

## **NCRI Breast Cancer Clinical Studies Group**

### **Introduction**

The Breast Clinical Studies Group (BCSG) remains the most active CSG, and has successfully initiated and recruited to a number of innovative and practise changing studies. The adjuvant systemic therapy trials and radiotherapy studies are seen as the areas of greatest achievement. Recruitment remains good and the Breast CSG continues to play a major role in the success of the NCRN, and accounts for 35% of all NCRN trials activity (23% if the large ovarian cancer screening trial is included). The portfolio is very large but within it, despite many successful trials, are unfortunately a number of failing randomised controlled trials (RCT), particularly in elderly patients and those with metastatic disease. Significant challenges face the Group and the breast cancer community in successfully concluding the remaining portfolio and activating new internationally competitive, high recruiting trials.

Among the notable events in 2008/9 were the publication of the results from the TACT trial comparing docetaxel containing chemotherapy (FEC-T) to one of two non taxane containing regimens (FEC or Epi-CMF) (Ellis et al, Lancet 2009) and of the START trial (Yarnold et al, Lancet 2008, Yarnold et al Lancet Oncology 2008).

### **Membership and structure**

The Group has welcomed three new scientific members this year and would like to thank the committee members who stepped down at the end of their terms of office for their most valuable contributions over several years. In total there are twenty-seven scientific members, three consumer representatives and seven observers or funding body representatives.

The scientific members continue to represent the multidisciplinary nature of breast cancer with breast surgery, clinical and medical oncology, pathology, radiology, cancer genetics, cancer nursing and translational research all represented as well as representation from the Clinical Trials Units (CTU).

The restructured Pathology and Functional Imaging Subgroup under the chairmanship of Dr Rob Stein has been active in terms of applications to TRICC/BIDD as well as investigating how best to develop the involvement of pathology into translational research. The UK Breast Intergroup (UKBI) and the Advanced Disease Subgroup have met several times in the past 12 months. Both act as subgroups of the BCSG and report to the main committee three times a year.

UKBI is an open membership group of over 650 breast cancer researchers co-ordinated by the chairman, Professor Ian Smith, a vice-chairman, Dr Peter Barrett-Lee and the BCSG Chairman. Two open meetings have been held in January and June to develop new trials in early breast cancer and a website for exchange of ideas established. Several trials are being developed as a result of these meetings. It is also clear that the new structure is leading to better communication with international collaborative groups (especially the Breast Intergroup (BIG)) and the pharmaceutical industry.

The Advanced Disease Subgroup is now chaired by Professor Ian Kunkler and a number of new research initiatives are in development with close involvement of consumers. It was clear through feedback from oncologists across the country that their priority for research was access to new agents. Consequently the Subgroup is promoting a broad range of industry sponsored studies as well as developing two pragmatic RCTs. These will assess the role of rechallenge with agents used in the

adjuvant setting and the value of adding a novel oral anticoagulant, dabigatran to standard chemotherapy on survival.

We have two successful project officers; Roger Burkinshaw who has investigated barriers to accrual to metastatic trials and is facilitating the development of new pragmatic trials and helping to co-ordinate the rapidly expanding industry portfolio. The other, Lucy Kilburn, is addressing the ever increasing problem of follow-up, trying to balance the need for long term outcome data against the volume of data management that is limiting the research capacity at network level. Additional administrative support is provided by the Institute for Cancer Research in terms of organising the annual trials day meeting and supporting UKBI.

### Portfolio and accrual

The BCSG has a large and varied portfolio which is listed in Table 1 below.

**Table1: Breast CSG portfolio**

Acronym	Title	PI(s)	Status
ACTION	Adjuvant chemotherapy in older women	Professor Robert Leonard	Abandoned
ACU-FATIGUE	The effectiveness of acupuncture and self-acupuncture in managing cancer-related fatigue in breast cancer patients: a pragmatic randomised trial	Professor Alexander Molassiotis	Open
AFFECT	Examination of affected tissue of BRCA1 variant carriers	Dr Jo Morris	Open
ALLTO	A randomised comparison of adjuvant trastuzumab or lapatinib alone, in combination or in sequence for HER2+ early breast cancer	Professor Ian Smith	Open
ALMANAC	A randomised trial of sentinel node guided axillary therapy compared with standard axillary therapy in early breast cancer	Professor Robert Mansel	Closed
AMAROS	After Mapping of the Axilla: Radiotherapy Or Surgery: EORTC 10981-22023	Professor Robert Mansel	Open
AMWELL-SL	An exploratory study to evaluate the use of acupuncture and moxibustion to promote wellbeing and improve quality of life in patients with secondary lymphoedema	Dr Beverley de Valois	Open
Annual zoledronate	Effect of an annual infusion of zoledronate on bone mineral density in patients with treatment induced bone loss	Professor Rob Coleman	Closed
ARTemis	Avastin randomised trial with neo-adjuvant chemotherapy for patients with early HER 2 negative breast cancer.	Dr Helena Earl	Open
ATN-224	A Cancer Research UK randomised phase II trial of ATN-224 (copper	Professor Adrian Harris	Abandoned

