Institution: University of Oxford

Unit of Assessment: 2 – Public Health, Health Services and Primary Care

Title of case study: Personalised Breast Cancer Care

Period when the underpinning research was undertaken: 2000 – 2018

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Sarah Darby	Professor of Medical Statistics	2007 – present
Richard Gray	Professor of Medical Statistics	2010 – Sept 2019
Carolyn Taylor	Clinical Research Fellow and Associate Professor	2004 – present
Robert Hills	Professor of Medical Statistics	2018 – present
Paul McGale	Medical Statistician and Associate Professor	1998 – present
Richard Peto	Professor of Medical Statistics and Epidemiology	1998 – March 2018

Period when the claimed impact occurred: August 2013 – December 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Through conducting large-scale population-level studies, University of Oxford researchers have quantified the long-term benefits and risks of different breast cancer treatments, providing conclusive evidence where there was previously uncertainty. These discoveries have already changed clinical practice, improving patient outcomes, and saving lives.

A series of meta-analyses of breast cancer-related clinical trials worldwide generated robust evidence into the effectiveness of treatments. These discoveries have been translated into clinical practice, ultimately benefitting the millions of women who are diagnosed with breast cancer worldwide each year. In particular, these studies identified a more effective treatment (aromatase inhibitors) than the standard endocrine therapy; identified new sub-groups of patients that would benefit from radiotherapy treatment; and demonstrated that bisphosphonates reduce the risk of bone metastasis and death from breast cancer.

For the first time, a model was developed to describe the relationship between the exposure of the heart to radiation during radiotherapy treatment, and the risk of radiation-induced heart disease (a major cause of death in breast cancer survivors). This has led to new, safer radiotherapy techniques and allowed clinicians to predict the absolute risk for each individual breast cancer patient.

2. Underpinning research

Improving the efficacy of breast cancer treatments using meta-analyses

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG), based at the University of Oxford (including Secretariat), has since the 1980s been using individual patient data meta-analysis to assess the long-term benefits and side-effects of different treatment options for early breast cancer, collaborating with breast cancer trialists worldwide to collect long-term outcome data. This provides the unique opportunity to assess late effects of treatment (either beneficial or harmful), which are not assessed reliably within the original clinical trial reports. These large datasets allow the most reliable estimates of treatment effects overall and exploration of any differences in the effects of treatments in different tumour subtypes, or between treatments within the same class, analyses which cannot be performed reliably using individual clinical trial publications.

Notable recent findings from the EBCTCG are:

a) A meta-analysis of 8,000 women in 22 trials of radiotherapy after mastectomy (published 2014) [1] showed that **radiotherapy reduced breast cancer recurrence and mortality** not only in women whose breast cancer had spread to many lymph nodes but also in those with spread to only 1-3 axillary lymph nodes.

b) A meta-analysis (published 2015) using individual data on almost 32,000 women determined conclusively that **aromatase inhibitors** (which block oestrogen production) are a **more effective treatment for breast cancer than tamoxifen in postmenopausal women** [2]. Specifically, aromatase inhibitors were found to reduce recurrence rates by 30% and 10-year mortality rates by 15% compared with tamoxifen.

c) A meta-analysis of 24 trials of the use of bisphosphonate therapy (19,000 women) (published 2015) demonstrated that **bisphosphonates reduce the risk of bone metastasis and death from breast cancer in postmenopausal women** [3]. Furthermore, bisphosphonates also strengthen bones and effectively reduce damage from osteoporosis caused as a side effect by aromatase inhibitors, therefore adding to their clinical benefit.

Reducing the harmful side-effects of breast cancer radiotherapy

Most patients with breast cancer receive radiotherapy as part of their treatment. However, analyses conducted during 1990 to 2013, including those from the EBCTCG, had found that radiotherapy treatment for breast cancer may lead to increased risks of heart disease and of some other cancers, through incidental exposure of tissues other than the tumour. These risks reduced the net benefit of the radiotherapy and, in some cases, the additional risk of death from these side-effects exceeded the reduction in death from breast cancer conferred by the radiotherapy. The precision with which radiotherapy beams can be delivered has changed since the women in those EBCTCG trials were treated and the magnitude of the risks from modern radiotherapy treatments were unknown. In response, the research team led from the University of Oxford conducted a study to relate the risk of heart disease after breast cancer radiotherapy to each woman's radiation dose to the heart and to any cardiac risk factors she had at the time of radiotherapy. This was used to produce the first heart radiation dose-response relationship model based on a large number of cardiac events [4]. Besides highlighting the cardiac risks from radiotherapy, this research enabled doctors for the first time to predict the size of the absolute risk for each woman using her estimated radiation heart dose and other cardiac risk factors.

