Institution: University of Cambridge		
Unit of Assessment: UOA1		
Title of case study: Curing with less cost: decreasing the intensity of breast cancer therapy, reducing side effects and treatment costs while maintaining survival rates.		
Period when the underpinning research was undertaken: October 2007 – July 2020		
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:**
Charlotte E. Coles	*(NHS Consultant, Addenbrooke's hospital)* NIHR Research Professor and Professor in Breast Cancer Clinical Oncology	*(Aug 2005-Aug 2017 Category C)* Jan 2017 -
Helena M. Earl	Professor of Clinical Cancer Medicine	Sep 1996 - Dec 2019
Period when the claimed impact occurred: August 2017-July 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

Breast cancer is the most common cancer in women. Each year >500,000 women worldwide die of the disease. Aggressive treatment strategies have doubled breast cancer survival rates since the 1970s; however, it is now recognised that many of these patients are over-treated, resulting in unnecessary long-term side effects and healthcare costs. Cambridge-led clinical trials involving >6,000 patients in >150 UK Centres have identified those breast cancer patients who can be treated with reduced-volume radiation and reduced-duration anti-HER2 antibody (trastuzumab) therapy. This research has directly changed practice in the UK, Canada, USA, Europe and India, underpinning a global de-escalation in breast cancer therapy that spares qualifying patients from unnecessary side effects, preserves excellent survival rates, and reduces NHS treatment cost by up to GBP46,000,000 each year.

2. Underpinning research (indicative maximum 500 words)

Breast cancer is the most common cancer affecting women: 55,000 new cases are diagnosed each year in the UK, and over 2,000,000 are diagnosed worldwide. The increased use of radiotherapy and chemotherapy, as well as therapeutic monoclonal antibodies e.g. trastuzumab which targets the HER2 receptor on breast cancer cells, have increased patient survival rates from 40% in the 1970s to >80% today. However, it is now recognised that many patients are over-treated, causing serious unwarranted side effects and unnecessary healthcare costs. To address these issues, Cambridge researchers led a series of UK-wide clinical trials to test if treatment can be reduced safely in women with certain forms of breast cancer.

Reducing radiotherapy: Whole breast radiotherapy is a highly effective treatment of breast cancer. But this treatment causes significant, long-term physical and psychological side effects in up to one third of patients [Coles CE *et al.*, Clinical Oncology 2005]. A further 0.5 to 1% of patients suffer life-threatening radiation-induced secondary malignancies and cardiac toxicities. The 2007-2010 **IMPORT Low** randomised controlled trial (Coles was Chief Investigator) recruited 2,018 breast cancer patients, across 72 UK centres. After surgical removal of the tumour, patients received either: standard full dose, whole-breast radiotherapy (control); reduced dose, whole-breast radiotherapy (reduced-dose group); or radiotherapy to the affected area only (partial-breast group). All three treatments produced equally excellent disease control, with 5-year ipsilateral breast tumour recurrence rates of only 1.1% (95% CI 0.5–2.3; control group), 0.2% (0.02–1.2; reduced-dose group) and 0.5% (0.2–1.4; partial-breast group) [1]. Women receiving partial breast treatment also experienced significantly fewer side effects, with half as many women reporting moderate/marked changes in breast appearance compared with whole-breast radiotherapy (15% vs 27%) [1,2]. Partial-breast radiotherapy also halved exposure of the heart to radiation – a validated predictor of major, long-term, cardiac side effects – in patients with left-sided breast cancer [Darby S *et al.*, NEJM 2013].

The 2011-2014 UK **FAST Forward** trial (Coles is a senior member of the Trial Management Group [TMG]) demonstrated that 1-week of whole-breast radiotherapy is as effective in achieving local breast cancer control as 3 weeks of treatment [3]. By leading both the IMPORT Low and serving on the TMG of UK FAST Forward, Coles ensured that the control groups in both trials received identical radiation schedules enabling rapid and robust comparability between the studies. NHS England has invited Coles to work with them to implement 1-week partial-breast radiotherapy as standard of care for patients with low risk breast cancer. This represents a sea change in treatment and patient experience by reducing radiotherapy from 15 to just 5 treatments.

