NIHR | National Institute for Health and Care Research

Journals Library

Health Technology Assessment

Volume 30 • Issue 29 • April 2026

ISSN 2046-4924

A novel methodology using direct patient contact and UK national registries to collect long-term data from randomised trials: TARGIT-X – an extended follow-up study of the TARGIT-A trial of targeted intraoperative radiotherapy for breast cancer

Jayant S Vaidya, Norman R Williams, Max Bulsara, Chris Brew-Graves, Ingrid Potyka, Nicholas Roberts, Julie Lindsay, Siobhan Laws, Sanjay Raj, Michael Douek, Mary Falzon, Gloria Petralia, Sarah Needleman, Anu Malhotra, Marcelle Bernstein and Jeffrey S Tobias

DOI 10.3310/GJJV2820

NIHR | National Institute for Health and Care Research

Health Technology Assessment

Extended Research Article

A novel methodology using direct patient contact and UK national registries to collect long-term data from randomised trials: TARGIT-X – an extended follow-up study of the TARGIT-A trial of targeted intraoperative radiotherapy for breast cancer

Jayant S Vaidya,[1*] Norman R Williams,[1] Max Bulsara,[1,2] Chris Brew-Graves,[1] Ingrid Potyka,[1] Nicholas Roberts,[1] Julie Lindsay,[3] Siobhan Laws,[4] Sanjay Raj,[5] Michael Douek,[6,7,10] Mary Falzon,[8] Gloria Petralia,[9,10] Sarah Needleman,[11] Anu Malhotra,[12] Marcelle Bernstein[13] and Jeffrey S Tobias[14]

[1]Division of Surgery and Interventional Science, University College London, London, UK
[2]Institute for Health Research, University of Notre Dame, Fremantle, Australia
[3]Department of Surgery, Ninewells Hospital, Dundee, UK
[4]Department of Surgery, Royal Hampshire Hospital, Winchester, UK
[5]Department of Clinical Oncology, Royal Hampshire Hospital, Winchester, UK
[6]Nuffield Department of Surgical Sciences, Botnar Research Centre, University of Oxford, Headington, Oxford, UK
[7]Department of Surgery, Guy's Hospital, London, UK
[8]Department of Pathology, University College London Hospital, London, UK
[9]Department of Surgery, University College London Hospital, London, UK
[10]Department of Surgery, John Radcliffe Hospital, Oxford University Hospitals, Headington, Oxford, UK
[11]Department of Clinical Oncology, Royal Free Hospital, London, UK
[12]Department of Pathology, Guy's Hospital, London, UK
[13]Patient advocate, London, UK
[14]Department of Clinical Oncology, University College London Hospital, London, UK

[*]**Corresponding author** jayant.vaidya@ucl.ac.uk

Published April 2026
DOI: 10.3310/GJJV2820

This report should be referenced as follows:

Vaidya JS, Williams NR, Bulsara M, Brew-Graves C, Potyka I, Roberts N, *et al.* A novel methodology using direct patient contact and UK national registries to collect long-term data from randomised trials: TARGIT-X – an extended follow-up study of the TARGIT-A trial of targeted intraoperative radiotherapy for breast cancer. *Health Technol Assess* 2026;**30**(29). https://doi.org/10.3310/GJJV2820

Health Technology Assessment

ISSN 2046-4924 (Online)

Impact factor: 4

A list of Journals Library editors can be found on the NIHR Journals Library website

Launched in 1997, *Health Technology Assessment* (HTA) has an impact factor of 4 and is ranked 30th (out of 174 titles) in the 'Health Care Sciences & Services' category of the Clarivate 2022 Journal Citation Reports (Science Edition). It is also indexed by MEDLINE, CINAHL (EBSCO Information Services, Ipswich, MA, USA), EMBASE (Elsevier, Amsterdam, the Netherlands), NCBI Bookshelf, DOAJ, Europe PMC, the Cochrane Library (John Wiley & Sons, Inc., Hoboken, NJ, USA), INAHTA, the British Nursing Index (ProQuest LLC, Ann Arbor, MI, USA), Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and the Science Citation Index Expanded™ (Clarivate™, Philadelphia, PA, USA).

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta.

Criteria for inclusion in the *Health Technology Assessment* journal

Manuscripts are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This article

The research reported in this issue of the journal was funded by the HTA programme as award number 14/49/13. The contractual start date was in July 2017. The draft manuscript began editorial review in April 2025 and was accepted for publication in August 2025. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).

Abstract

Background: Many diseases, including breast cancer, have a long natural history; therefore, longer-term effects of treatments are important for patients and for their full evaluation. However, trial follow-up data are collected by specific staff and are funded for a relatively short duration.

Objective: We evaluated whether we could collect follow-up information for patients in a breast cancer randomised clinical trial by direct patient contact and data from national registries.

Setting: The TARGIT-A randomised clinical trials of targeted intraoperative radiotherapy during lumpectomy versus whole-breast external beam radiotherapy (n=2298), and delayed TARGIT-IORT vs. external beam radiotherapy (n = 1153), recruited women with early breast cancer diagnosed in 33 centres in 12 countries, between March 2000 and June 2012. We planned to recruit all United Kingdom patients from the TARGIT-A trials for extended follow-up. These were the first randomised trials of intraoperative radiotherapy for breast cancer.

