Institution: The Institute of Cancer Research

Unit of Assessment: Clinical Medicine

Title of case study: Improved radiotherapy approaches for breast cancer treatment

Period when the underpinning research was undertaken: 2006 to 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:
Professor Judith Bliss	ICR Team Leader	01/10/1985–Present
Mrs Joanne Haviland	ICR Principal Statistician	01/01/2001–22/05/2013; 28/11/2016–Present
Dr Anna Kirby	ICR Associate Honorary Faculty	16/03/2015–Present
Dr Navita Somaiah	ICR Team Leader	28/10/2013–Present
Professor John Yarnold	ICR Team Leader	01/11/1980–31/07/2020

Period when the claimed impact occurred: 2009 onwards

Is this case study continued from a case study submitted in 2014? Yes. The impact of the research described in the 2014 impact case study has continued. In addition, and building on this work, ICR researchers led the FAST-Forward trial (involving 4,150 patients) which reported in April 2020 and confirmed that 26Gy in 5 fractions (1 week) is as effective as the standard of 40Gy in 15 fractions (3 weeks). There has been rapid uptake of this new schedule, again creating significant impact.

1. Summary of the impact

The Institute of Cancer Research (ICR) led clinical radiotherapy fractionation research in breast cancer that resulted in impact on:

- **Clinical practice.** Shorter standard curative radiotherapy regimens have been adopted internationally for patients with breast cancer, the most common malignancy in women in UK and other developed nations.
- **Patients.** The shorter regimens led to reduced side-effects, less time off work and savings in travel time and costs without loss of very high levels of cancer control.
- **The economy.** Healthcare systems benefit from reduced treatment costs. The switch from 15 to 5 fractions for women with breast cancer became an internationally-recommended standard in May 2020 for breast cancer radiotherapy during the COVID-19 pandemic. Full implementation is expected to save the NHS GBP40,000,000 annually.

2. Underpinning research

Initiating the development of new radiotherapy dose-fractionation practices. Historical assumptions that radiotherapy is always best delivered in multiple small doses (called fractions) to the highest tolerated total dose was first challenged by a retrospective analysis of treatment outcomes in the mid-1980s, suggesting that breast cancer might be an exception. The ICR, with its clinical partner The Royal Marsden NHS Foundation Trust (RM), led the initiation of research which underpinned the development of new radiotherapy dose-fractionation practices.

The ICR team, comprising clinicians and statisticians, showed in the Standardisation of Breast Radiotherapy (START) pilot trial—involving 1,410 patients—that excellent cancer control with no increase in adverse effects could be maintained with fewer larger fractions and a lower total dose. The 10-year results published in 2006 challenged 70 years of highly conservative attitudes to radiotherapy dose-fractionation **(Ref. 1)**.

Building on the first START trial for women with early breast cancer. Teams led by ICR Professors John Yarnold and Judith Bliss subsequently designed and implemented the START

trials A and B funded by Cancer Research UK (CRUK), the Medical Research Council (MRC), and the Department of Health. These studies involved 35 UK radiotherapy centres and recruited 4,450 patients. Five-year results were published in 2008 **(Ref. 2 and 3)** and the results of these two parallel trials led to the recommendation, endorsed by the National Institute for Health and Care Excellence (NICE) in 2009, that a 15-fraction protocol over 3 weeks (total 40Gy) should be the standard treatment protocol, replacing commonly-used 5-week schedules (total 50Gy). Definitive 10-year results published in 2013 **(Ref. 4)** confirmed the long-term safety and effectiveness of 40Gy delivered over 3 weeks. The 3-week schedule became a standard of care for women in the UK as well as internationally, including mainland Europe and North America.

The NIHR-funded FAST-Forward trial, involving 4,150 patients, was developed by Professors Yarnold and Bliss to compare the safety and effectiveness of 26Gy in 5 fractions (1-week schedule) compared to the current 40Gy in 15 fractions (3-week schedule). Five-year results were fast-tracked to publication in The Lancet in April 2020, confirming that 26Gy (1-week schedule) is as effective as the standard of 40Gy (3-week schedule) for local tumour control and as safe in terms of normal tissue effects for patients prescribed adjuvant local radiotherapy after primary surgery for early-stage breast cancer **(Ref 5)**. The FAST-Forward protocol was rapidly adopted in 2020 (see *Section 4*).