Reducing targeted therapy: Trastuzumab, given as a 12-month course of treatment, has increased ten-year survival rates for women with HER2+ breast cancer from 75% to 84% [Perez EA, JClinOncol, 2014]. With funding from the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme, Earl led the PERSEPHONE randomised trial to test whether trastuzumab treatment could be reduced safely from 12 to 6 months among patients with HER2+ breast cancer. 4,088 patients across 153 UK centres were enrolled. Four-year disease-free survival rates were equally excellent among patients receiving 6 months (89.4%) or 12 months (89.8%) trastuzumab (hazard ratio 1.07 [90% CI 0·93–1·24]; non-inferiority p=0·011). These results were reflected in similar overall survival. Importantly, patients receiving 6 months of treatment experienced significantly fewer severe adverse side effects (19% *vs* 24%, p=0·0002) and significantly fewer of these patients stopped trastuzumab early because of cardiac toxicities (3% *vs* 8%, p<0·0001) [4,5]. Together, the research of Coles and Earl has validated the notion that breast cancer treatment can be safely reduced to decrease side-effects and unnecessary healthcare costs [6].

3. References to the research (indicative maximum of six references)
Evidence of research quality: *Research published in peer-review journals. Research was supported by competitively won grants.

[1]Coles CE** *et al.*, IMPORT Trialists. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. ***Lancet. 2017; 390:1048-1060. doi.org/10.1016/S0140-6736(17)33316-0.
[2]**Bhattacharya IS, …. and **Coles CE**; IMPORT Trialists. Patient-reported outcomes over 5 years after whole or partial breast radiotherapy: Longitudinal analysis of the IMPORT LOW (CRUK/06/003) Phase III randomized controlled trial.J Clin Oncol***. 2019;37(4):305-317. doi: 10.1200/JCO.18.00982.
[3]** Brunt AM,..**Coles CE**, *et al.*, on behalf of the FAST-Forward Trial Management Group. 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. ***Lancet.2020; 395:1613-1626. doi.org/10.1016/ S0140-6736(20)30932-6
[4]Earl HM** *et al.* 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. ***Lancet.2019;393(10191):2599-612: doi.org/10.1016/S0140-6736(19)30650-6
[5]Earl H** *et al*. Six versus 12 months' adjuvant trastuzumab in patients with HER2-positive early breast cancer: the PERSEPHONE non-inferiority RCT. ***Health Technol Assess. 2020; 24(40):1-190. doi: 10.3310/hta24400.
[6]**Hall P, ….**Earl HM**.PERSEPHONE: 6 versus 12 months of adjuvant Trastuzumab in patients with HER2 positive early breast cancer: cost effectiveness analysis results. ESMO Munich, October 2018. Oral Presentation, Early Breast Cancer Session. ***Annals of Oncology. 2018; 29, Issue suppl_8, October 2018.doi.org/10.1093/annonc/mdy424.001.

Competitive funding received

- PERSEPHONE: Adjuvant trastuzumab duration in early breast cancer: Six versus twelve months **(Earl lead applicant).** Awarded **GBP 2,676,510** by NIHR HTA in April 2007. Co-applicants**:** D Cameron, J Dunn, D Miles, A Wardley, C McCabe.Ref: HTA 06/303/98.
- Trans-PERSEPHONE *and* Trans–PERSEPHONE-*SNPs*: The pharmacogenomics and pharmacogenetics of adjuvant trastuzumab **(Earl as co-applicant)**. Awarded **GBP**

418,708 by Cancer Research UK in 2008 for 84 months. Lead applicant: C Caldas, co-applicant JE Abraham. Ref: C507/A9675.