Methods: We assessed the feasibility of recording whether patients are alive and their current health status, including events related to breast cancer, and effects of radiotherapy such as lung cancer diagnoses, by direct patient contact and data from NHS Digital (health episodes, diagnoses and death). Patients were consented in collaboration with the recruiting site and were then contacted annually, if appropriate, directly by the trial centre. We calculated the proportion of eligible patients whose status could be ascertained, contacted, consented and provided follow-up information via direct patient contact and/or NHS Digital data. We estimated the additional years of follow-up and its cost.

Results: Six hundred and seven of 714 United Kingdom patients originally recruited in the TARGIT-A trials were initially eligible. We ascertained the current status or reason for non-participation of 574 (94.5%); 87% (502/574) of these patients' health status could be determined. Of these, 73% (366/502) or 60.3% of the total (366/607) were found to be in good health, provided valid consent for TARGIT-X and their health status. One hundred and thirty-six patients did not participate in TARGIT-X because: 105/136 (77%) were too unwell or had died, and for 6 patients, the consent was either incomplete or the physical form could not be traced. Less than 5% (25/502) of patients were unwilling to participate: 23 declined and 2 withdrew. We recorded an additional 103 deaths, more than doubling the initial number to 203. The quality of data returned by patients was very good [e.g. mismatch rate for recording date < 0.1% (1/1470 forms)]. Patients who participated increased their follow-up by a median 6 years [to 14 years (interquartile range 13–16)]. We found a much lower incidence of lung cancer diagnoses with TARGIT-IORT compared with EBRT (16-year incidence 1.8% vs 7.2%). The cost, including research funds, was < £60/patient/year of follow-up. Limitations included difficulties in receiving data from NHS Digital due to their repeated organisational changes, plus unexpected price rises in the costing of data download.

Strengths and limitations: We were able to establish direct contact with the patient while they are alive, as well as gathered data from the national registries about their hospital episodes/new diagnoses and checked if they had died. Another strength is that despite the study management being considerably disrupted due to the COVID-19 pandemic (2020–present), which erupted in the midst of the study (2017–24), we believe we have shown that the approach is an effective means of continuing follow-up in the United Kingdom. A limitation of our approach is that the initial consent from the patient requires the site principal investigators to contact the patient, but this is just once. If consenting for direct patient contact and data collection from national registries is included in the initial trial set up, then our approach will enable very long-term follow-up of clinical trials.

Future work: We recommend a study of using electronic secure systems for direct patient contact from the outset of a clinical trial to investigate the organisational and systemic bottlenecks in NHS Digital services, with a view to reduce bureaucracy and cost, and to investigate why results of large international well-conducted randomised trials that have been shown to be beneficial to patients and cost-effective to the health system are not widely adopted in the United Kingdom, while they are included in almost every other country's clinical practice guideline and get widely adopted worldwide to assess the influence of preconceived notions, conflicts of interest, that could prompt improvements in the National Institute for Health and Care Excellence processes.

Conclusion: In the United Kingdom, 95% of patients are willing to be followed up in the long term. It is feasible to collect follow-up data for long-term health conditions accurately from patients with direct patient contact together with NHS Digital. It leads to a substantial increase in the length of follow-up and number of relevant events, at a low cost. Our new approach could be adopted as an efficient method of obtaining long-term follow-up data from patients in randomised clinical trials.

Trial registration: This trial is registered as Current Controlled Trials ISRCTN (ISRCTN86287193) and ClinicalTrials.gov (NCT03501121) in April 2018, UK R&D ID Number: 17/0774, Ethics – REC reference: 18/LO/0181.

Funding: This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 14/49/13) and is published in full in *Health Technology Assessment*; Vol. 30, No. 29. See the NIHR Funding and Awards website for further award information.

Contents

List of tables

List of figures

List of supplementary material

Report Supplementary Material 1	Letter from trials unit to PI
Report Supplementary Material 2	Letter from site to patient
Report Supplementary Material 3	Patient information sheet from site to patient
Report Supplementary Material 4	Informed consent form from site to patient
Report Supplementary Material 5	Case report form from site to patient
Report Supplementary Material 6	Contact details form from site to patient
Report Supplementary Material 7	General practitioner letter from site to GP
Report Supplementary Material 8	Letter from trials unit to patient
Report Supplementary Material 9	Case report form from trials unit to patient

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/GJJV2820).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

The supplementary materials (which include but are not limited to related publications, patient information leaflets and questionnaires) are provided to support and contextualise the publication. Every effort has been made to obtain the necessary permissions for reproduction, to credit original sources appropriately, and to respect copyright requirements. However, despite our diligence, we acknowledge the possibility of unintentional omissions or errors and we welcome notifications of any concerns regarding copyright or permissions.

