-applicants L Turner, J Rose, I White, L Hughes). The programme aims to develop a self-management support tool for women with breast cancer, who have recently been prescribed AET to adhere to the therapy for the length of time prescribed without stopping permanently or skipping doses. A website application and mobile app are the core of the intervention containing a facility to set reminders, collect prescriptions and other tools to support adherence based on behavioural change techniques (e.g. goal setting) and external links. To date the Subgroup have had a number of patient forum/expert clinical forum discussions and a video for use in the app and website has been produced. The study is progressing well, despite the restriction of the COVID-19 pandemic. The next stage will be to test the prototype with a pilot group of patients, and ultimately a RCT.

3. **Support translation of research findings into practice**

The Subgroup had hoped that the results of the MENOS4 (CI Prof Fenlon) study which demonstrated the benefits of BCN-led CBT for the management of hot flushes would be put into practice in conjunction with Maggie's Centres but the COVID-19 pandemic has made this difficult. However, a study looking at the same therapy in men with prostate cancer is funded and underway.

Related Work

The Subgroup continues to be proactive in raising awareness of SM issues and we will submit evidence to the UK governments Women Health Strategy call.

4. Cross-cutting research

1. UK Optimal Duration of Adjuvant Trastuzumab Working Group

The leadership of this group has passed to Professor Dan Rea (previous Breast Group Chair) and is working to make recommendations for the implementation of PERSEPHONE results into UK clinical practice. This work is ongoing, with the results of a patient-level meta-analysis of the relevant trials pending.

2. Standardisation of Ki67 assessment within clinical trials

The ongoing lack of standardisation of this biomarker across the UK has limited its utility both in clinical trials and routine practice, and this project has been a key aim of both the Early Disease and Translational and Imaging Subgroups. As outlined above, the Subgroup Chairs have met with NEQAS and a Quality Assurance pilot is being rolled out by NEQAS with the support of the Subgroups to address this issue.

5. Funding applications in last year

Table 1 Funding submissions in the reporting year

Study	Committee & application type	CI	Outcome	Level of Group input	Funding amount
Cancer Research UK*					
March 2021					
Predicting relapse with circulating tumour DNA analysis in early stage breast cancer	Biomarker Project Award	Professor Nicholas Turner	Not Supported	Proposal presented electronically to Early Disease Subgroup and extensive feedback provided	
Other committees**					
Study	**Committee & application type**	**CI**	**Outcome**	**Level of Group input**	**Funding amount**
HER2-RADiCAL: Response Adaptive Care pLan – tailoring treatment for HER2 positive early breast cancer	NIHR Health Technology Assessment Programme	Dr Iain Macpherson	Funded	Study iteratively developed over several years through UKBI, Early Disease Subgroup and main Breast Research Group	£1,656,350.85
EndoNET: neoadjuvant endocrine therapy in postmenopausal women with breast cancer	NIHR Health Technology Assessment Programme	Prof Michael Douek/Prof Ramsey Cutress	Funded	Study developed through UKBI, Early Disease Subgroup and main Breast Research Group, with input from these Groups in order to develop a single feasible study from several initial competing proposals	£2,739,412.11
PARABLE: Proton beam theRapy in patients with Breast cancer: evaluating early and Late Effects	NIHR Efficacy and Mechanism Evaluation	Prof Charlotte Coles	Funded	Study developed through UKBI, Early Disease Subgroup	£1,343,394.08

				and with input from CTRad	
Fast-MRI	NIHR Health Technology Assessment Programme	Dr Lynne Jones	Unsuccessful	Proposal developed with extensive input from both main Group and Translational and Imaging Subgroup	£5, 945,220.03

**CRUK CRC applications for table 1 completed by NCRI Executive.*
***Other applications in the table to be completed by Group Chair*

6. Consumer involvement

The UK breast cancer research community has a strong track record of PPI involvement in the development and delivery of its clinical research portfolio, working closely in partnership with organisations such as Independent Cancer Patients' Voice (ICPV), the NCRI's Consumer Forum and with membership of the main Group and all Subgroups (including a PPI Chair of the Symptom Management Subgroup). The main Group has two consumer representatives, Ms Lesley Stephen and Mrs Janice Rose, who with their input support both the Group's overall strategy and that of the Subgroups.

Janice Rose

With support from the Consumer Forum to use virtual meeting platforms, Jan has attended the meetings for the main Breast Group, the Early Disease and Symptom Management Subgroups during the year. Jan has continued to work with researchers throughout the year representing the patient perspective in the studies that she is involved with. She has commented on new proposals submitted to the Subgroups both directly and via the UKBI.

The ATNEC trial started recruiting this year. Jan is one of the co-applicants on this study and is a member of the Trial Management Group. As well as working on the Patient Information Sheet and Consent Form for the study, she has been involved in making a video showing a discussion between a patient eligible to enter the ATNEC trial and a research nurse. The Research Ethics Committee commented "how well made, clear and sensitive the video clip is", and it has been viewed over 100 times. Both Jan and the other patient on the study have contributed the patient involvement section of a newsletter for clinicians about the study.

Jan is also on the Trial Management Group of POETIC-A, which has now started recruiting. Both ATNEC and POETIC-A are on the Breast Group's Early Disease Subgroup portfolio.