- Intensity Modulated Partial Organ Radiotherapy (IMPORT) HIGH and LOW Trials **(Coles as co-applicant)**. Awarded **GBP 1,654,889** by CRUK in 2006 for 192 months. Co-investigators: J Yarnold, E Donovan, J Haviland, P Hopwood, K Venables & C Chan. Ref: C1491/A6035.

4. Details of the impact (indicative maximum 750 words)

Coles and Earl's research has directly informed clinical practice, sparing major side effects for patients while markedly reducing healthcare costs.

Impact on practitioners and the delivery of professional services

Changing national guidelines and practice for breast cancer therapy: Cambridge research has had a direct impact on national and international clinical practice for the treatment of Stage I-II breast cancer:

- As a result of IMPORT Low, NICE 2018 guidance for early and locally advanced breast cancer: diagnosis and management [A] states: *'Consider partial breast radiotherapy (as an alternative to whole breast radiotherapy) for women who have had breast conserving surgery for invasive cancer (excluding lobular type) with clear margins and low absolute risk of local recurrence'.*
- UK Royal College of Radiologists breast radiotherapy consensus guidelines recommends partial breast radiotherapy for low risk patients (patients ≥50 years with grade 1-2, ≤30mm, oestrogen receptor positive and HER2 negative with minimum 1mm surgical resection margins and no lymphovascular invasion) [B].
- As a direct result of IMPORT LOW, regional NHS guidelines have been introduced by the North East Yorkshire and Humber Clinical Alliance and the West Midlands Expert Advisory Group for Breast Cancer, recommending the use of surgical clips on the wall of the tumour bed to enable partial radiotherapy as a standard approach, via increased accuracy of radiotherapy [C].
- As a direct consequence of the PERSEPHONE trial, UK recommendations have been developed by an optimal duration of trastuzumab working group. In a 2020 survey of breast specialists, the majority (78%) agreed with 6 months as a standard option for those receiving single agent trastuzumab [C]. In addition, the 3,200 breast cancer patients treated with single agent trastuzumab each year in the UK could now benefit from reduced-duration 6-month treatment [D].

Changing international breast cancer therapy practice: Internationally, the results of IMPORT Low have motivated numerous countries to change standard practice, implementing partial breast radiotherapy for low risk breast cancer patients. These include the Netherlands and Denmark, where national breast cancer guidelines have been changed to incorporate these new radiotherapy parameters [E]. IMPORT Low partial breast radiotherapy is now being used routinely in some of the largest and most technologically advanced cancer centres worldwide including: Australasia, Canada (Princess Margaret Cancer Centre), Canada Cancer Centres, and USA (Memorial Sloan Kettering Cancer Center) [E].

Impact on health and wellbeing of people

Reducing side effects for woman receiving radiotherapy: The IMPORT Low trial demonstrated that women with low risk breast cancer can be treated safely and effectively with reduced-dose or partial breast radiotherapy, causing fewer side effects than standard treatment. Importantly, this includes halving the number of women reporting marked changes in breast appearance or hardness that are associated with significant psychological sequelae. In the UK alone, 10,000 women per year are eligible for partial breast radiotherapy [F], which annually equates to 1,200 women spared physical changes in breast appearance and 500 patients spared breast hardness because of treatment [1,2]. Partial breast radiotherapy halves the mean heart dose for patients with left-sided cancer, which reduces the predicted absolute lifetime risk of life-threatening cardiac events to less than 0.5%, i.e. reducing from 50 to 25 such events per year (DarbyS *et al.*NEJM 2013). The reduction from 15 to 5 radiotherapy

treatments will also have a positive effect on the patient experience, by minimising hospital visits and treatment-associated side-effects.

Reducing side effects for women receiving targeted therapy: The PERSEPHONE trial provides evidence for safe reduction of single agent trastuzumab therapy from 12 to 6 months. This reduced therapy, provides the same excellent survival benefit, but 5% (365/1929 vs 460/1935) fewer patients treated now suffer severe side effects and only 3% (61/1977) of women who receive 6 months of trastuzumab are likely to have to stop treatment because of heart problems, compared with 8% (146/1941) who receive 12 months [D]. Patients on trastuzumab most frequently report severe aches and pains (9.3% - 524/5610) and fatigue (8.2% - 461/5610), which can be minimised by reduced treatment [D].