List of abbreviations

APC	admitted patient care
COVID-19	coronavirus disease 2019
CRF	case report form
DARS	Data Access for Research Services
DPC	direct patient contact
EBRT	external beam radiotherapy
FAE	Finished Admission Episodes
FAEem	Finished Admission Episodes by emergency admission
FCE	Finished Consultant Episodes
IORT	intraoperative radiotherapy
NHSCR	National Health Service Central Register
NICE	National Institute for Health and Care Excellence
NRS	National Records of Scotland
ONS	Office of National Statistics
PI	principal investigator
RFH	Royal Free Hospital
TARGIT	TARGeted Intraoperative radioTherapy
UCL	University College London
UCLH	University College London Hospitals
TARGIT-IORT	TARGeted Intraoperative radioTherapy - IntraOperative RadioTherapy

Plain language summary

As patients with breast cancer live far longer, and treatments have long-term effects, follow-up longer than normally funded is important for patients, clinicians and policy-makers. We evaluated (TARGeted Intraoperative radioTherapy-X study) whether we could collect follow-up data by ‘direct patient contact’ with which the patient could update the trials unit with their health status directly and from NHS Digital.

We had recruited (March 2000–June 2012) 3451 patients in the TARGeted Intraoperative radioTherapy-A randomised clinical trials, which compared single-dose targeted intraoperative radiotherapy versus standard of postoperative whole-breast external beam radiotherapy given as daily doses over a course of 3–6 weeks.

Six hundred and seven of 714 UK patients were eligible. The health status or the reason for non-participation was available for 574 (95%), and health status was determined in 87% of cases (502/574). Of these, 73% (*n* = 366, 60.3% of the total) were healthy and participated. Of the patients who did not participate, 105/136 (77%) were too unwell or had died, 23 declined and 2 withdrew, and in 6, consent was invalid. Less than 5% (25/502) of patients declined participation.

We doubled our knowledge about survival (recorded deaths increased from 100 to 203).

Patients recorded their own data very accurately: only 1 error among the 1470 case report forms – an error rate of < 0.1%. NHS Digital adds substantially to the number of events and lengthens the available follow-up.

The length of follow-up increased by 6 years, to a median of 14 years (interquartile range 13–16). We found that using TARGIT-IORT reduced lung cancer incidence by two-thirds compared with EBRT. The cost was < £60 per patient per year of follow-up.

We conclude that in the UK, it is feasible and cost-effective to roll out direct patient contact as a method of accurate long-term follow-up of patients at a low cost. Our new approach could be adopted as an approach in other randomised clinical trials.

Scientific summary

Many diseases, including breast cancer, have a long natural history, and effects of treatments in the longer term are important for patients and for their full evaluation. However, the follow-up data are collected by specific staff employed for the purposes of the trial, and typically, the funding duration is relatively short. We evaluated whether we could collect follow-up data for patients in a breast cancer clinical trial by direct patient contact (DPC) and data downloads from routinely collected NHS data.

We had designed and recruited women with early breast cancer (*n* = 3451) in the TARGeted Intraoperative radioTherapy (TARGIT)-A randomised clinical trials in 33 centres in 12 countries from March 2000 to July 2012. The main trial (*n* = 2298) compared risk-adapted, single-dose, targeted intraoperative radiotherapy (IORT) given during lumpectomy surgery (TARGIT-IORT) versus conventional postoperative whole-breast external beam radiotherapy (EBRT) given as daily doses over 3–6 weeks. The subsequently started parallel trial (*n* = 1153) compared delayed TARGIT-IORT given after reopening the initial lumpectomy wound with conventional postoperative whole-breast EBRT given as daily doses over 3–6 weeks.

In the current study, we planned to recruit all UK participants who participated in the TARGIT-A trials to assess whether it is feasible to collect longer-term follow-up information from patients by DPC plus data downloads from routinely collected NHS data.

We assessed the feasibility of recording whether patients are alive and well, and also their current health status, and other radiotherapy-related health effects such as other cancer diagnoses by DPC and data from NHS Digital service (health episodes, diagnoses and death). Patients were planned to be first consented in collaboration with the recruiting site. One year after this consent was received by the University College London trials office, and annually thereafter, the trials office staff contacted each patient after first confirming with the recruiting centres that they had not already died or had become too unwell. There were no medical interventions performed as part of this study. We complemented this patient-reported information from data download for patient's health status data from NHS Digital.

The main outcome measure was the proportion of eligible patients whose status could be ascertained, contacted, consented and provide follow-up information via DPC and/or NHS Digital data download.

We found that 607 of 714 UK patients originally recruited in the TARGIT-A trial were initially eligible by the time the TARGIT-X study was started in 2018. The age of entry into TARGIT-X was about 10 years older (median 73 vs. 63 years). We found that a large proportion of patients who were still alive and well were happy to sign the consent form. We could ascertain the status or reason for non-participation of 574 (94.5%) of eligible patients; 87% (502/574) of these patients' status could be determined. Of these 502 patients, 73% (*n* = 366, 60.3% of the total) were found to be in good health, willing to participate, had a valid signed consent form and provided at least one follow-up case report form (CRF). One hundred and thirty-six patients did not complete a consent for TARGIT-X (DPC + NHS Digital tracking) for the following reasons: 105/136 (77%) were too unwell or had died already, 23 declined and 2 withdrew, and in 6, the consent was either incomplete or the physical form could not be traced. Thus, < 5% (25/502) of patients declined participation.

We recorded an additional 103 deaths – 77 from the site staff before attempting DPC, and 26 from NHS Digital. Thus, out of the total 203 deaths, TARGIT-X contributed 103 events – more than doubling the number of events from before TARGIT-X started. Data quality of CRFs returned by patients was found to be very good. Error in the date on the form was in < 0.1%. The contribution towards relevant outcome data from NHS Digital is considerable. It adds to the number of trial-related events and lengthens the available follow-up substantially.