Jan is a co-applicant and member of the Patient Advisory Group (PAG) of the SWEET study, one of the studies on the Symptom Management Subgroup's portfolio. It has links to the NCRI Living With and Beyond Cancer (LWBC) initiative in terms of side effects after treatment, and started in 2020, and aims to encourage adherence to hormone therapy prescribed after breast cancer treatment. The PAG has been central to the work of the study so far. Jan and Lesley Turner are on the Programme Management Committee for SWEET which allows for information flow between this and the PAG.

Jan worked on a proposal for Breaking Bad News Remotely to Breast Cancer Patients with Cliona Kirwan, Ann Armstrong, Janet Brown, all members of the Breast Group, and gathered views of patients from the Consumer Forum and ICPV to support the proposal for funding. Unfortunately, the study was not funded but the experience of working with the Group of researchers was very positive, with the patient voice highly valued.

Jan is supported by her scientific mentor, Iain Lyburn, and together with support from the Consumer Forum, helps her to fulfil her role as a Consumer Member on the Breast Group and to work effectively with the researchers on the Group.

Lesley Stephen

Lesley is a Consumer member of the main Breast Group, but mainly works with the Advanced Disease Subgroup, where she is the only Consumer member.

On the PRIMROSE TSC Lesley sought feedback from other patients on the PIS, and The Trial Investigator said this led to "smoother HRA and REC reviews". She helped expedite the set-up of

the TSC by quickly recruiting another patient representative and has informed her wider patient network, enabling the study to recruit and deliver results more quickly.

Lesley has created a short survey on the use of alternative therapies by MBC patients. The results will indicate how many patients use unapproved drugs and supplements, and the amount of money they spend. The Advanced Disease Subgroup hopes to use the results to deliver patient educational materials on alternative therapies and lead to greater awareness that these therapies do not 'cure' cancer.

Lesley led the development of a national survey on metastatic breast cancer patients' experiences of clinical trials, which will be launched in May 2021. She was involved from study design through to attending the final REC meeting, where she clarified why we need this data to better plan and support patients through trials. The results of the survey will be published in 2021 and may improve clinical practice.

Lesley's other main focus has been developing a new role within NHS Scotland, that of Patient Trial Advocate. A pilot is being run to educate MBC patients about research and match them to suitable UK clinical trials. If the pilot is successful, it will be rolled out to other areas. The impact could be significant – offering MBC patients the opportunity of a clinical trial which may improve their outcomes.

Other Consumer Members of the Breast Group's Subgroups

Mairead MacKenzie and Hilary Stobart are Consumer members on the Early Disease Subgroup. Hilary is also contributing to the Translational and Imaging Subgroup. Between them they represent patients on the SMALL study, HER2-Radical, PRIMETIME, C-TRAK and POETIC-A, all studies discussed at various stages in these Subgroups and also the UKBI.

The HER2-RADiCAL study involved de-escalation of treatment and Mairead and Hilary worked more widely with patients to explore the acceptability to patients on the extent of de-escalation studies.

They are both part of the Breast International Group patient partnership initiative and both are involved with UKBI which encourages new breast cancer studies.

Lesley Turner is a consumer member on the Symptom Management Subgroup. She Co-Chairs this group. She is a co-applicant and member of the Patient Advisory Group on the SWEET study.

With Mairead MacKenzie, Hilary Stobart and Lesley Turner, together with Lesley Stephen and Janice Rose as Consumer Members on the main Breast Group, there is patient representation on all the Subgroups.

7. Collaborative partnership studies with industry

There are numerous studies within the portfolio that involve industry collaboration, and many of these are in the area of metastatic disease, where the majority of studies are conducted in partnership with industry, who provide access to novel agents and/or funding to support such studies.

Recent key examples of these include:

- POETIC-A: this industry-funded, CRUK endorsed study of adjuvant abemiciclib in patients where pre-operative endocrine therapy causes incomplete suppression of Ki67 has been delayed by COVID-19. However, the trial is now in the process of set-up across the UK
- PHOENIX: this is 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). Again, the study has been delayed significantly due to COVID-19 but has recently opened several sites, with others in active set-up, and will commence recruitment in mid-2021

- The Group plans to develop further collaborative studies with industry in association with BIG over the coming year.

8. Priorities and challenges for the forthcoming year

The past year has been an enormously challenging year for the Breast Research Group, as it has been for all the NCRI Groups. While the restart and recovery of clinical research remains the current focus of the NIHR, and thus will not be discussed further here, this does present substantial ongoing challenges for the Group. Nevertheless, recovery from this difficult period does provide us with both key priorities as well as opportunities, as we seek to shape our vision of future UK breast cancer research, in line with the Government initiation for the future of research, as outlined in "The future of UK clinical research delivery".