To accompany the dose-response relationship for radiation-related heart disease, the Oxford research team also performed a systematic review to assess which radiotherapy techniques resulted in the lowest heart doses, whilst maintaining adequate radiation dose to target regions (breast and/or lymph nodes) [5]. This found that the breath-hold technique, where the patient takes a deep inspiratory breath to expand the chest and move the heart away from the treatment area, approximately halved the mean heart radiation dose.

3. References to the research (University of Oxford employees in bold, students in italics)

1. Early Breast Cancer Trialists' Collaborative Group (2014). Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet.* 383:2127-2135. DOI: 10.1016/S0140-6736(14)60488-8. Writing committee included **P McGale, C Taylor,** *D Cutter*, **R Gray, R Peto** and **S Darby**.
2. Early Breast Cancer Trialists' Collaborative Group (2015). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet* 386:1341-52. DOI: 10.1016/s0140-6736(15)61074-1 Writing committee included **R Peto, R Gray, C Davies, H Pan** and **R Bradley**.
3. Early Breast Cancer Trialists' Collaborative Group (2015). Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet* 386:1353-61. DOI: 10.1016/S0140-6736(15)60908-4 Writing committee included **R Peto, R Gray, V Evans, H Pan, R Peto** and **R Bradley**.
4. **Darby SC**, Ewertz M, **McGale P**, Bennet AM, Blom-Goldman U, Brønnum D, Correa C, *Cutter D*, Gagliardi G, Gigante B, Jensen M-B, Nisbet A, **Peto R**, **Rahimi K**, **Taylor C** and

Hall P (2013). Risk of ischemic heart disease in women after radiotherapy for breast cancer. *New England Journal of Medicine* 368:987-998. DOI: 10.1056/nejmoa1209825

5. **Taylor CW**, **Wang Z**, Macaulay E, Jagsi R, *Duane F*, **Darby SC** (2015). Exposure of the heart in breast cancer radiotherapy: A systematic review of heart doses published during 2003-2013. *Int J Radiat Oncol Biol Phys* 93:845-853. DOI: 10.1016/j.ijrobp.2015.07.2292

Funding to the University of Oxford for EBCTCG includes Cancer Research UK programme grants to Gray & Hills (GBP4,615,825, C53005/A27961, 2019-24), and to Darby (GBP4,598,661, C8225/A21133, 2016-21); the Medical Research Council; the Department of Health; and contributions from the BHF Centre for Research Excellence and Oxford Clinical Trial Service Unit; and from the NIHR Oxford Biomedical Research Centre.

4. Details of the impact

The research projects directly addressed clinical problems identified by clinicians and statisticians in the University of Oxford teams and by several hundred international breast oncologists who are EBCTCG collaborators. The meta-analyses provided conclusive evidence in areas where previously there was uncertainty because of the inconclusive nature of many of the individual trials, which were too small to detect moderate treatment effects. In addition, the work on side-effects has enabled radiotherapy to be delivered more safely, thus increasing its net benefit.

As EBCTCG engages almost all breast cancer clinical trialists across the world, it is in a highly effective position to disseminate its discoveries. For instance, all the main international European, USA and UK guideline groups (identified below) include EBCTCG members in their steering committees. The findings of these studies have led to changes in the international guidelines used by oncologists worldwide. In changing clinical practice and improving patient outcomes and survival following breast cancer, this work has directly benefitted the over 2,000,000 women who are newly diagnosed with breast cancer each year.

Changes in clinical practice to improve breast cancer treatment
EBCTCG papers published between January 2005 and May 2017 were primary references in important updates to each of the major international guidelines for the management of early breast cancer. These include those produced by the National Institute for Health and Care Excellence (NICE) [A], the UK's Royal College of Radiologists (RCR) [Bi] and the Scottish Intercollegiate Guidelines Network (SIGN) [Bii]; the European Society for Medical Oncology (ESO-ESMO) [Ci], the Japanese Breast Cancer Society [Cii] and the St Gallen international consensus on breast cancer [Ciii]; the American National Comprehensive Cancer Network (NCCN) [Di], Cancer Care Ontario and the American Society of Clinical Oncology (ASCO) [Dii], and the American Society for Radiation Oncology (ASTRO) [Diii]. These updated guidelines brought in new recommendations (detailed below) based on EBCTCG evidence, to improve the survival of breast cancer patients. Speaking of the 2014 update to the NICE guidelines on Early and locally advanced breast cancer: diagnosis and management, the Director for Guidelines for NICE wrote:

> '*NICE's recent (almost completed) major update of our guideline on early and locally advanced breast cancer has been helpfully informed by the analyses conducted by [EBCTCG] over the preceding few years. Your recent work on systemic therapies was central to determining the scope of the current update'* (April 2018) [E].