	binding agent) in combination with exemestane versus exemestane alone in postmenopausal women with recurrent or advanced, oestrogen and/or progesterone receptor positive breast cancer		
aTTom	A large, uniquely simple, randomised study to assess much more reliably the balance of benefits and risks of prolonging adjuvant tamoxifen treatment in early breast cancer	Professor Richard Gray, Dr Daniel Rea	Closed
AZURE (including the 'Bone Cancer in breast cancer survivors' sub-study)	Does adjuvant zoledronic acid reduce recurrence in patients with high risk localised breast cancer	Professor Rob Coleman	Closed but substudy in set up
B-AHEAD	Randomised comparison of 3 weight control programmes during adjuvant treatment for early breast cancer (Breast - Activity & Healthy Eating After Diagnosis)	Dr Michelle Harvie	Open
BASO DCIS II	Observation versus radiotherapy in low risk completely resected DCIS on adjuvant endocrine therapy	Professor Nigel Bundred	Abandoned
BBC Study	A national population-based study of treatment effect and endocrine, genetic and cellular risk factors for contralateral primary breast cancer in women in Britain	Professor Julian Peto	Open
BBC-NCRN cohort study	British Breast Cancer study - NCRN cohort	Professor Julian Peto	Open
BEATRICE	An international multi-centre open-label 2-arm phase III trial of adjuvant bevacizumab in triple negative breast cancer	Professor David Cameron	Open
BETTER-CARE Study	Breast cancer, early disease: toxicity from therapy with adjuvant epirubicin regimens: cardiac assessment and risk evaluation study	Dr Hugh Montgomery	Open
Biology of the Normal Breast	Biology of the normal breast	Prof Clare Isacke	Open
BISMARK	Cost-effective use of BISphosphonates in metastatic bone disease - a comparison of bone MARKer directed zoledronic acid therapy to a standard schedule	Professor Rob Coleman	Closed
BRESDEX	A decision explorer for women	Professor Glyn Elwyn	Open

	deciding about breast cancer treatments: BresDex		
BRCA Trial	Breakthrough Breast Cancer & Cancer Research UK genetic breast cancer trial: A randomised phase II pilot trial of docetaxel compared to carboplatin for patients with metastatic genetic breast cancer	Dr James Mackay	Open
CADET 2	Prospective study to compare computer aided detection versus conventional double reading in the breast cancer screening programme	Professor Fiona Gilbert	Closed
Chronic Pain after Breast Surgery	Chronic pain after breast cancer surgery	Dr Julie Bruce	Open
Childhood Trauma	Towards the prediction and management of long-term distress after treatment for breast cancer: the role of childhood trauma	Professor P Salmon	Closed
CliMB/EGF100151	Capecitabine +/- lapatinib in metastatic breast cancer – a randomised phase III study	Professor Rob Coleman	Closed
Cognitive Effects of Chemotherapy	Observational longitudinal study of the effects of adjuvant chemotherapy on cognition on women with breast cancer	Dr David Bloomfield,	Closed
COMICE - 99/27/05	Multi-centre randomised controlled trial examining the cost-effectiveness of contrast-enhanced high field magnetic resonance imaging in women scheduled for wide local excision	Professor Lindsay Turnbull	Closed
Continuity of Cancer Care	Concern and continuity in the care of patients with cancer and their carers: A multi-method approach to enlightened management.	Professor Michael King	Closed
Coombes Study 77	A randomised, double-blind, multicentre phase ii trial to evaluate the biological effects, safety and pharmacokinetics of single agent zd1839 (iressatm) and zd1839 in combination with anastrozole (Arimidex®) in patients with primary breast cancer	Professor Charles Coombes	Closed
Coping with cancer	Socio-economic status and coping with cancer – Examining the experience of people recently diagnosed with cancer	Miss Alice Simon	Closed
COS	Case-Only Study on the interaction of diet and genetic predisposition in the occurrence of breast cancer in young women.	Ms L Sharp	Closed
DEVA	A multicentre randomised trial of sequential epirubicin and docetaxel vs.	Professor Charles	Closed