Priority 1 Continuing the development of the breast cancer trial portfolio The reporting year has been a very successful one for the Group in terms of funding of studies, with several large NIHR-funded studies now in set-up. As we consolidate this success and start to deliver these studies within a difficult post-COVID environment, it is important that the Group continues to look to the future in this area and consider the development of further studies (both treatment de-intensification and intensification where appropriate, as well as non-IMP studies). The integral role of our PPI partners and the multidisciplinary nature of the Group and Subgroups will be integral to the successful continued development of our portfolio. We would also seek to avail of the open NIHR rolling call for studies to address NICE research recommendations, and we will seek to develop specific study priorities through our strategy work later in the year, including studies to address the needs of specific patient populations where there remains unmet need, including premenopausal breast cancer patients, patients with metastatic disease (particularly brain metastases) and studies in the key area of symptom management.
Priority 2 Build on existing international links to develop opportunities for working with international organisations The Group currently has the opportunity to participate in the next Breast International Group study in the adjuvant space, and this is a key opportunity for us to cement our links with international organisations. Importantly, particularly in light of the challenges brought to bear by Brexit, and the differences between research landscapes in the UK and the rest of the world, it is a priority for the Group to explore whether/how we can set up a UK-led BIG-supported trial in the coming year.
Priority 3 Developing trials to meet the requirements of the post-COVID research landscape In the future, it will be key for trials in our portfolio to be "future-proofed" to meet the challenges of delivering clinical research following the changes resulting from the pandemic, learning from how trials were designed and delivered rapidly during this time and translating these lessons into the cancer space. This will include modifying design and

delivery to incorporate innovations such as remote consent, digital data collection (including electronic patient reported outcomes) and the use of routinely collected NHS data for follow-up. Our priority will be to build these advances into future trials in our portfolio, ensuring that trials developed and endorsed by the Group meet with the vision of "The future of clinical research delivery".

Challenge 1

Balancing clinical service delivery with research and maintain trial recruitment in a challenging service environment

Embedding clinical research within service delivery has always been a challenge within the NHS, and it is likely that under current circumstances and with a backlog of clinical work resulting from the pandemic that this will remain the case. A key challenge for the Group in the coming year(s) will be to ensure that studies facilitate this wherever possible, simplifying design and processes to ensure that studies are rapid to set up and easy to deliver (incorporating approaches such as remote consent, use of routine data for follow-up). The integration of better uses of technology (both for trial delivery, such as electronically collected patient-reported outcomes) as well as its use for collaborative working (as demonstrated in the innovative use of online platforms for successful investigator meetings across many of our studies) will clearly also be integral to meeting this challenge.

Challenge 2

The current research funding landscape in the UK

In addition to funding bodies such as the NIHR, many trials in breast cancer have non-governmental funding sources, including charitable funder such as Breast Cancer Now and CRUK. Clearly, the financial position of these charities has been impacted by the pandemic, meaning that funding is likely to become ever more constrained and competitive. The challenge for the Breast Group will be to continue to develop its portfolio of innovative and practice changing studies within this difficult landscape. In addition to the need for recognition of this issue by the NIHR, this will require the Group to explore and exploit alternative funding streams such as commercial funding, as well as maximising opportunities such as the existing NIHR rolling call to meet research recommendations identified in NICE guidance.

Mr Stuart McIntosh (Breast Cancer Group Chair)

Appendix 1

Membership of the Breast Group

Name	Specialism	Location
Dr Carolyn Taylor	Clinical Oncologist	Oxford
Dr Duncan Wheatley	Clinical Oncologist	Cornwall
Ms Lesley Stephen	Consumer	Edinburgh
Mrs Janice Rose	Consumer	Gloucester
Dr Jean Abraham	Medical Oncologist	Cambridge
Dr Anne Armstrong	Medical Oncologist	Manchester
Professor Janet Brown	Medical Oncologist	Sheffield
Professor Carlo Palmieri	Medical Oncologist	Edinburgh
Dr Vijay Sharma	Pathologist	Liverpool
Dr Hannah Markham	Pathologist	Southampton
Professor Chris Lord	Scientist	London
Dr Kienan Savage	Molecular Oncologist	Belfast
Professor Janet Dunn	Professor of Clinical Trials	Warwick
Professor Iain Lyburn	Radiologist	Cheltenham
Dr Muthyala Sreenivas	Radiologist	Coventry
Professor Judith Bliss	Statistician	London
Mr Ramsey Cutress	Surgeon	Southampton
Ms Cliona Kirwan	Surgeon	Manchester
Mr Stuart McIntosh	Surgeon	Belfast
Ms Shelley Potter	Surgeon	Bristol
Ms Pankaj Roy	Surgeon	Oxford

Consumer Representation

Name	Location
Mrs Janice Rose	Gloucester
Ms Lesley Stephen	Edinburgh

Trainee Members

Name	Specialism	Location
Dr Indrani Bhattacharya*	Clinical Oncologist	London
Dr Adam Heetun*	Clinical Research Fellow	Southampton

Membership of the Subgroups

Early Disease Subgroup (UK Breast Intergroup)		
Name	**Specialism**	**Location**
Professor Andrew Tutt	Clinical Oncologist	London
Ms Mairead MacKenzie	Consumer	London
Mrs Hilary Stobart	Consumer	Nottingham
Mrs Janice Rose	Consumer	Gloucester
Professor Judith Bliss	Statistician	London
Ms Cliona Kirwan	Surgeon	Manchester
Dr Stuart McIntosh (Chair)	Surgeon	Belfast
Dr Adam Heetun	Surgeon	Southampton

Advanced Disease Subgroup		
Name	**Specialism**	**Location**
Dr Duncan Wheatley	Clinical Oncologist	Cornwall
Dr Catherine Pembroke	Clinical Oncologist	Cardiff
Dr Sara Meade	Clinical Oncologist	Birmingham
Ms Lesley Stephen	Consumer	Edinburgh
Dr Anne Armstrong	Medical Oncologist	Manchester
Dr Gianfilippo Bertelli	Medical Oncologist	Sussex
Dr Catherine Harper-Wynne	Medical Oncologist	London
Dr Iain MacPherson	Medical Oncologist	Glasgow
Professor Carlo Palmieri (Chair)	Medical Oncologist	Liverpool
Dr Rebecca Roylance**	Medical Oncologist	London
Professor Peter Schmid	Medical Oncologist	Brighton
Dr Nicholas Turner**	Medical Oncologist	London
Nicky Marshall	Patient representative	London
Professor Jason Carroll	Senior Group Leader	Cambridge