Widespread adoption of aromatase inhibitors:
Following the publication of a meta-analysis of aromatase inhibitors versus tamoxifen [2] aromatase inhibitors have been adopted as standard-of-care: as a result, starting endocrine therapy with an aromatase inhibitor is now recommended for postmenopausal women with breast cancer whereas previously they were managed with either tamoxifen or an aromatase inhibitor. A study in 2019 found the majority of older women (55+) received aromatase inhibitors [F].

Extension of radiotherapy treatment
Life-saving radiotherapy treatment is now recommended to a wider range of breast cancer patients, including those whose cancer spreads to 1-3 axillary lymph nodes. This policy change was supported by the EBCTCG study [1], as reflected in the ASCO guidelines [Div]:

> *'The 2014 publication of the EBCTCG meta-analysis [citing reference 1 as above] provided the signal for this focused update. Based in large part on this signal, the ASCO Breast*

Cancer Advisory Group ranked updating the ASCO PMRT guideline question concerning use of PMRT for patients with one to three positive lymph nodes as a high priority'. [Div]

Reducing deaths and adverse side-effects using bisphosphonates

The results of the meta-analysis [3] prompted an immediate policy change, with bisphosphonates now being globally recommended for breast cancer patients, when they were not before [A, E, D]. The joint American Society of Oncology and Clinical Care Options guidelines acknowledged the importance of the work, stating: *'Results of the recently published Oxford Overview (Early Breast Cancer Trialists' Collaborative Group [EBCTCG]) analysis of individual patient data have provoked particular interest in this area [citing reference 3 as above] and are a key portion of the evidence on this topic'* [Dii]. An increase in bisphosphonates use was confirmed by a survey in March 2020 by the charity Breast Cancer Now, finding that 94% of NHS Trusts who have a breast cancer service were routinely prescribing them and a further 3% in process of making them available [Gi].

The results presented in [3] were recognised by policy makers and used to lobby for improved patient access to bisphosphonates. For instance, during a 2017 debate in the House of Commons on Breast Cancer Drugs, Baroness Blackwood argued in favour of bisphosphonates being licensed as treatment for breast cancer patients, saying '*research in The Lancet in 2015…found that bisphosphonates can be used to help women who are being treated for early breast cancer after the menopause by reducing the risk of the breast cancer spreading to the bone by 28%*' [H]. At least 35,700 postmenopausal women are diagnosed with primary breast cancer in the UK each year. Routine treatment with bisphosphonates prevents 1,180 women from dying from breast cancer annually: equivalent to one in ten breast cancer deaths with an overall net NHS saving of GBP5,090,000 per annual cohort of patients [Gii].

Quantifying the risk of heart damage from radiotherapy for individual patients

Before the heart radiation dose-response relationship model was published [4], it was not possible to assess the risk of heart damage radiotherapy for individual patients, based on cardiac risk factors and the amount of radiation received by the heart. The model has influenced practice worldwide for all cancers treated with thoracic radiotherapy, with over 100 references in national or international guidelines [A, Bi, Div, I]. In breast cancer, this enables patients for whom the estimated risk is larger than the benefit to be identified, so that they can avoid radiotherapy, whilst radiotherapy is recommended for women in whom the benefit is larger than the risk [A].

Reducing the radiation load experienced by vital organs during radiotherapy

In response to the heart radiation dose-response relationship [4], techniques were developed to spare the heart in several cancer types [J] and are now being used in the clinic. The Royal College of Radiologists' voted unanimously that the heart should be excluded from breast radiotherapy fields, and that all UK radiotherapy departments should use a breath-hold technique [Bi].

The widespread introduction of heart-sparing radiotherapy has been welcomed by oncologists and patients. Patient representatives from the organisations Independent Cancer Patients Voice and National Cancer Research Institute contacted the research team to thank them for developing the heart dose-response model, noting, for example: *'I welcome this research that can calculate cardiac risk and give patients the information I did not get. When I was treated the aim was 'alive after 5 years'. Today breast cancer patients can look forward to a long life, so they need to know what their risk is and how to weigh up options.'* [K].