The length of follow-up of patients who participated increased by up to 6 years, to a median of 14 years (interquartile range 13–16). We found significantly more lung cancer diagnoses with EBRT vs TARGIT-IORT, HR 3.3 (95% CI 1.1 to 10.2), *p = 0.0266*; 16-year incidence of lung cancer: EBRT: 7.2% vs. TARGIT: 1.8%. Using the grant funding of the project for cost calculation (even though it includes research costs), it was estimated to be < £60 per patient per year of follow-up. Limitations to the study included difficulties in receiving data from NHS Digital due to their repeated organisational changes, plus unexpected price rises in the costing of data download.

In conclusion, we found that in the UK, it is feasible and cost-effective to roll out DPC together with NHS Digital as a method of continuing follow-up of patients with long-term health conditions. Patients are willing and report data accurately. It leads to a substantial increase in the length of follow-up and number of events at a low cost. Our new approach could be adopted as an efficient method of obtaining long-term follow-up data from patients in randomised clinical trials.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN (ISRCTN86287193) and ClinicalTrials.gov (NCT03501121) in April 2018, UK R&D ID Number: 17/0774, Ethics – REC reference: 18/LO/0181.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 14/49/13) and is published in full in *Health Technology Assessment*; Vol. 30, No. 29. See the NIHR Funding and Awards website for further award information.

Chapter 1 Introduction (background and rationale)

In 2022, there were 2.3 million new cases of breast cancer diagnosed worldwide and 666,000 deaths,[1] a 10% increase in incidence since 2018.[2] Breast cancer remains the commonest female malignancy in most countries of the world and its incidence continues to rise.[1]

There has been a steady decline in mortality from breast cancer over the last 30 years. In the UK, the age standardised mortality rate decreased from approximately 30 deaths per 100,000 women in 1985 to 15 deaths per 100,000 women in 2017.[3,4] The continuing downwards trend is likely due to the introduction of adjuvant systemic therapy and incremental improvements in surgery, radiotherapy and potentially earlier presentation of the disease.[5]

The need for a new approach to collect long-term follow-up

We need to recognise that this fantastic reduction in population mortality from breast cancer has occurred due to breakthrough new treatments and confirm their benefits via the conduct of well-designed randomised clinical trials. Also, with better treatments, the 'event rates' have thankfully reduced greatly. Breast cancer has a long natural history, measured in 5, 10 and 20 years, rather than 1, 2 or 5 years. Therefore, there is a well-recognised need for really long follow-up of patients recruited in randomised trials of breast cancer. However, the usual method of clinical trial follow-up through dedicated staff at each hospital site is very expensive, and funding bodies typically prefer to fund new trials rather than continue to fund longer-term follow-up of older trials.

This was the reason we thought of collecting data by direct patient contact complemented by routinely collected NHS data.

The main reason for this study

The TARGeted Intraoperative radioTherapy (TARGIT)-X study was designed to assess whether it is possible to collect long-term data from patients by using:

a. Direct Patient Contact (DPC)
b. Data from routinely collected hospital and national registry data.

The TARGIT-A trials

With the great improvement in length of life after breast cancer in the last three decades, long-term effects of treatments and the quality of life after breast cancer have become increasingly relevant. One important factor determining the quality of life is the extent of surgery for breast cancer, which used to be a full mastectomy – the removal of the whole breast.

Today, a large proportion of patients can avoid removal of the whole breast and can instead have removal of just the cancerous lump, checking the glands under the arm. This is normally followed by radiation (X-ray) treatment given over several days or weeks of daily treatments in the radiotherapy centre at the hospital in order to reduce the risk of local recurrence.

Based on laboratory data and clinical trial results, we proposed in the early 1990s that while the usual long course of radiotherapy to the whole breast after lumpectomy remains an effective treatment, it can be an overtreatment in many patients.[6] We proposed that radiotherapy to the tissue only around the tumour (within a risk-adapted approach) may be as effective. This led to the development, during 1996–8, of a radiation therapy device and a new surgical technique called targeted intraoperative radiotherapy (TARGIT-IORT).[7,8] TARGIT-IORT was formally compared with whole-breast external beam radiotherapy (EBRT) in the TARGIT-A trials.

The TARGIT-A trials (henceforth called TARGIT-A trial) were based on the rationale that microscopic tumour foci are found well distant from the index tumour site, but their growth does not appear to be affected by giving or omitting whole-breast radiotherapy, and most early in-breast recurrences occur at the site of the original tumour site. Thus, it made sense to focus radiation only to the tumour bed, and deliver it during surgery. The approach has the advantage of delivering the radiation immediately, accurately aimed at the tumour bed under direct vision, thus avoiding a 'geographical miss'. With this academic insight, the TARGIT (TARGeted Intraoperative radioTherapy) technique using INTRABEAM™ (Carl Zeiss Meditec) was developed by our team at University College London (UCL)[6–8] in collaboration with the manufacturers (originally Photoelectron Corporation, Boston, USA, and then Carl Zeiss Surgical, Oberkochen, Germany). TARGIT-IORT enables the patient to have her radiotherapy as soon as the cancerous lump is removed during the same anaesthetic.[7,8] The radiation treatment is completed immediately, at the same time as the lumpectomy to remove the cancer, and the radiation is delivered precisely where required. Thus, precision and immediacy are both achieved. Vital organs (particularly the heart and the lungs) are spared, and the device can be used in a standard operating theatre. It is substantially more convenient to patients who prefer it even to the newer 5-day course of postoperative EBRT.[9] Finally, it is also less expensive for the tax-payer[10] and significantly reduces the carbon footprint of cancer treatment.[11]