Translational & Imaging Subgroup		
Name	**Specialism**	**Location**
Dr Kienan Savage	Scientist	Belfast
Mrs Hilary Stobart	Consumer	Cambridge
Professor Rob Stein	Medical Oncologist	London
Professor John Bartlett *	Pathologist	Ontario, Canada
Professor Sarah Pinder	Pathologist	London
Professor Emad Rakha	Pathologist	Nottingham
Professor Alastair Thompson *	Surgeon	Houston, USA
Professor Janet Dunn	Statistician	Warwick
Mr Stuart McIntosh	Surgeon	Belfast
Professor Nick Stone	Scientist	Exeter
Professor Keith Rogers	Scientist	Cranfield
Dr Vijay Sharma	Pathologist	Liverpool
Dr Colin Purdie	Pathologist	Bristol
Dr Muthyala Sreenivas	Radiologist	Coventry
Dr Sarah Storr	Pathologist	Leeds

Professor Iain Lyburn (Chair)	Radiologist	Cheltenham

Symptom Management Subgroup		
Name	**Specialism**	**Location**
Dr Adrienne Morgan	Consumer	London
Mrs Lesley Turner (Co-Chair)	Consumer	Southampton
Ms Janice Rose	Consumer	Gloucester
Dr Jenifer Sassarini	Clinical Lecturer	Glasgow
Dr Lyndsay Hughes	Psychologist	London
Dr Anne Armstrong (Co-Chair)	Medical Oncologist	Manchester
Dr Debbie Fenlon	Nurse	Swansea
Dr Melanie Flint	Senior Lecturer in Immunopharmacology	Brighton
Professor Janet Dunn	Statistician	Warwick

* denotes trainee member
**denotes non-core member

Appendix 2

Breast Group & 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.

The overarching strategic aim of the Group remains as above. In 2021 we will undertake a review of the overall Group strategy, with a strategy round table review in Summer 2021 to include the Chair and Subgroup Chairs as well as other key stakeholders (consumers, funders, collaborating groups such as BIG) as well as international invited experts. Subsequently the Chairs will develop a strategic plan which will be taken to the wider group in Autumn 2021 for further discussion and refinement, and specific strategic objectives with metrics and timelines will be developed to align with the Group's restructure.

In the interim, the existing strategic aims can be grouped into a number of main headings, with some key associated objectives and timelines outlined below.

1. **Facilitate clinical trial access for breast cancer patients**

    a. Ensure that all breast cancer patients have the opportunity to take part in research with access to a wide range of studies.
    b. Increase patient expectation of being involved in a clinical trial.
    c. Empower and educate patients and the public to drive a research-oriented culture within the provision of routine care.
    d. Ensure equality of access for all patients through developing appropriate referral pathways and extended PIC sites for complex studies.
    e. Embed a research culture across the entire patient pathway within all healthcare professionals and in all institutions providing breast cancer services.

The Group's patient advocates have been at the forefront of leading this work, with a national survey on metastatic patients' experiences of clinical trials led by Lesley Stephen due to be published in 2021. The pilot work within NHS Scotland on Patient Trial Advocacy will also begin in 2021, and if successful ways of rolling this out more widely will be evaluated.

2. **Support and develop multidisciplinary and international collaborations**
    a. Develop international collaboration with the Breast International Group
    b. Strengthen links with other NCRI CSGs, HCIS and Advisory Groups.
    c. Strengthen links other professional associations which impact on the ability to deliver trials.
    d. Extend trainee collaborative to oncologists, radiologists and pathologists.
    e. Further develop the interaction with the CSG and the CLRN subspecialty research leads.

The Group continue to work with BIG, and in 2021/22 will seek to more clearly define the links between BIG and the UK member organisations (NCRI BRG and ICR-CTSU). The UK has the opportunity to participate in the next BIG study which will commence in 2021/22. Additionally, the

set-up of a UK-led BIG-supported trial remains a potential challenge, but this will be explored in 2021 through the development of the brain metastases prevention study being led by Carlo Palmieri.

Within the UK, the Group will continue to develop links with other professional associations such as the Association of Breast Surgery and will support the completion of the Breast Cancer Surgery Research Priority Setting Partnership in 2021. We will continue to support the Trainee Collaborative in the completion and presentation/publication of their ongoing projects, with the CNS disease registry expected to be presented in 2021. Furthermore, the Group will provide input for the Collaborative's Annual Meeting later in 2021, whether virtual or in person, in order to support the development of future projects. The Group will engage with the NCRI's Proposal Guidance meetings and other cross-cutting NCRI initiatives in 2021 – including the SPED proposal guidance workshop in May 2021 and the upcoming NCRI Bone Metastases workshop, with the aim of supporting the development of new cross-cutting proposals where appropriate.

3. **Continue to develop the trials portfolio to improve methodology and clinical utility**
    a. Optimise trial design to adequately answer specific questions within the confines of the current and future health care environment.
    b. Ensure a balanced portfolio of clinical trials with appropriate mix of complexity to allow full exploitation of clinical trial expertise and capacity.