In the USA, heart-sparing breast cancer radiotherapy has also increased, with >80% (around 430) radiation oncologists using heart-sparing techniques in 2017. Heart sparing radiotherapy is now recommended in national and international clinical guidelines [Bi, Diii]. Worldwide average mean heart dose in left breast radiotherapy reduced by almost half (4.6 to 2.6 Gy) from 2014 to 2017.

Survival improvements for breast cancer patients

These changes in practice have improved survival outcomes of women diagnosed with breast cancer, particularly since the benefits are largely additive. Between 2010 and 2017, the mortality rate for breast cancer fell from 37.4 per 100,000 females to 33.4 (Cancer Research UK statistics). In particular, the reductions in heart dose during radiotherapy are a significant improvement since in breast cancer survivors, heart disease is the most common cause of death (after breast cancer). In the USA, for instance, approximately 250,000 women are newly diagnosed with breast cancer

each year, with around 60% receiving radiotherapy. Assuming that half of them had disease on the left side, the results of the study [4] indicate that of the approximately 875,000 women who received radiotherapy to treat breast cancer between 2013-2020, these reductions in heart dose translate to approximately 1,500 fewer deaths from heart disease over the next 30 years.

Improving breast cancer decision aids

The EBCTCG meta-analyses have informed prognostic tools used to model patient outcomes, including the most widely-used decision aid, PREDICT [L]. This is recommended in the UK by NICE, and used to provide prognostic information for women with breast cancer around 20,000 times per month i.e. around 240,000 times per year. These decision aids enable clinicians to estimate the absolute effects of treatment for individual women.

5. Sources to corroborate the impact

A. NICE Guideline NG101 (July 2018). Early and locally advanced breast cancer: diagnosis and management – July 2018. https://www.nice.org.uk/guidance/ng101

B. UK Clinical guidelines: (i) The Royal College of Radiologists. Postoperative radiotherapy for breast cancer: UK consensus statements. November 2016. (ii) SIGN 134. Treatment of primary breast cancer. A national clinical guideline September 2013.

C. International clinical guidelines: (i) Cardoso F et al. (2019) Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 30:1194-1220; (ii) Komoike Y et al. (2015) Japan Breast Cancer Society clinical practice guidelines for surgical treatment of breast cancer. *Breast Cancer* 22: 37-48; (iii) Burstein HJ et al (2019). Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. *Annals of Oncology* 30(10):1541-1557.

D. US Clinical guidelines: (i) National Comprehensive Cancer Network Clinical Practice Guideline in Oncology: Breast cancer Version 3.2020; (ii) Dhesy-Thind S et al (2017). Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 35:2062-81. (iii) Smith BD et al. Radiation therapy for the whole breast: An American Society for Radiation Oncology (ASTRO) evidence-based guideline. *Pract Radiat Oncol* 2018; 8: 145-52 (supplemental materials). (iv) Recht A et al. (2017) Postmastectomy Radiotherapy: An American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Focused Guideline Update. *Ann Surg Oncol* 24: 38-51.

E. Letter from Director for Guidelines for NICE (April 2018).

F. Journal article: Emanuel et al (2019), Endocrine therapy in the years following a diagnosis of breast cancer: A proof of concept study using the primary care prescription database linked to cancer registration data, *Cancer Epidemiology* 61:185-189.

G. Statements from Breast Cancer Now: (i) Survey of NHS Trusts: 'An update on access to bisphosphonates' (March 2020), including reference to [3]. https://breastcancernow.org/about-us/news-personal-stories/update-access-bisphosphonates; (ii) Summary of adjuvant bisphosphonates (June 2016) including estimate of savings and reference to EBCTCG.

H. Hansard, House of Commons Debate: Breast Cancer Drugs, 26 January 2017.

I. Clinical Guideline: Armenian SH et al (2017). Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 35:893-911.

J. Journal articles: (i) Bergom C et al (2018). Deep inspiration breath hold: Techniques and advantages for cardiac sparing during breast cancer irradiation. *Front Oncol* 8; 87; (ii) Dabaja BS et al. (2018) Proton therapy for adults with mediastinal lymphomas: the International Lymphoma Radiation Oncology Group guidelines. *Blood* 132:1635-46.

K. Corroborator 1: Secretary, Independent Cancer Patients' Voice. May be contacted to corroborate patient feedback.

L. Technical account of PREDICT tool, e.g. version 2.1 includes reduction in mortality rate following bisphosphonates from [3]. https://breast.predict.nhs.uk/about/technical/technical