***Establishing therapy-reduction research for patient benefit*:** Both IMPORT Low and PERSEPHONE were completed within the NHS Clinical Research Network with active patient advocate partnership throughout design, recruitment, analysis and dissemination [G]. The success of these two trials with non-inferiority design, has been pivotal in establishing a priority theme of treatment reduction in National Cancer Research Institute (NCRI) breast cancer trials and has received consistent and positive feedback from doctors and patients [G]. Benjamin Smith, Professor of Radiation Oncology and Health Services Research at The University of Texas MD Anderson, said regarding IMPORT Low: "*In my opinion, this is one of the most important articles on early breast cancer to be published in this decade*." Maggie Wilcox, who is the patient lead for the PERSEPHONE trial, said "*I am delighted to have been part of this landmark trial which is an important step to reduce the length of treatment whilst not changing effectiveness."* Professor Hywel Williams, Director of the NIHR HTA Programme that funded the PERSEPHONE study said: "*This is a hugely important clinical trial that shows that more is not always better. Women will now have the potential to avoid unnecessary side effects of longer treatment without losing any benefit. In turn, this should help save vital funds for the NHS and prompt more studies in other situations where the optimum duration of treatment is not known. It is unlikely that research like this would ever be done by industry, so I am delighted that the NIHR are able to fund valuable research that has a direct impact on patients*." [H].

Extending excellence in care to Low- and Middle-Income Countries (LMICs): Trastuzumab has had World Health Organisation Essential Medicine designation since November 2015. However, the cost associated with 12 months of treatment precludes its widespread use in LMICs where it is estimated that over 1,000,000 people are diagnosed with breast cancer; ~120,000 of these patients have HER2+ disease. Demonstration by PERSEPHONE that 6 months of treatment are as effective as 12 months has increased directly the use of the drug in several LMICs, resulting in improvement in the uptake of this curative treatment [I]. IMPORT Low uses a simple technique and conventional, widely available radiotherapy equipment, so can be implemented in any centre worldwide.