	epirubicin in node +ve postmenopausal breast cancer	Coombes	
DietCompLyf	The role of diet, complementary treatment and lifestyle in breast cancer survival	Dr Tony Leathem	Open
EATIMS	A pilot study to evaluate the effectiveness and acceptability of using auriculotherapy in a small group setting to manage the menopausal-type symptoms (specifically hot flushes and night sweats) in women taking tamoxifen, anastrozole (Arimidex) or letrozole (Femara) as an adjuvant treatment for early breast cancer.	Dr Jane Maher, Teresa Young, Beverley de Valois	Closed
EORTC 22922	Phase III randomized trial investigating the role of internal mammary and medial supraclavicular (IM-MS) lymph node chain irradiation in stage I-III breast cancer (joint study of the EORTC Radiotherapy and Breast Groups)	Walter Van Den Bogaert	Closed
EMBRACE	Epidemiological study of BRCA1 and BRCA2 mutation carriers	Professor Doug Easton	Open
ERISAC	Effects of exemestane and COX-2 inhibition on oestrogen receptor positive ductal carcinoma in situ.	Professor Nigel Bundred	Closed
ESTeEM	Endocrine therapy or surgery for elderly patients with early breast cancer	Miss Lynda Wyld	Closed
Exercise Study SHERBERT	The effects of exercise therapy upon quality of life in women who have had breast cancer	Dr Amanda Daley	Closed
FABCC	Familial Association in Breast Cancer Collaboration	Professor Julian Peto	Closed
FAST	Prospective randomised clinical trial testing 5.7Gy and 6.0Gy fractions of whole breast radiotherapy in terms of late normal tissue responses and tumour control	Professor John Yarnold	Closed
FEMALE	A randomised, multicentre study of first-line treatment of postmenopausal metastatic breast cancer, comparing concurrent vs. sequential chemoendocrine therapy with letrozole vs. letrozole single agent.	Dr Andreas Makris	Abandoned
FH01 - HTA Mammography Trial	Evaluation of mammographic surveillance services in women under 50 with a family history of breast cancer	Dr James Mackay	Closed
GLACIER	A study to investigate the genetics of	Dr Rebecca	Open

	lobular carcinoma in situ in Europe	Roylance	
GBG 26/ TBP	A multicentre randomized phase III study to compare capecitabine alone or in combination with trastuzumab in patients with HER2 positive metastatic breast cancer and progression after previous treatment with trastuzumab	Dr Rob Stein	Closed
Gem Carbo in breast	A phase II evaluation of carboplatin plus capecitabine in anthracycline resistant breast cancer	Dr Nick Murray	Closed
GENFABARCA	Genetic factors affecting breast cancer progression	Dr Angela Cox	Open
HERA	Trial of 1 vs. 2 years of Herceptin vs. no Herceptin in women with HER2-positive primary breast cancer who have completed adjuvant chemotherapy	Professor Ian Smith	Closed
HighREX	Photon Counting Tomosynthesis vs Digital Mammography: observer study	Dr Matthew Wallis	Set-up
HOT	Randomised phase II trial of hyperbaric oxygen therapy in patients with chronic arm lymphoedema after radiotherapy for early breast cancer	Professor John Yarnold, Professor Peter Mortimer	Closed
HRT	UK randomised trial of Hormone Replacement Therapy (HRT) in Women with a history of early stage breast cancer	Miss Jo Marsden, Mr Nigel Sacks	Closed
IBIS-II Prevention	An international multicentre study of anastrozole vs. placebo in postmenopausal women at increased risk of breast cancer.	Professor Jack Cuzick	Open
IBIS II DCIS	An international multicentre study of anastrozole vs. tamoxifen in postmenopausal women with Ductal Carcinoma in Situ (DCIS)	Professor Jack Cuzick	Open
ICICLE	A study to Investigate the geneticCs of In situ Carcinoma of the ductal subtype	Dr Rebecca Roylance	Open
IMPORT HIGH	A phase III randomised controlled trial testing dose escalated intensity modulated radiotherapy in women with higher than average local tumour recurrence risk after breast conservation surgery and appropriate systemic therapy for early breast cancer	Professor Judith Bliss, Professor John Yarnold	Open
IMPORT LOW	A phase III randomised trial testing intensity modulated and partial organ radiotherapy following breast conservation surgery for early breast	Professor Judith Bliss, Professor John Yarnold	Open