Partial breast and reduced dose radiotherapy trial. Research has shown that having whole breast radiotherapy after breast-conserving surgery reduces the risk of relapse. Traditionally, patients have full dose radiotherapy to the whole breast after surgery even if they are considered at relatively low risk of their cancer coming back. However, breast cancer patients may experience long-term side effects from whole breast radiotherapy. For example, their breasts may become harder and/or smaller, and arm movement may be limited. Subsequently, ICR clinicians and statisticians designed the IMPORT LOW (Intensity-Modulated and Partial-Organ Radiotherapy Low Risk) trial to investigate efficacy of partial-breast versus whole-breast irradiation using standard UK hypofractionated radiotherapy either 30Gy or 40Gy in 15 fractions (3-week schedule). The CRUK-funded IMPORT LOW trial (Chief Investigator: originally Professor Yarnold, ICR and then replaced by Professor Charlotte Coles, Cambridge) was a multicentre, randomised, controlled trial conducted in 30 UK radiotherapy centres. This trial, involving 2,018 patients, showed that partial-breast was as effective as whole breast radiotherapy in controlling the cancer at 5 years. All treatment groups received simple forward-planned intensity-modulated radiation techniques to optimise dose homogeneity **(Ref. 6)**. Further analysis of the trial data showed that partial-breast radiotherapy reduces long-term radiotherapy side effects in women with breast cancer with over 50% of the patients not reporting moderate or marked side effects at any time and most side effects reducing over time **(Ref. 7)**.

3. References to the research

Key: **ICR employed staff** at the time of publication, **ICR Team Leaders and independent researchers (including Honorary Faculty)** at the time of publication.

1. Owen JR, Ashton A, **Bliss JM, Homewood J**, **Harper C**, **Hanson J**, **Haviland J**, Bentzen SM, **Yarnold JR.** 2006, Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial, Lancet Oncol. 7 (6), 467-471. (http://dx.doi.org/10.1016/S1470-2045(06)70699-4). *Times Cited: 368 (WOS).*
2. Bentzen SM, Agrawal RK, Aird EGA, Barrett JM, Barrett-Lee PJ, Bentzen SM, **Bliss JM**, Brown J, Dewar JA, Dobbs HJ, **Haviland JS**, Hoskin PJ, Hopwood P, Lawton PA, Magee BJ, **Mills J**, Morgan DAL, Owen JR, **Simmons S**, **Sumo G**, **Sydenham MA**, Venables K, **Yarnold JR.** 2008, The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet. 371 (9618), 1098-1107. (http://dx.doi.org/10.1016/S0140-6736(08)60348-7). *Times cited: 675 (WOS).*
3. Bentzen SM, Agrawal RK, Aird EGA, Barrett JM, Barrett-Lee PJ, Bentzen SM, **Bliss JM**, Brown J, Dewar JA, Dobbs HJ, **Haviland JS**, Hoskin PJ, Hopwood P, Lawton PA, Magee BJ, **Mills J**, Morgan DAL, Owen JR, **Simmons S**, **Sumo G**, **Sydenham MA**,

Venables K, **Yarnold JR.** 2008, The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol. 9 (4), 331-341. (http://dx.doi.org/10.1016/S1470-2045(08)70077-9). *Times cited: 661 (WOS).*

4. **Haviland JS**, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, Dobbs HJ, **Hopwood P**, Lawton PA, Magee BJ, **Mills J**, **Simmons S**, **Sydenham MA**, Venables K, **Bliss JM***, **Yarnold JR***, START Trialists' Group. 2013, The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet. 14 (11), 1086-1094. (http://dx.doi.org/ 10.1016/S1470-2045(13)70386-3). *Times cited: 631 (WOS).* *Contributed equally.
5. Brunt AM*, **Haviland JS***, Wheatley DA, **Sydenham MA**, Alhasso A, Bloomfield DJ, Chan C, Churn M, Cleator S, Coles CE, Goodman A, Harnett A, **Hopwood P**, **Kirby AM**, Kirwan CC, Morris C, Nabi Z, Sawyer E, **Somaiah N**, **Stones L**, Syndikus I, **Bliss JM#**, **Yarnold JR#**; 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 May 23;395(10237):1613-1626. (http://dx.doi.org/10.1016/S0140-6736(20)30932-6). *Times cited: 54 (WOS)*. *Joint first authors. #Joint senior authors.
6. Coles CE, **Griffin CL**, **Kirby AM**, **Titley J**, Agrawal RK, Alhasso A, **Bhattacharya IS**, Brunt AM, Ciurlionis L, Chan C, Donovan EM, **Emson MA**, Harnett AN, **Haviland JS**, **Hopwood P**, Jefford ML, **Kaggwa R**, Sawyer EJ, Syndikus I, Tsang YM, Wheatley DA, Wilcox M, **Yarnold JR***, **Bliss JM***; IMPORT Trialists. 2017, 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. 9;390(10099):1048-1060. (http://dx.doi.org/10.1016/S0140-6736(17)31145-5). *Times cited: 172 (WOS).* *Contributed equally.
7. **Bhattacharya IS***, **Haviland JS***, **Kirby AM**, Kirwan CC, **Hopwood P**, **Yarnold JR**, **Bliss JM#**, Coles CE#; IMPORT Trialists. 2019, 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. 1;37(4):305-317. (http://dx.doi.org/10.1200/JCO.18.00982). *Times cited: 19 (WOS).* *Joint first authors. #Joint senior authors.