The TARGIT-A international randomised trial – in which 3451 patients from 33 centres in 11 countries participated – compared the TARGIT treatment given during the operation (i.e. just one treatment) with conventional radiotherapy (15–30 doses given every day for 3–6 weeks). The main trial compared immediate TARGIT-IORT given during the initial lumpectomy surgical procedure for removing the breast cancer versus whole-breast radiotherapy, and the main results were published in the *Lancet* (twice), *British Medical Journal*, *British Journal of Cancer* and the *Red Journal*.[12–15] The subsequently started parallel trial compared delayed TARGIT-IORT given by reopening the wound versus EBRT, and the results were published in *JAMA Oncology*.[16] The recruitment in the trials was started in March 2000 and completed in June 2012. The early and long-term results published in high-profile journals[12–20] showed that conventional EBRT given over several weeks and TARGIT-IORT given at the time of lumpectomy within a risk-adapted individualised approach are as effective in controlling breast cancer. Furthermore, with TARGIT-IORT, there were significantly fewer deaths from causes other than breast cancer because of fewer deaths from cardiovascular causes, lung problems and other cancers by avoiding the scattered radiation to surrounding normal tissues and vital organs (e.g. the heart and the lungs) that inevitably accompanies EBRT.

The main results were published in 2010, 2014, 2020 and 2021. The initial and 5-year results found that TARGIT-IORT is non-inferior to EBRT.[21] Subsequent results found that, when given during the lumpectomy procedure, TARGIT-IORT yields comparable breast cancer outcomes to whole-breast radiotherapy and significantly reduces deaths from other causes,[12,13,15,18–20] leading to an overall survival benefit in patients with grade 1 or 2 cancers that comprise 78% of cases – with a 12-year overall mortality reduction from 15% to 10.5%.[12]

Several studies have now documented that TARGIT-IORT has several other benefits to the patient (see https://bit.ly/TARGIT-IORT-Bibliography). It improves breast-related and radiotherapy-related quality of life, improves cosmetic outcome, reduces pain, reduces social burden and travel (~730 miles per patient), has a lower carbon footprint and is preferred by patients over mastectomy, EBRT or 'no-radiotherapy'.[9–11,22–38]

TARGIT-IORT has been adopted by over 250 centres in over 35 countries around the world and ~50,000 patients have been treated.[39] Several groups from around the world have published over 270 scientific papers that have confirmed the original oncological results of the TARGIT-A trial[40] from several countries, including Australia, Brazil, Bulgaria, Canada, China, Czech Republic, Denmark, France, Germany, Indonesia, India, Islamic Republic of Iran, Italy, Malaysia, Mexico, Philippines, Poland, Russia, Singapore, South Africa, Republic of Korea, Spain, Saudi Arabia, Taiwan (Province of China), UK, USA and Venezuela. TARGIT-IORT is included in several international guidelines, including Australia, Germany, European Society of Breast Cancer Specialists, France, Italy, Mexico, National Institute for Health and Care Excellence (NICE), UK, Spain, St Gallen Consensus, Singapore, USA (https://targit.org.uk/targit-iort-in-guidelines): the full list of papers is available at https://bit.ly/TARGIT-IORT-Bibliography, and some recent papers, including those where it is used in special situations (when EBRT is not feasible, has had previous radiotherapy, to avoid a mastectomy after local recurrence, patient cannot lie still, has a pacemaker, has implants, is pregnant, etc.), are cited in the reference list.[9,41–99,100] For patients, the biggest benefit of having TARGIT-IORT during their lumpectomy procedure, under the same anaesthetic, is that they complete their local treatment in one session and with lower toxicity and far less disruption of their normal working life: patients prefer it even when compared with the newer, shortened, high-intensity 5-day radiotherapy schedule.[9] In 2021, the National Institute for Health and Care Research (NIHR) hailed the TARGIT research as one of the five amazing health breakthroughs alongside two COVID-19 treatments and the Oxford COVID-19 vaccine https://bepartofresearch.nihr.ac.uk/news-and-features/breakthroughs-2020-to-2021.[101]

We recognised the need for longer follow-up for the randomised TARGIT-A trial of targeted intraoperative radiotherapy during lumpectomy for breast cancer. This extended follow-up study was launched in 2018 to assess the feasibility of collection of longer-term outcomes by DPC and by data from national records such as the Office for National Statistics, NHS England and Data Access for Research Services (DARS).

Here, we report our experience of collecting follow-up data by using DPC and NHS digital data contribution.