	cancer		
Improving older women's knowledge and confidence to present early with breast symptoms	Improving older women's knowledge and confidence to present early with breast symptoms: A randomised controlled trial of a radiographer-delivered intervention	Professor Amanda Ramirez	Closed
IMRT trial	Radiotherapy in early breast cancer: cosmetic outcome	Dr Margaret Moody	Closed
Lapatinib Presurgical Study	Lapatinib Pre-Surgical Phase II Study in Primary Breast Cancer breast cancer	Professor Nigel Bundred	Open
LATTE	Long-term Anastrozole vs. Tamoxifen	Professor Jack Cuzick	Set-up
Living with Secondary Breast Cancer	Treatment Effects A study of the experience of living with secondary breast cancer	Professor Jessica Corner	Closed
Long term effects of chemo on bone	An investigation of the long term effect of chemotherapy on bone, particularly focusing on the incidence of osteoporosis	Professor Robert Coleman	Closed
Lymphoedema after surgery	Identification of women at risk of developing arm swelling (lymphoedema) after axillary node surgery	Professor Nigel Bundred	Open
MATCH	Attitudes of men with breast cancer in the United Kingdom	Dr Jonathon Gray	Closed
MAPLE	Presurgical study to assess molecular effects of lapatinib in primary breast cancer	Professor Stephen Johnson	Open
MARIBS	UK Study of MRI for Breast Screening	Professor Martin Leach	Closed
MINDACT	Randomised prospective evaluation of genetic profiling of primary breast tumours versus standard clinical criteria in the selection of patients for adjuvant chemotherapy.	Professor Alistair Thompson	Open
Mechanisms of fatigue in breast cancer patients	An investigation in to the biological mechanisms and clinical correlates in disease free breast cancer patients following primary treatment	Dr Ollie Minton	Open
NEAT	Nationwide breast cancer study of Epirubicin plus CMF versus classical CMF Adjuvant Therapy (NEAT)	Professor Lawrence Young	Closed
NEAT-A	A multicentre phase II feasibility study of accelerated chemotherapy -	Dr Daniel Rea	Closed

	sequential epirubicin followed by IV CMF - using pegfilgrastim for women with early stage breast cancer		
Neo-Comice Pilot	Establishing the efficacy of advanced semi-automated functional MR imaging in the early prediction of response of locally advanced breast cancer to neoadjuvant chemotherapy (Pilot)	Professor Lindsay Turnbull	Set up
Neoadjuvant	The role of magnetic resonance imaging (MRI) and spectroscopy in predicting early response of breast cancer to chemotherapy	Professor Lindsay Turnbull	Closed
NEOcent	A neoadjuvant study of chemotherapy versus endocrine therapy in postmenopausal patients with primary breast cancer	Dr Carlo Palmieri/Dr Susie Cleator	Open
Neo-Excel	Neoadjuvant trial of pre-operative exemestane or letrozole +/-celecoxib in the treatment of ER-positive postmenopausal early breast cancer	Miss Adele Francis	Open
Neo-tAnGo	A neoadjuvant study of sequential epirubicin + cyclophosphamide and paclitaxel ± gemcitabine in the treatment of high-risk early breast cancer with molecular profiling, proteomics and candidate gene analysis.	Dr Helena Earl	Closed
OPTION	Ovarian protection trial in oestrogen non-responsive premenopausal breast cancer patients receiving adjuvant or neo-adjuvant chemotherapy	Professor Robert Leonard	Open
PARP-BRCA trial	A Cancer Research UK phase II proof of principle Tptrial of the activity of the intravenous PARP-1 inhibitor, AG-014699, in known carriers of a BRCA 1 or BRCA 2 mutation with locally advanced or metastatic breast or advanced ovarian cancer	Dr Ruth Plummer	Open
PATH-IES	Intergroup exemestane study pathology sub-study	Professor Charles Coombes	Open
PERSEPHONE	Duration of Trastuzumab with chemotherapy in women with early stage breast cancer: six months versus twelve	Dr Helena Earl	Open
p53 Study	First prospective Intergroup Translational Research trial assessing the potential predictive value of p53 using a functional assay in yeast in patients with locally	Dr Herve Bonnefoi, Professor David Cameron	Closed