The Group will continue to support the twice-yearly UK Breast Intergroup meetings, which provide a key opportunity to engage with the broader research community beyond the Research Group, both to support the development of new trial concepts, and to inform researchers of progress with the portfolio.

In 2021 the Group will open several new key trials, including HER2-RADiCAL and POETIC-A, both of which clearly align with our key strategy of risk-adapting treatment in early disease. We will continue to explore the possibilities of risk-adapted studies, including potential escalation studies in the neoadjuvant setting where patients do not have a complete response to neoadjuvant therapy; however, the development of further such studies will depend on the successful delivery of the portfolio currently in set-up.

The Group, through the Early Disease Subgroup will build on themes identified in recent work with patients in identifying research priorities (Boundoki et al, BMJ Open 2021) and will seek to develop proposals for trial concepts around non-IMP trials, to broaden the portfolio, in particular exploring topics such as exercise and prehabilitation. In light of the recently opened current NIHR rolling call for research studies addressing NICE research recommendations, the main Group and Subgroups will seek to develop to address these recommendations.

4. **Support the future delivery of breast cancer clinical research within the NHS**
    a. Support the embedding of clinical research delivery into NHS practice
    b. Integrate streamlined, efficient and innovative approaches to trials within the breast portfolio
    c. Support the use of routine data and digital tools in the design and delivery of future trials
    d. Continue to support the engagement of the broader clinical workforce with the trial portfolio, including training the next generation of clinical researchers

The Breast Research Group will work towards ensuring that future trials will be designed to meet the contemporary needs of the post-COVID research landscape, allowing simplification of trial requirements and utilising novel approaches which have become more common during the pandemic, such as the use of remote consent, the use of routine data for follow-up and the use of electronic patient reported outcomes. Future trials developed through the Group will be expected to agree with this aim of simplifying aspects of their design wherever possible.

The Group is known for its multidisciplinary nature as exemplified by the breadth of membership of the main Group and Subgroups and we wish to continue to build on that. The use of virtual meetings and videoconference has undoubtedly allowed us to extent our reach and engage more widely than previously across the research and clinical communities as a whole. We would seek to maintain the use of such virtual platforms in future, in combination with conventional "face to face" meetings to continue this engagement. The Group will also ensure that new studies are members of the NIHR's Associate PI Scheme, to support the development of the clinical researchers of the future.

B – Early Disease Subgroup Strategy

1. Portfolio development

a. Risk adaptation studies:

The Subgroup has contributed to a successful year of portfolio development, with several key studies successfully funded and now in set-up. One of the main themes of the Early Disease Subgroup remains risk-adaptation trials, with treatment in these trials being modulated according to risk – with the emphasis in many of these studies being treatment de-intensification. Currently the Subgroup will aim to consolidate this aspect of the portfolio, with a view to developing further risk-adapted studies as appropriate (e.g. treatment escalation in non-complete responders to neoadjuvant therapy)

b. Non-CTIMP trials

As highlighted by recent published patient engagement work (Boundoki et al, BMJ Open 2021) and discussed at the most recent UK Breast Intergroup meeting, there is a need to broaden the portfolio to include areas such as the impact of exercise on breast cancer risk and outcomes, and prehabilitation. The Early Disease Subgroup will develop a working group to examine the opportunities and possibilities in these areas.

c. Systemic therapy

The Subgroup will coordinate the participation of the Breast Research Group in the upcoming BIG-led study in the adjuvant endocrine therapy space, ensuring that the UK is able to maximise its contribution to this important global study.

d. Translational research

The Subgroup will continue to work with the Translational and Imaging Subgroup to ensure that translational research is integrated into all trials wherever possible.

2. **Collaborative approach to trial development and participation**

a. Building on an excellent track record of collaborative trial development, the Subgroup will continue to engage with the breast cancer clinical research community to develop and deliver highly competitive international studies, through the UK Breast Intergroup, the UK Interdisciplinary Breast Cancer Symposium
b. Continue to promote PPI involvement in discussion of both concepts and generic considerations (e.g. multiple tissue and blood sampling),. This will be done by continuing to ensure that appropriate forums for discussion exist, that PPI representatives are adequately represented at all meetings, and that meeting formats are optimised to ensure efficiency and minimise inconvenience for PPI representatives (building on the increasing usual of videoconferenceing and virtual meetings seen in the last 12 months).
c. Continued linkage with CTRad to develop radiotherapy studies
d. Engagement with the Association of Breast Surgery will allow the Subgroup to support initiatives to increase clinical research engagement across specialties
e. Maximise opportunities for international collaboration (e.g. with BIG as both a member group and a lead group).

3. **Improve trials methodology and clinical utility**

a. Continued engagement with trials methodologists for optimised trial designs, to maximise efficiency.
b. Continue to ensure compatibility of studies within the UK portfolio as far as possible.
c. Work towards "future-proofing" of studies as outlined in the main group strategy to ensure that trials are efficient and utilise appropriate novel approaches to facilitate rapid set-up and delivery.