Additional Quality Indicators

Selected peer reviewed research grant support:

- National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme, 2011 to 2020: GBP3,053,251: FAST-Forward: a randomised clinical trial testing a 1-week course of curative whole breast radiotherapy against a standard 3-week schedule in terms of local cancer control and late adverse effects in women with early breast cancer.
- Cancer Research UK Clinical Trial grant, 2006 to 2021, GBP1,940,900: IMPORT LOW: Randomised trial testing intensity modulated and partial organ radiotherapy following breast conservation surgery for early breast cancer.

Prizes/Recognition:

- In 2017 Professor John Yarnold was awarded the Weiss Medal by The Association for Radiation Research in recognition of his work examining the clinical benefit of hyperfractionation.
- NIHR Senior Investigator Award to Professor Judith Bliss (2017 to 2021) recognising her strategic contribution in driving the national and international cancer research agenda by changing practice via radiotherapy clinical trials.

4. Details of the impact

There are approximately 55,200 new breast cancer cases in the UK annually (2014–2017). Radiotherapy is an important part of the treatment for these patients with 63% of breast cancer patients receiving radiotherapy as part of their primary treatment.

International guidelines/recommendation and uptake of the improved radiotherapy techniques. The interim results of the START trials led to the NICE recommendation in 2009 that a 15-fraction regimen over 3 weeks (total 40Gy) should be the standard treatment protocol, replacing commonly used 5-week schedules (total 50Gy) and remaining the standard of care since 2009 **[A]**. NHS commissioning guidance states: "*At least 80% of patients for whom radiotherapy is indicated as part of treatment for breast cancer should receive no more than 15 fractions*". Uptake of the 40Gy in 15-fraction protocol (3-week schedule) has been widespread across the UK. Data from April 2019 showed that the use of 40Gy in 15 fractions was used for 92% of weekly courses in adjuvant breast cancer treatment **[B]**. This 40Gy in 15-fraction protocol in breast cancer radiotherapy has also been adopted globally and is recommended by the American Society for Radiation Oncology (ASTRO), the National Comprehensive Cancer Network (NCCN), the European Society for Radiotherapy, and the Brazilian Society for Radiotherapy (SBRT). In Canada, by 2014, 75%–85% of patients were reported to be following the 40Gy in 15-fraction protocol developed in the START trials **[C]**.

The results from the FAST-Forward trial are already changing clinical practice. The trial found that delivering a shorter course (26Gy in 5 fractions, 1-week schedule) compared to women who have undergone surgery for early-stage breast cancer was as safe and effective as the standard of 3 weeks, which will reduce treatment times and save healthcare resources. Professor Nick Lemoine, Medical Director of the NIHR Clinical Research Network (CRN), said:

> "*Breast cancer is the most common cancer amongst women and the largest user of radiotherapy facilities in the UK. NIHR is committed to funding practice-changing research and this landmark study supports that position. This study shows how innovation can be both clinical and cost-effective and it's an important marker for broader impact of healthcare treatments and tests for those who plan, provide or receive care from NHS and social care services*." **[D]**

The FAST-Forward approach, 26Gy in 5 fractions (1-week schedule), means that the number of hospital visits is reduced from 15 to only 5 and is expected to save the NHS GBP40,000,000 annually. For example, Swansea's Singleton Hospital introduced the FAST-Forward approach in June 2020 as their standard of care. This quick adoption was made possible by a GBP12,000,000 investment in new equipment at the radiotherapy department, funded by the Welsh Government and Swansea Bay University Health Board. The reduction in treatment times could allow the hospital to treat more patients every year **[E]**. In addition, in May 2020, the 26y in 5 fractions (1-week schedule) regimen was recommended for immediate adoption during the COVID-19 pandemic by an international panel of experts **[F]**. By adopting these recommendations it allows centres to target radiotherapy to those with the highest risk of relevant breast recurrence, protects patients and health care professionals from potential exposure to COVID-19, and reduces the workload for health care providers and/or infrastructure at the moments that resources face strain due to the pandemic. The use of the 26Gy in 5 fractions (1-week schedule) radiotherapy regimen rapidly increased during the first lockdown in England from 0.2% in April 2019 to 60% in April 2020 **[B]**. To enable this impact, the FAST-Forward protocol and radiotherapy planning pack were made publically available on the ICR external website.