	advanced/inflammatory or large operable breast cancer prospectively randomised to a taxane versus a non taxane regimen.		
PCI study	Randomised evaluation of prophylactic radiotherapy in women with HER 2 positive metastatic breast cancer	Dr Peter Canney	Open
PIMMS	A psycho-social evaluation of the impact of mammographic surveillance services on women under 50 at increased risk of inherited breast cancer	Ms Joan Austoker	Closed
PG-SNPS	The Pharmacogenetics of Early Breast Cancer Chemotherapy (sub-study)	Dr Jean Abraham	Open
POETIC	A comparison of preoperative or post-operative endocrine treatment with prospective evaluation of Ki-67 as a surrogate marker of outcome	Professor Ian Smith	Open
POSH	Prospective study of outcomes of treatment in hereditary versus sporadic breast cancer	Professor Diana Eccles	Closed
PRIME	The PRIME breast cancer trial (postoperative radiotherapy in minimum-risk elderly)	Dr Robin Prescott	Closed
PRIME II	Post-operative Radiotherapy In Minimum-risk Elderly phase II	Professor Ian Kunkler	Open
QUEST	A multi-centre randomised trial to assess the impact of the type and timing of breast reconstruction on quality of life following mastectomy	Ms Zoe Winters	Set up
RACE	Radiation complications and epidemiology – Inherited factors contributing to radiotherapy side effects	Professor John Yarnold	Closed
RAACS	Rural accessibility and cancer survival	Dr Andy Jones	Closed
REACT	Randomised EuropeAn Celecoxib Trial. A phase III multicentre double blind randomised trial of celecoxib versus placebo following chemotherapy in primary breast cancer patients.	Professor Charles Coombes	Open
Reflexology Study	RCT of the effects of reflexology on QoL (including mood, adjustment, function coping & patient satisfaction) and host defences in early breast cancer	Professor Leslie Walker	Closed
RIB	A multicentre randomised trial of single dose radiotherapy compared to ibandronate for localised metastatic bone pain	Professor Peter Hoskins	Open
SEARCH	A population based study of genetic predisposition and gene-environment	Professor Doug Easton	Open

	interactions in breast cancer		
SECRAB	Sequencing of chemotherapy and radiotherapy in adjuvant breast cancer	Dr I Fernando	Closed
Sentinel Node Biopsy - Breast	Sentinel node biopsy in primary breast cancer – a randomised controlled trial assessing morbidity, quality of life and cost effectiveness	Mr AD Purushotham	Closed
SoFEA	Study of Faslodex with or without concomitant Arimidex Vs, Exemestane following progression on non-steroidal Aromatase inhibitors	Professor Stephen Johnston	Open
SOFT	Suppression of ovarian function trial	Professor Rob Coleman	Open
SPROG	Prospective randomised comparison of G-CSF (filgrastim) secondary prophylaxis versus conservative management of chemotherapy-induced neutropenia to maintain dose intensity in chemotherapy for breast cancer	Professor Robert Leonard	Closed
START	Standardisation of breast radiotherapy (START) trial	Professor John Yarnold	Closed
SUPREMO	Selective use of postmastectomy radiotherapy after mastectomy	Prof Ian Kunkler, Dr Peter Canney	Open
Surgical management choices in breast cancer	Patient and professional factors influencing choice of surgery in the management of breast cancer: a qualitative and quantitative study	Professor MWR Reed, Miss Lisa Caldon	Closed
TAC	A randomised multicentre trial of neoadjuvant Taxotere and Adriamycin/Cytosan (AC): a biologic correlative study	Dr Jenny Chang	Closed
TACT	A randomised trial of standard anthracycline-based chemotherapy with fluorouracil, epirubicin and cyclophosphamide (FEC) or epirubicin and CMF (Epi-CMF) vs. FEC followed by sequential docetaxel as adjuvant treatment for women with early breast cancer	Dr Paul Ellis, Prof Peter Barrett-Lee,	Closed
TACT QOL	TACT trial long term quality of life sub-study	Professor Penny Hopwood	Open
TACT2	Trial of accelerated adjuvant chemotherapy with capecitabine in early breast cancer	Professor David Cameron	Closed
tAnGo	A phase III randomised trial of gemcitabine in paclitaxel-containing, epirubicin based adjuvant chemotherapy for higher risk early stage breast cancer	Professor Chris Poole	Closed
TEAM	An open label, randomised multicentre comparative trial of 5 years adjuvant Exemestane treatment versus 5 years	Dr Daniel Rea	Closed