Impact on commerce and the economy

Standard whole breast radiotherapy consists of 25 fractions over 5 weeks in many countries worldwide. Based on UK tariffs (GBP159 per fraction), a reduction to 15 fractions of partial breast radiotherapy saves GBP1,590 per patient. The 2020 publication of the FAST Forward trial has enabled seamless adoption of just 5 radiation fractions for partial breast radiotherapy in the UK and in countries where 15 fractions are standard of care. Around 10,000 women are eligible for partial breast radiotherapy per year in the UK where the standard of care is 15 fractions: this saves 100,000 fractions of radiotherapy per patient and a saving of ~GBP16,000,000 per year for the NHS. Each year the NHS treats ~3,200 women with 12 months of single agent trastuzumab (GBP22,000/patient) total ~GBP70,000,000). The Health Economic Analysis in PERSEPHONE showed within-trial cost savings of GBP9,793 per patient by reducing treatment to 6-months of trastuzumab [J]. Patients receiving single agent trastuzumab, which accounts for approximately half of all HER2+ cases, equates to an annual cost-saving of ~GBP30,000,000 to the NHS.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[A] NICE guideline changes for breast cancer radiotherapy
Early and locally advanced breast cancer: diagnosis and management, NG101, July 2018; p23 section 1.10.4.
[B] National guideline changes for breast cancer radiotherapy Royal College of Radiologists Postoperative radiotherapy for breast cancer: UK Consensus Statements 2016. Partial breast radiotherapy after breast conserving surgery p22.
[C] Changes to national clinical practices for breast cancer therapy based on these trials. (i) NHS North East Yorkshire and Humber Clinical Alliance: Guidelines for the Management of Adult Breast Cancer Patients, published January 2014. Section 3.6, p19 - Surgical Management: '*Clips should be placed at the tumor bed as per the IMPORT Trial protocol*.'(ii) NHS England: Clinical Guidelines for the Management of Breast Cancer West Midlands Expert Advisory Group for Breast Cancer, published December 2016. Margins of excision, p19: '*Marking of the tumour bed with metal clips should be considered to allow accurate planning and delivery of radiotherapy.*' Appendix 5, section 1.1, p41: '*Use of gold seeds or metallic clips to the tumour bed to allow accurate localisation is recommended*.'(iii) New UK recommendations for Trastuzumab treatment. Earl HM et al. Clinical Oncology, https://doi.org/10.1016/j.clon.2020.07.006. (In press July 2020).
[D] Evidence of reduced side effects in women receiving shorter duration of trastuzumab. Earl H, *et al. Health Technol Assess.* 2020;24. doi.org/10.3310/hta24400: Ch4 Cardiac toxicity, p55-65; Ch6 Quality of life, patient-reported experiences and reporting of results to patients, pp.87-104.
[E] Evidence of international practice change in partial breast radiotherapy.
(i) The Netherlands: Statement from Prof Liesbeth Boersma, Director of Patient Care Maastro& Head of Dept Radiotherapy Maastricht University; (ii) Scandinavia: Statement from Prof Birgitte VrouOffersen, Senior Consultant, Aarhus University Hospital, Department of Experimental Clinical Oncology, Danish Center for Particle Therapy, Department of Oncology, Denmark; (iii) Australasia: Statement from Dr Yvonne Zissiadis, Radiation Oncologist & President of the Australasian Society of breast disease; (iv) Canada: Statement from Dr Anne Koch, Leader of Breast Cancer Program & UHN Staff Radiation Oncologist, Radiation Medicine Program, Princess Margaret Cancer Centre, Toronto; (v) US: Statement from Dr Erin Gillespie, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York.
[F] Evidence of the number of breast cancer patients eligible for partial breast radiotherapy. Taylor C W, *et al*.Clin Oncol. 2020;32(4):217-220. doi: 10.1016/j.clon.2019.09.061.
[G] Patient advocate involvement and support from the NCRI Breast Cancer Study Group. (i) Testimonial from Adrienne Morgan, Chair of Independent Cancer Patients' Voice (ICPV); (ii) Testimonial from Prof Dan Rea, Chair of the NCRI Breast Cancer Studies for De-escalation theme for breast cancer clinical trials patient advocate partnership.
[H] Evidence of support for establishing therapy reduction research for patient benefit. NIHR 2018 press release about the PERSEPHONE trial, contains testimonials from Prof Hywel Williams, Director NIHR HTA, Prof Charles Swanton, CRUK's chief clinician and Maggie Wilcox, lead patient for PERSEPHONE and past president of ICPV.
[I] Changes in treatment of HER2+ patients in LMICs, based on PERSEPHONE data.
(i) Statement from Dr Sanjoy Chatterjee, Tata Memorial Centre, Kolkata, India - All India Consensus Breast Cancer Meeting, August 2019; (ii) Policy amendment in South Africa for 6 months adjuvant trastuzumab to improve access in many localities where it is currently unaffordable. R J Wiseman. S Afr Med J2020;110(4):271-273. doi.org/10.7196/SAMJ.2020.v110i4.14621; see ref 8.
[J] Evidence of cost savings for 6 months of trastuzumab versus 12 months.
(i) ESMO Press release about PERSEPHONE trial. PERSEPHONE: 6 versus 12 months of adjuvant Trastuzumab in HER2 positive early breast cancer patients: cost effectiveness analysis results. ESMO Munich, October 2018. Annals of Oncology; Volume 29, Issue suppl_8, October 2018; (ii) Earl H, *et al.*Health Technol. Assess. 2020 Aug; 24(40):1-190. Ch5 pp.65-85.