C – Advanced Disease Subgroup Strategy

1. **Portfolio development and management**

The Subgroup collaborates with pharmaceutical partners and charities to develop of a broad portfolio of academic portfolio. The Subgroup continues to collaborate with pharmaceutical partners and charities to deliver academically led studies. The most recent examples include:

(1) The PAveMenT Trial: Phase Ib Study of Palbociclib and Avelumab in Metastatic AR+ Triple negative breast cancer (CI: Alicia Okines) funded via the Breast Cancer Now Catalyst programme.
(2) Phase II study of Crizotinib in E-cadherin negative ER positive lobular breast and diffuse gastric cancer, triple negative lobular breast cancer or CDH1-mutated solid tumours (ROLO study), this study will recruit breast as well as a basket cohort of CDH1-mutated tumours.

2. **Patient Advocates**

Patient representatives remain a central and key part of the activities of the subgroup and are very active. The input and involvement of our patient advocates is intrinsic to all the activities of the group. All academic led studies continue to have involvement of a patient advocate in their development and delivery; and all studies presented at the UK Breast Intergroup meetings have patient feedback as part of the RAG assessment process. A national patient questionnaire to understand the needs of the patients with metastatic breast cancer in the context of clinical studies has recently been launched following ethical approval. The questionnaire is being distributed widely via clinicians, patient forums and breast cancer now and Maggie's centres. The aim is to gather at least a thousand responses. It is hoped that the questionnaire can help inform and shape future approaches to research in regard to metastatic breast cancer. The planned MBC

patient led conference, that was planned in October 2020 was cancelled because of the pandemic. The aspiration remains for an in-person conference therefore the plan is to revisit when it might be possible to hold such an event. Lesley Stephens our patient advocate remains key in helping to deliver this.

3. **Current challenges**

The SARS-CoV-2 pandemic impacted on clinical trial activity and while trial activity has restarted there remain significant issues. The impact of funding for translational and clinical studies by the charitable sector given the significant loss of income due to the pandemic remains an ongoing risk.

4. **Brain metastasis studies**

Development of translational and clinical trials for CNS disease remains a strategic priority for the subgroup. A project to collect 300 paired primary and metastatic tissue blocks is to begin recruitment very shortly and it is hoped this help drive forward translational research in this area, the project is funded by Daiichi-Sankyo (PI: Carlo Palmieri). While a study to assess the feasibility of collecting CSF to enable the characterisation of cfDNA funded by NW Cancer (CI: Carlo Palmieri), the collected samples will be used to assess the genomic landscape of tumours will open in the summer of 2021. A proposal developed by Prof Palmieri via the Breast International Group (BIG) Brain Metastasis Task Force, to undertake a primary prevention study in patients with HER2 positive metastatic breast cancer is in the advanced stages of development. The proposal would involve patients with extracranial disease only being randomised to standard of care versus standard of care plus tucatinib with the aim to assess the potential to prevent CNS disease. The proposal has been discussed with Seagen and the company has requested a formal submission for consideration.

5. **Trainees and education**

A number of studies developed via the Breast Cancer Trainee Research Collaborative Group (Led by Ellen Copson) are ongoing. 1. The long term herceptin project is currently recruiting with 11 UK centres enrolled and collecting data (ALTRA). This study is seeking to end recruitment towards the end of 2021. 2.The National investigation of tolerability of CDK4/6 inhibitors in the elderly population has received supported from industry to facilitate its delivery and 3. Registry for CNS disease in breast cancer and to date over 400 patients have been registered and an initial abstract submitted for the San Antonio Breast Cancer Symposium 2021. All projects have been affected by the SARS-CoV-2 pandemic. An annual meeting of the Breast Cancer Trainee Research Collaborative Group is being planned for September/October 2021.

D – Translational & Imaging Subgroup Strategy

As the new model of the wider CSGs evolves the Translational & Imaging Subgroup may further morph into a panel of experts with particular niche interests, which clinical members of main breast CSG (and other tumour sites) will be encouraged to approach for advice and information on trial ideas and the practical aspects of feasibility and set up. It would aim to keep an international perspective with overseas panel members who can frequently provide a different perspective. It is recognized that the diversity of the group is both a strength and a weakness. A great strength is the range of expertise across the domains of translational medicine and imaging. A weakness however is the absence of a central focus probably not feasible given the breadth of subspecialties. The group feels it is best placed as a bank of potential friendly advisers. As alluded to above it is likely there will be a large focus on the appropriate evaluation and deployment of artificial intelligence in translational and imaging elements in trial design in the future.

E - Symptom Management Subgroup Strategy

The Symptom Management Subgroup's ongoing strategy currently has its main focus on urogenital atrophy and sexual health issues. The same strategy that was used for hot flushes and night sweats will be used to develop three streams of work:

1. Identifying gaps in current research in symptom management
2. Supporting the development of new research into these newly identified gaps
3. Supporting the development of new interventions in these key research areas.

As always, we will liaise with other NCRI Research Groups where appropriate, to ensure that research into other symptoms related to breast cancer is being supported in the most relevant Group.

Appendix 3

Top 5 publications in the reporting year

Trial name & publication reference	Impact of the trial	CSG involvement in the trial
1. FAST-FORWARD Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial AM Brunt, JS Haviland,DA Wheatley, MA Sydenham, A Alhasso, DJ Bloomfield, C Chan, M Churn, S Cleator, CE Coles,A Goodman, A Harnett, P Hopwood, AM Kirby, CC Kirwan,C Morris, Z Nabi, E Sawyer, N Somaiah, L Stones, I Syndikus, JM Bliss, JR Yarnold, On behalf of the FAST-Forward Trial Management Group The Lancet 2020;395:1613-1626 DOI:https://doi.org/10.1016/S0140-6736(20)30932-6	NIHR HTA-funded FAST FORWARD study showing that hypofractionated radiotherapy delivered in 1 week is non-inferior in terms of local control to an international standard 15 fraction regimen. Hypofractionated treatment was rapidly adopted across the UK in 2020 as a consequence of this practice-changing trial	This study was developed through the Group with several Group members directly involved with the trial design and delivery.