	adjuvant tamoxifen treatment in postmenopausal women with early breast cancer		
Telephone follow-up study	Comparing hospital and telephone follow-up for women with breast cancer: a randomised controlled trial	Dr Kinta Beaver	Closed
TEXT	Tamoxifen and EXemestane trial	Dr Helena Earl	Open
The Sheffield DEBRA study	The effects of a combined diet and exercise intervention on biomarkers associated with disease recurrence after breast cancer treatment: The Sheffield DEBRA trial.	Dr John Saxton	Closed
TOPIC2	Randomised phase III trial of navelbine/epirubicin vs. adriamycin/cyclophosphamide as pre-operative chemotherapy in patients with greater than or equal to 3cm diameter early breast cancer	Professor Ian Smith	Closed
TNT	Triple Negative Breast Cancer Trial: A randomised phase III trial of carboplatin compared to docetaxel for patients with metastatic or recurrent locally advanced ER-, PR- and HER2-breast cancer.	Dr Andy Tutt	Open
Uptake and response to dietary intervention	Reshaping breast care services – a role for dietitians	Ms Jillian Milne	Closed
W.I.N.S. (UK) - Stage 1	Women's Intervention Nutrition Study (UK arm)	Mr Richard Sainsbury	Closed
Will Weekly Win	A randomised 2-arm, prospective, multi-centre, open-label phase III trial comparing the activity and safety of a weekly versus a 3 weekly paclitaxel treatment schedule in patients with advanced or metastatic breast cancer	Dr Mark Verrill	Closed
ZICE	Zoledronate versus ibandronate comparative evaluation trial.	Dr Nick Murray, Prof Peter Barrett-Lee	Open
Zoledronate & Letrozole study	A phase II study of the short term biological effects of Zoledronate and Letrozole on invasive breast cancer (pre-operative study)	Professor Nigel Bundred	Closed

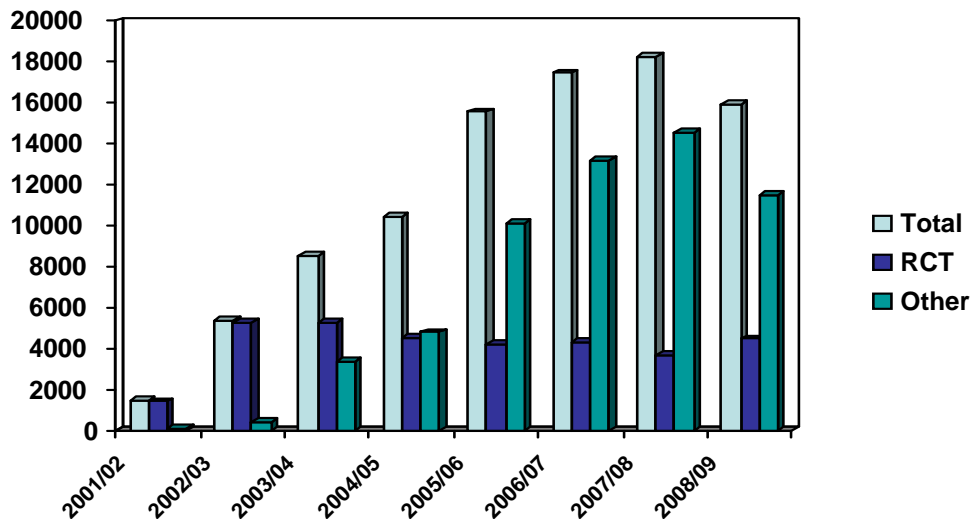
#### Open trials

There are currently 52 academic NIHR Breast Cancer Trials open to accrual across the entire spectrum of the disease including prevention, lifestyle, survivorship and psychosocial studies as well as the more traditional treatment studies. This includes a number of ongoing studies developed independently of the NCRN but which have been included in the newly formulated comprehensive portfolio of NIHR studies. A

further five studies are in set up as of June 2009 and 66 studies are closed, many of which are still in follow up. There is also a rapidly expanding number of fully funded industry led and sponsored studies within the breast portfolio that have been approved through the Industry Trials Advisory Committee (ITAC); four are closed and in follow up, eight are open to accrual, one on hold and five are in set up. Another seven trials are currently under consideration. The problems of monitoring the uptake of these studies across the networks and trial performance in terms of accrual rates has been largely resolved with regular information provided to the Chairman on a confidential basis from the NIHR Coordinating Centre. Currently, the BCSG is responsible for 67% of total UK recruitment to industry portfolio cancer studies.

The total number of breast cancer patients entered into NCRN trials during the period April 2008 to March 2009 was 15808. Of the 4443 patients (subjects) included in RCTs, 3295 with a diagnosis of cancer took part in an academic study, 405 were included in industry portfolio studies, 175 had a premalignant diagnosis and 520 were considered at risk for the breast cancer and took part in screening or prevention studies. 9.1% of incident cases were recruited to a RCT in 08/09, an absolute increase of 0.6% over the previous year. Of the 11540 patients included in non randomised studies, 9792 had a diagnosis of cancer, 644 had a premalignant condition, 929 did not have a diagnosis of cancer and 179 took part in optional sub-studies.