Following the initial results of the IMPORT LOW trial, the UK Royal College of Radiologists 2016 breast radiotherapy consensus stated that partial-breast radiotherapy could be considered for selected patients using the IMPORT LOW technique **[G]**. In addition, the Danish Breast Cancer Oncology Group adopted this partial-breast radiotherapy technique in 2016 **[H]**. It is currently being applied in Australia and enquiries regarding the technique have been received from other international groups, including North America. Moreover this approach is recognised as an important improvement for generations of women diagnosed with breast cancer. The British

Association of Surgical Oncologists introduced a best practice recommendation in the wake of this trial to insert surgical clips around the tumour bed for all patients undergoing breast conserving surgery, in order to optimise partial-breast radiotherapy **[I]**.

Patient benefit of the improved radiotherapy techniques. With the START regimen, women are spending less time and money travelling for treatment, and also report less late tissue damage effects (e.g. breast shrinkage and induration)—without any loss of cancer control. We estimate each patient saves over 14 hours in travel and appointment—a total of 345,166 hours each year for all patients.

The IMPORT LOW approach has significant benefits for patients as it can substantially reduce the side effects, with >50% of women in the study having no long-term side effects at all 5 years after treatment **(Ref. 4** and **Ref. 5)**. In addition, it has facilitated the development of 3D intensity modulated radiotherapy, a more accurate way of delivering radiotherapy, throughout the UK. 30 UK radiotherapy centres participated in the trial, many of which were using 2D breast radiotherapy routinely at the start of the trial **[I]**. There are no extra training or resources required by sites so the treatment is easily implementable without any additional costs or resources.

Cost saving for the NHS and global healthcare as a result of improved radiotherapy techniques. The NHS is saving substantially on treatment costs and also has increased capacity for radiotherapy delivery. The START protocol (40Gy in 15 fractions) has been recommended since 2009. We have estimated that 25,000 women per year were treated with the START protocol (2009 to 2019) with a saving of GBP1,610 per patient which represents a total NHS saving of GBP40,000,000 per year. Therefore during the REF impact period, the START protocol has saved the NHS an estimated GBP240,000,000 (2014 to 2019). The FAST-Forward protocol (26Gy in 5 fractions) being adopted from 2020 onwards will bring further cost saving.

The change from the previous conventional course of 50Gy in 25 fractions (5-week schedule) to 40Gy in 15 fractions (START protocol, 3-week schedule) has seen a decrease in cost per patient from USD13,358 to USD8,328 in the United States—a decrease of 38%. Australian data shows a comparable cost decrease of 32% (from USD8,272 to USD5,613). These figures consider both the additional costs per fraction delivered and the associated weekly management costs, which are substantially burdensome beyond week 4 of breast cancer treatment **[J]**.

5. Sources to corroborate the impact

A. NICE recommendation of the START protocol: https://www.nice.org.uk/guidance/ng101
B. Increased use of the FAST-Forward protocol during COVID-19: https://doi.org/10.1016/S1470-2045(20)30743-9
C. Uptake of START protocol in Canada: http://dx.doi.org/10.2147/BCTT.S81710
D. NIHR press release: https://www.nihr.ac.uk/news/one-week-course-of-radiotherapy-could-benefit-women-with-early-stage-breast-cancer/24680
E. BBC news article about the adoption of the FAST-Forward approach: https://www.bbc.co.uk/news/uk-wales-53181436
F. International Guidelines on Radiation Therapy for Breast Cancer During the COVID-19 Pandemic: https://doi.org/10.1016/j.clon.2020.03.006
G. UK Royal College of Radiologists 2016 breast radiotherapy consensus: https://www.rcr.ac.uk/clinical-oncology/service-delivery/postoperative-radiotherapy-breast-cancer-uk-consensus-statements
H. Danish Breast Cancer Oncology Group recommendation of partial breast radiotherapy: http://dx.doi.org/10.1080/0284186X.2017.1408962.
I. Impact of the IMPORT LOW trial: https://www.nihr.ac.uk/documents/case-studies/import-low-trial/21952
J. Cost saving in Australia and the United states: http://dx.doi.org/10.1002/jmrs.273.