2. Monarch-E Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2−, Node-Positive, High-Risk, Early Breast Cancer (monarchE) SRD Johnston, N Harbeck, R Hegg, M Toi, M Martin, MD, ZM Shao, QY Zhang, JLM Rodriguez, M Campone, E Hamilton, J Sohn, V Guarneri, M Okada, F Boyle, P Neven, J Cortés, J Huober, A Wardley, SM Tolaney, I Cicin, IC Smith, M Frenzel, D Headley, R Wei, B San Antonio, M Hulstijn, J Cox, J O'Shaughnessy, P Rastogi on behalf of the monarchE Committee Members and Investigators Journal of Clinical Oncology 2020;38:3987-3998	This study showed abemiciclib in combination with endocrine therapy to be the first CDK4/6 inhibitor to demonstrate a significant improvement in invasive disease free survival in patient with high risk hormone receptor positive HER2 negative disease in the adjuvant setting (HR 0.75, 95% CI 0.60-0.93).	Monarch-E is an international industry sponsored and NCRI badged study with leadership from within the UK breast cancer research community. The success of this study demonstrates the ability of the UK to work with industry and contribute at a global level to practice changing research
3. PALLAS Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study EL Mayer, C Dueck, M Martin, G Rubovszky, HJ Burstein, M Bellet-Ezquerra, KD Miller, N Zdenkowski, EP Winer, G Pfeiler, M Goetz, M Ruiz-Borrego, D Anderson, Z Nowecki, Sibylle Loibl, S Moulder, A Ring, F Fitzal, T Traina, A Chan, HS Rugo, J Lemieux, F Henao, A Lyss, SA Novoa, AC Wolff, M Vetter, D Egle, PG Morris, EP Mamounas, MJ Gil-Gil, A Prat, H Fohler, OM Filho, M Schwarz, C DuFrane, D Fumagalli, KP Theall, DR Lu, CH Bartlett, M Koehler, C Fesl, A DeMichele, M Gnant Lancet Oncology 2021;22:212-222	PALLAS compared adjuvant endocrine therapy alone with adjuvant endocrine therapy plus Palbociclib in HR+ HER2- early breast cancer, and did not show a benefit for the combination treatment in this interim analysis (HR 0.93, 95% CI 0.76-1.15)	PALLAS was a BIG-led global trial badged by the NCRI and delivered at multiple UK sites, once again demonstrating the Breast Group's ability to deliver key trials within an international collaboration

4. POETIC Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial I Smith, J Robertson, L Kilburn, M Wilcox, A Evans, C Holcombe, K Horgan, C Kirwan, E Mallon, M Sibbering, A Skene, R Vidya, M Cheang, J Banerji, J Morden, K Sidhu, A Dodson, JM Bliss, M Dowsett Lancet Oncology 2020;21:1443-1454	This large (> 4000 patients), multidisciplinary UK study demonstrated that a failure to suppress Ki67 using pre-operative endocrine therapy could predict patients with hormone receptor positive breast cancer who may be at high risk of recurrence and who may benefit from additional adjuvant therapies. This trial has informed the development and design of the industry funded, CRUK endorsed POETIC-A study which is currently in set up in the UK.	This study demonstrates the ability of the NCRI Breast Group to develop leading-edge research subsequently delivered through national multidisciplinary collaboration between surgeons and oncologists, supported by the Group and Subgroups. It has informed the development of the subsequent POETIC-A study which has also been developed through the Group.
5. plasmaMATCH Circulating tumour DNA analysis to direct therapy in advanced breast cancer (plasmaMATCH): a multicentre, multicohort, phase 2a, platform trial C Turner, B Kingston, LS Kilburn, S Kernaghan , AM Wardley, IR Macpherson, RD Baird, R Roylance, Stephens, O Oikonomidou, JP Braybrooke, M Tuthill, J Abraham, MC Winter, H Bye, M Hubank, H Gevensleben, R Cutts, C Snowdon, D Rea, D Cameron, A Shaaban, K Randle, S Martin, K Wilkinson, L Moretti, M Bliss, A Ring Lancet Oncology 2020;21:1296-1308	This study has shown that 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. 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.	This innovative study was developed through the NCRI Breast Group and shows the key role of the Group's multidisciplinary collaborations in developing internationally leading research with the potential to change practice in advanced breast cancer.

Appendix 4

Recruitment to trials in the NIHR portfolio

Summary of patient recruitment by Interventional/Non-interventional and number of studies opened/closed.

Year	All participants		Cancer patients only*		Number of studies	
	Non-interventional	Interventional	Non-interventional	Interventional	Opened	Closed
2016/17	4155	7869	4152	7860	51	44
2017/18	3338	9750	3330	9750	45	41
2018/19	5025	9998	4547	9998	51	50
2019/20	3907	13960	3706	12380	51	39
2020/21	2834	5282	2468	5256	27	25

*This data is based on a proxy from CPMS (the NIHR database used to collect patient recruitment data) and includes diagnostics, screening and prevention patients.