Accrual into all NIHR trials and studies in the year 2008/9 was 33.3% of the estimated



annual incidence of breast cancer. This was down by 7.3% due to the closure of the large CADET screening trial at the beginning of the year. However, the breast cancer portfolio continues to have a disproportionately large impact on the overall performance of the NCRN.

In common with the NCRN as a whole, recruitment in 2008/09 into RCTs increased slightly from 3364 cancer patients in 07/08 to 3923 this year. However, the level of RCT accrual has not managed to exceed the peak levels of 2002-2004.

The level of recruitment into RCTs reflects both local and national issues. Locally, the heavy workload for the networks due to the influence of increasing follow up and research governance demands is limiting capacity to recruit and severely hindering the initiation of new studies. Nationally, the very long set up time for new studies persists, such that it now takes about two years to develop a study, obtain scientific approval and funding, work with a CTU to develop the CRFs, obtain MHRA and ethics approval and set up with individual sites. Our large adjuvant chemotherapy trial (TACT2) has closed and was recruiting 1500-2000 patients per year (more than half of our RCT

activity). Initiation of POETIC was meant to fill the gap in the portfolio but has been slow to start not only for the reasons stated above but also because of the requirement for service reconfiguration to enable rapid provision of ER status in order to approach patients for this pre-surgical study. As a result it is unlikely that RCT accrual in 2009/10 will be maintained at previous levels.

Unfortunately two early disease (ACTION and ESTEEM) and one metastatic disease (BISMARCK) studies have been abandoned or closed early due to poor accrual. Others, especially within the metastatic portfolio are recruiting relatively poorly and are threatened with closure. Completing our existing portfolio is a major challenge and is our top priority. Unfortunately, many commitments to participate in a clinical trial are not honoured, either due to unrealistic recruitment targets at individual centres or loss of interest in an individual study by the time it is activated. Additionally recruitment to randomised trials, especially in elderly patients and with major treatment differences between the study arms e.g. chemotherapy versus no chemotherapy (ACTION) or surgery versus endocrine therapy (ESTEEM) are very difficult to recruit to. Alternatives to the classic RCT are needed to address some of these important clinical questions.

#### **Closed trials**

There are 66 academic NCRN breast cancer specific trials closed to recruitment plus many national adjuvant studies that predate the NCRN (ABC, BIG1-98, IES etc) but with ongoing follow up that make demands on the NCRN staff.

Publications are now appearing at regular intervals and a number of trials have already changed clinical practice and had a bearing on NICE reviews of new technologies and treatments e.g. adjuvant trastuzumab (HERA) and START. Appendix 2 provides a list of BCSG publications from 2008 and early 2009.

#### **Trials in set-up**

There are currently only five trials in set up. These include QUEST, a trial designed to evaluate different breast reconstruction strategies and EPHOS-B, a trial to evaluate biological changes induced by HER2 targeted therapies in the pre-surgical setting. This trial has been in set up for two years and illustrates some of the practical difficulties of achieving acceptable contracts between multiple institutions and industry. In addition there are continued concerns about the ability of the current service arrangements in most centres to obtain HER 2 status, assess cardiac function for safety purposes and commence treatment in a timely manner to fit within the limited pre-surgical window between diagnosis and surgical treatment without compromising the mandatory treatment target times. However, time spent trying to achieve the necessary service changes will be well spent as this pre-surgical window is likely to be a setting for evaluation of many new agents in the future.

#### **Trials in development**

The Group has a number of trials in development including the CHEMOSARE study which looks at the role of chemotherapy in post menopausal women and joining the EORTC Male Breast Cancer Study.

#### **Meetings**

Another successful Annual Trials Day was held at Church House, Westminster in March and, as in previous years, was very well attended. An excellent programme was well received by delegates and enhanced by the inclusion of the Cridlan lecture, a named lecture supported by the Cridlan Trust that funded Professor Peter Ravdin to visit from Houston to present an overview of risk assessment and the use of the Adjuvant On-Line risk prediction programme. A range of pharmaceutical companies generously supported the meeting for which we are most grateful. The interaction between investigators and industry representatives was mutually beneficial.