Chapter 2 Methods (as planned and as executed)

This is an extended follow-up study designed to enable the collection of longer-term outcomes by DPC and by data from national administrative databases. Participation requires enrolment in the TARGIT-A randomised clinical trial, which compared a risk-adapted approach with use of single-dose, targeted TARGIT-IORT versus conventional EBRT given as a daily course over 3–6 weeks. The initial and 5-year results have been published and found that TARGIT-IORT is non-inferior to EBRT. The recruitment to the TARGIT-A Trial was completed in June 2012. Outcomes were published at three time points (data locks): in July 2010, November 2013 and finally in August 2020, May 2021 and January 2023. In order to assess new methods of collecting further follow-up, we used the following methods.

For the purposes of this study, we included both the trials of immediate TARGIT-IORT versus EBRT (*n* = 2298) and delayed TARGIT-IORT versus EBRT (*n* = 1153) = total 3451 are included.

Study schedule

For convenience, the study has been divided into two work packages. The schedule is illustrated in *Figure 1* and *Table 1*.

Work package 1: direct patient contact

The objective was to continue to gather efficacy, safety and follow-up data from participants in all UK centres as per the TARGIT-A protocol, using direct contact between the trial's unit and participants.

We approached, as planned, the original principal investigators (PIs), or the individuals who took over from them, at the UK sites which had participated in the TARGIT-A trial. All PIs recognised the rationale and need for longer-term follow-up of all patients in a breast cancer trial and the rationale was explained in a formal letter to each PI (see *Report Supplementary Material 1*).

Lists of patients were sent to participating site staff who were thought to be eligible based on the information held on the TARGIT-A database. The individual site teams were asked to confirm eligibility, and telephone patients to make them aware that they would receive a letter in the post inviting their participation. If the patient had any questions, she was invited to telephone the office of the hospital site staff.

Once the patient was primed to receive something from their local clinical team, they sent them via post a pack, which was sent to them from the UCL trials unit.

This pack included written material and stamped addressed envelopes for the site staff to add the patient address and send through the mail. Included in each letter were the following:

- Letter (on local hospital letterhead) explaining the study and inviting participation (see *Report Supplementary Material 2*).
- Participant information sheet (see *Report Supplementary Material 3*).
- Informed consent form (see *Report Supplementary Material 4*).
- The single-page follow-up case report form (CRF) (see *Report Supplementary Material 5*).
- A form requesting contact information (see *Report Supplementary Material 6*).
- A stamped reply-paid envelope addressed to the trial's unit (to send the consent form, contact information form and the CRF).

Alternatively, patients could be approached when they came to the clinic for their routine follow-up.

The site staff also informed the general practitioner that their patient is being approached for participation in the study (see *Report Supplementary Material 7*).