Appendix 5

Annual report feedback 2019-20

06 November 2020

Dear Andrew

Re: NCRI Breast Group Annual Report 2019-20

Thank you for submitting an annual report for the Breast Group for 2019/20, especially given the challenges with the ongoing COVID-19 pandemic which will have impacted on both the Group and the report itself.

All the Group's annual reports were reviewed at a two-day meeting on the 12th and 13th October 2020 by a panel consisting of some former NCRI Group Chairs, NCRI CMPath Chair, former NCRI CTRad and the current NCRI Strategic Advisory Group (SAG) Chair, NCRI Head of Research Groups and representatives from the NIHR Cancer Coordinator Centre, NHS Cancer Alliances, epidemiology, CTU/basic science, allied health profession, NCRI Consumer Forum and the Canadian Cancer Clinical Trials Network.

We are writing to you now with a summary of the feedback which is based on the information provided in the report. It was noted that there is likely to be more activity taking place within the Group than is documented.

Please share the contents of this letter with your members for discussion at the next Group meeting.

Generic feedback for all the Groups

Strategic objectives and the impact of COVID 19

- Due to the research funding challenges and restrictions on NHS resources resulting from COVID 19, the Panel recommended the Groups evaluate their strategic objectives and focus on the most important priorities or questions that need to be answered as it would not be feasible for the Groups to be doing everything they planned or continue to "plug in the gaps." Additionally, the Panel suggested looking for more cost-efficient methods of working where they can.
- The Panel felt that the strategic objectives for most Groups were too broad especially in the current climate. The Groups were asked to provide specific, measurable aims for their strategic objective and attach timelines/metrics to them.

Multidisciplinary approach to research and membership

- The Panel noted the importance of collaborative and multidisciplinary working, especially in the current climate, and would encourage all Groups to continue to reach out to other relevant NCRI Groups and consider the NCRI strategic priorities where appropriate.

Linking with the wider research community

- The Groups were asked to link with the wider research community and engage with relevant networks, in particular, with researchers who are developing or are running large national platform studies when there is one available in the disease site e.g. PrecisionPanc (Upper GI Group) and TRACERx (Lung Group). The NCRI recognised that there is a role for them to play in promoting collaboration and will be working with the partners to encourage greater interaction between the Groups and the networks in future.

Funding opportunities

- Given the potential decrease in funding opportunities, the Groups are encouraged to explore alternative funding sources and collaborations e.g. with industry, government funders, NHS Cancer Alliances etc.

Consumers involvement:

- The Panel encouraged Groups to integrate public and patient involvement (PPI) in all aspects of the Group's activities e.g. study design, proposal development, prioritisation of strategic areas etc.
- The Panel wanted to ensure that the consumer activity was captured throughout the report and not just in the consumer section, especially where the consumer reports are missing.

Specific feedback for the Breast Group

Areas of strength:

- The Panel felt that Group's research is highly impactful and practice changing and extends beyond conventional trials of new drugs.
- The Group demonstrated a clear strategy, unified with the subgroups and with the top four strategic aims being entirely patient-centred.
- The multidisciplinary nature of the Group's work and membership was commended by the Panel, with the outstanding consumer contribution and inclusion of translational science being of note.
- The Group's interest in improving trials methodology was recognized by the Panel including the recruitment of two very keen methodologists to explore novel trial design.
- The Panel was impressed with the interaction of the Group with the Breast Intergroup (BIG), displaying the Group's strong links with international networks.
- The Panel recognised the strength of the consumer involvement. In particular having a consumer member co-chair the Symptom Management Subgroup was praised; the NCRI will explore whether this could be adopted by other Groups/Subgroups as appropriate.
- The Group was commended for their use of a questionnaire to investigate the barriers to trial set-up, which has been valuable when referring back to funders and others as to the importance - and challenges of - the work being undertaken.

- The Panel suggested that the Group include a pathologist to aid the implementation of digital methods such as AI into their research and diagnostics.
- The Panel recommended that the Group think about including innovative radiotherapy as part of their objectives and consider collaborating with CTRAD to discuss this further.
- The Panel thought that including nurses and specialists in supportive care interventions on the Group may be useful. The Group should think about which objectives might be best to incorporate these specialists and the benefits they would achieve from these additions.
- Configuring the service to enable forward looking research and having the molecular data at the time of the first diagnosis to allow neoadjuvant chemotherapy or systemic therapy to be offered (or trials using these treatment methods).
- The Panel thought that there could be more interaction with the NCRI Groups, for instance, Gynaecological Group to look at risk reduction for the BRCA1/2 patients, the Sarcoma Group for breast sarcomas and Prostate Group for overlapping mechanisms in nuclear receptor/hormone receptor driven malignancies (this was a minor point).

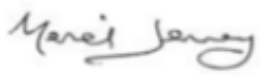
Areas requiring further clarity due to limited information provided in the report as a result of COVID 19:

- The Panel agreed that the report was focused on the progress the Group had made towards their strategic aims but would have liked to see a little more about their future plans. The Panel suggested that the Group gain support from the NCRI to aid in the creation of clear timelines, outputs and priorities at their strategy day in the coming year.

Congratulations to you and your members for all your hard work and achievements in 2019/20.

If you have any comments on this year's process, please send them to Nanita Dalal (Nanita.Dalal@ncri.org.uk) for collation.

Best wishes,



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Appendix 6

Quinquennial review feedback - 2019

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.

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