### **Other activities**

Over the past year there have been a large number of NICE appraisals of relevance to breast cancer management that requested input from the BCSG. These have included the two Clinical Guidelines Documents for Early and Advanced Breast Cancer as well as the Single Technology Assessments for bevacizumab in advanced breast cancer, lapatinib in HER 2+ advanced breast cancer progressing on or after trastuzumab or with the endocrine agent letrozole, and denosumab to treat cancer induced bone loss and bone metastases. The Group has been able to feed its comments into NICE through the Royal College of Physicians on behalf of a number of stakeholders, ensuring a single robust response on behalf of the NCRI and the Royal Colleges of Physicians and Radiology. This has resulted in very comprehensive feedback, especially in terms of comments on the Guidelines. However, despite widely held major reservations with many aspects of both consultation documents, our comments and input seem to have had very little impact on the final published version. Whether a single co-ordinated response really is an improvement on multiple responses from individual stakeholders remains to be seen.

### **3-year strategy**

The BCSG was encouraged at its triennial review in 2008 to continue its high level of research activity, retain many of its structures, balance of skills and meeting format but address a number of areas for improved performance.

Four key priorities in our updated three year strategy are:

- To ensure the continuous availability of a large randomised study in early breast cancer at all times.
- Identify the problems with recruitment to metastatic disease studies and develop an attractive portfolio of advanced disease studies.
- Integrate translational research including biomarker development and functional imaging into clinical trials.
- Address the increasingly important issue of follow up and how to reconcile the data demands of continued follow up with the clinical imperative to collect long term outcome data.

The first three priorities are being addressed primarily through the establishment of subgroups with the expertise and appropriate membership to optimise the chances of success.

The fourth priority depends on our excellent links with the CTUs and liaison with other CSGs with similar needs for long-term data collection. Lucy Kilburn, as part time project officer, is supporting this work stream and devising a simple system for collecting follow up efficacy and relevant adverse events data.

The workload of the BCSG will continue to be devolved by giving specific responsibilities to individual members. This includes named members to oversee sections of the portfolio, liaising with chief investigators and networks where necessary and to comment on submissions to CTAAC and other funding bodies when requested.

The BCSG has an important role in overseeing trial development and continuation of a broad and active portfolio. This continues in concert with the activities of UKBI and Advanced Disease subgroup to:

- Define research priorities and encourage trial development to address these.
- Facilitate trial development through open membership workshops.
- Mentor less experienced trialists.
- Promote early clinical trials office / statistical input.
- Provide opportunity for trial proposals to be presented to the committee for advice and comment prior to CTAAC outline submission.

**Priorities for next year:**

- Further prioritisation of RCTs and increase in accrual into these studies
- Addressing the NCRN priority that 80% of trials set up since 2008 are on target for accrual.
- Completion of the current portfolio of RCTs
- Stimulation of the metastatic disease portion of the portfolio
- Increased partnership with industry through both the ITAC mechanism and the development of academic led but industry supported studies.
- Development of a large adjuvant therapy successor trial to TACT 2.

Professor Robert Coleman, Chair

## Appendix 1

### 2008/09 Publications and abstracts

#### aTTom

**Gray RG, Rea DW, Handley K, Marshall A, Pritchard MG, Perry P, Earl HM, Poole CJ, Salma A, Lee M, aTTom collaborators.** aTTom (adjuvant tamoxifen – to offer more?): Randomised trial of 10 versus 5 years of adjuvant tamoxifen among 6934 women with oestrogen receptor positive (ER+) or untested breast cancer – preliminary results. *J Clin Oncol* 26 (15s) part 1, 10s, abs 513, 2008.

#### AZURE

**Winter M, Thorpe H, Burkinshaw R, Beevers S, Coleman R.** Potential influence of zoledronic acid on primary tumour response during neoadjuvant chemotherapy for breast cancer. *Cancer Treatment reviews* 34 (Suppl1) S55, abs OC15, 2008.

**Burkinshaw R, Winter M, Thorpe H, Pedlar J, Coleman R.** Osteonecrosis of the jaw and dental related adverse events during adjuvant therapy for early breast cancer: Initial safety findings from the AZURE study. *Cancer Treatment reviews* 34 (Suppl1) S75, abs P53, 2008.

#### EMBRACE

**Antoniou AC, Spurdle AB, Sinilkova OM and 84 others.** Common breast cancer predisposition alleles are associated with breast cancer risk in BRCA1 and BRCA2 mutation carriers. *American Journal of Human Genetics* 82:937-948, 2008.

#### HERA

**Untch M, Gelber RD, Jackisch C et al.** Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial. *Annals of Oncology*. 19:1090-1096, 2008. PMID 18296421

#### IES

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