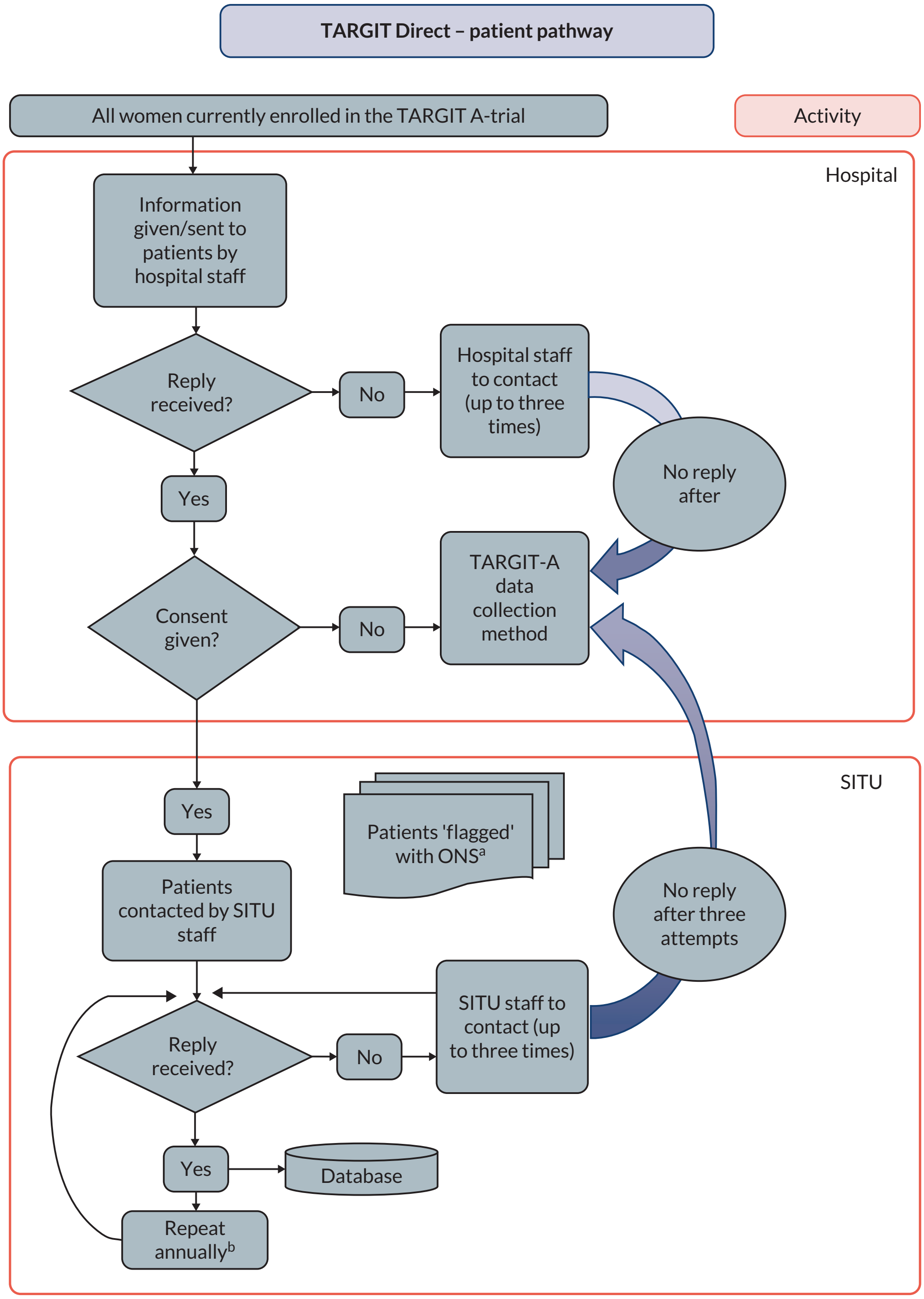

FIGURE 1 Trial overview. a: and other databases such as HES, cancer registry, etc.; b: until patient dies or withdraws consent for further follow-up. HES, Hospital Episode Statistics; ONS, Office of National Statistics.

Our ethics approval included the allowance to try and contact the patient at the most three times, before giving up. We supplied a set of pre-paid envelopes to each of the PIs. The rest of the documents/their templates were sent electronically. For each patient, there was a letter from the PI, a blank consent form and a single-page CRF for recording their health status and any health problems they may have suffered in the previous year. The patients were requested to

TABLE 1 Timing of events and data collection

	Consent	Direct Patient Contact	
Visit No:	1	2, 3, 4, etc.	–
	Day 1	Annually, on the anniversary of day 1	Death, withdrawal of consent, or loss of contact (after three attempts)
Window of flexibility for timing of visits:	–	± 3 months	–
Informed consent	X		
Eligibility confirmation	X		
Health status	X	X	X
Adverse events review	X	X	X

return their signed consent forms, an updated contact details form and the first health status CRF (one page) to the UCL trial team. The trials unit then sent annual requests for collecting their health status to consented patients who were still alive and well. Before any requests for either the initial consent and follow-up form or for subsequent follow-up forms, we had confirmation (verbal or in writing) from the local PI about whether the patient is alive and well enough to receive and send back the short questionnaire. We found that the patients welcomed the opportunity of a follow-up and felt less abandoned by the system. The consent form and follow-up CRF were to be returned in the enclosed pre-paid envelope supplied by our own trials unit, with the address of UCL trials unit already printed on the envelope. This CRF was specifically designed for direct-to-patient contact and was approved by the national ethics committee. In addition to breast cancer outcomes, it specifically seeks information on cardiovascular disease and new cancer diagnosis. The latter is relevant for diagnosis of lung and oesophageal cancer that have been causally linked to EBRT.

Upon receipt in the trial's unit, the consent form was checked for completeness and validity. Site staff were informed when letters had been received in the trial's unit. If the consent form was incomplete or invalid, the site staff were asked to contact the patient again and resend a blank consent form, explaining the problem (e.g. the form had not been signed). For patients who had not returned the letter, site staff were asked to contact the patient again and determine the cause. If the patient declined participation, this information was sent to the trial's unit and no further contact was attempted. In some cases, the site staff decided that no further contact should be made (e.g. if the patient had cognitive decline or was very unwell).

For the collection of annual follow-up, a list of patients' due follow-up was sent to site staff to verify that they knew of no reason why the patients should not be contacted (e.g. if they were known to have died). These patients were then sent a letter directly from the trial's unit and included the trial CRF and a stamped addressed envelope (see *Report Supplementary Material 8* and *Report Supplementary Material 9*). For patients who did not return the letter, site staff were requested to contact the patient directly and resolve if there was a problem.

In all cases, no more than three attempts were made to contact patients who did not respond to the letters.

If the information returned by the patient on the CRF revealed anything other than 'healthy' follow-up, site staff were contacted directly to obtain further information, which was added to CRFs designed for the collection of details of recurrence, new primary cancer, etc.

Patients could refuse consent at any time by contacting either the trials unit or the hospital site staff, in which case, no further study-specific contact was made.

During the early part of the COVID-19 pandemic, there was a substantial backlog of postal delivery. Access to the university buildings where patients had been instructed to send their consent forms and follow-up CRFs was also restricted, which led to a gap in the data entry of the consent forms. This was mitigated by working diligently and adapting to the circumstances. The trial co-ordinator was supplied with a printer (paid by discretionary funds from the Chief Investigator), which could be used at their home. One member of the trials unit visited the unit to collect any follow-up/consent forms that may have arrived. We made an amendment that would allow an electronic method of contact when possible.

Data were held on two databases. If consent was valid, the contact information was added to a list held in a secure environment (to ISO270001) and the information from the CRF was added to a second database, identified by a unique trial identifier (e.g. TT001146P). The de-identified database was made available to the to the Trial Statistician for analysis.

The Direct Patient Contact (DPC) will determine if it is effective to obtain follow-up information directly from participants.

Work package 2: collection of health information data from United Kingdom patients through administrative databases

The intention was to seek permission to obtain information from patients in England from NHS England [linked data from Hospital Episode Statistics and Office of National Statistics (ONS) datasets] and for patients in Scotland from the National Health Service Central Register (NHSCR) and National Records of Scotland (NRS) (coded Scottish death and Scottish anonymised Cancer registrations).

This information would include hospital episodes and cause of deaths inside and outside of hospital and new primary cancer registrations.

The list of consented patients was also meant to be sent to National Registries to obtain their health status at least three times during the project. However, the repeated changes of the government organisations and the administrative system have been a great hindrance. The names have changed (e.g. from ONS to Public Health England to NHS Digital to DARS under NHS England, which has been dissolved only in March 2025). Most importantly, there has been an exponential increase in the cost of receiving the data downloads, including introduction of charges per download rather than a single charge for multiple downloads for each patient. Therefore, we had to limit the downloads to a single download near the end of the study.

Permission to obtain information from patients in England from NHS England was obtained in November 2024, and a list of 221 consented patients residing in England was submitted soon after database lock. There was 100% validation and matching, and linked data were released from NHS England in January 2025.

For the 145 patients residing in Scotland, we could not seek permission from the NHSCR and NRS firstly because of devolution, then due to lack of their staff during COVID-19 which led to considerable delays.

The linked data obtained from NHS England included hospital episodes and cause of deaths inside and outside of hospital and new primary cancer registrations.

Sample size

The TARGIT-A Trial accrued 3451 patients between March 2000 and June 2012. Seven hundred and fourteen of these patients had been recruited in sites based in the UK and were therefore potentially eligible for inclusion in this study.

Data collection

All data obtained were held securely in UCL. Patient identifiers (such as name, address, etc.) were held on a separate Data Safe Haven, which has been certified to the ISO27001 information security standard and conforms to NHS

Digital's Information Governance Toolkit. This has been built using a walled garden approach, where the data are stored, processed and managed within the security of the system, avoiding the complexity of assured end point encryption. A file transfer mechanism enables information to be transferred into the walled garden simply and securely.

Statistical analyses

Analysis was performed as per a prespecified statistical analysis plan using Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) and Stata® (ver 18, StataCorp LP, College Station, TX, USA), which was signed off before the data were available for analysis. We used descriptive statistical methods to analyse the various proportions, chi-squared test and analysis of variance to assess the differences in means. Survival curves were plotted using the Kaplan–Meier method and 'two-way' command was used to illustrate the improvement in the follow-up duration with TARGIT-X.

Chapter 3 Results

Seven hundred and fourteen patients from the UK were randomised in the TARGIT-A trial. Of these, 107 patients had died or withdrawn before TARGIT-X started. Therefore, at the start of TARGIT-X, 607 patients were deemed eligible and all 607 were considered to have been recruited in the study. The patient flow and overview of results is shown in *Figure 2*. Site activation details are given in *Appendix 1*.

The age at the time of consent for TARGIT-X was 11.6 years older {mean 71.95 [95% confidence interval (CI) 59 to 61] vs. 60.3 [95% CI 71 to 73] years; $p < 0.0001$} than their age at randomisation for TARGIT-A trial. We found that a large proportion of patients with a diagnosis of medium risk breast cancer are still alive and well (73%) at a median age of nearly 80 years and are able to send accurate health status information in a formal CRF.

Patient approach, contact, first determination of state of health and consent

Unlike most clinical studies, the process of signing the consent form was done by patients at their home, unsupervised by the clinical team. At one centre (Winchester), many patients were approached and consented when they came for their clinic appointments.

- 574/607 (94.5%) of patients: We could determine the state of health, or found a reason for their non-participation. For 33 patients (5.8% of the total initially eligible), the reason for non-participation could not be determined by the local clinical team. It is possible that they may have been too unwell or have died.
- 502/607 (82.7%) of patients: We successfully found information from the local clinical team. Seventy-two were not contactable (12%): 40 had no current address on file, and 32 did not respond to telephone calls or letters sent to the address on file.
- This group of 502 patients was made up of 2 cohorts of 366 and 136 patients:
  - 366/502 (73%), that is 60.3% of the total (366/607) of patients were found to be in good health and aggregable for participation and returned a signed consent form directly to UCL trials unit and submitted at least one follow-up CRF between August 2018 and December 2024. Up to four follow-up CRFs were obtained from participants.
  - 136/607 (21.9%) patients were unable to participate for the following reasons:
    - Sixty-seven patients died (of these, 33 died before the last TARGIT-A data lock of 2019, and 30 died before they could be approached for TARGIT-X).
    - Thirty-eight were considered too unwell to approach (terminal illness, dementia, etc.) by the local clinical team.
    - Twenty-three declined participation in TARGIT-X (DPC + tracking via NHS Digital).
    - Two patients withdrew from the TARGIT-A trial after TARGIT-X started.
    - Six patients consent forms had been recorded as received but were not subsequently traceable: in fact, the paper consent forms of 45 patients were lost (assumed to be misfiled within the departmental safe storage) during the disruption of offices in the COVID-19 pandemic and staff changes. All of these patients were requested to re-sign their consent form, and 40/45 kindly returned completed. Of these, one patient's consent form was received unsigned (only initialised first question).
    - Thus, < 5% patients were not willing to participate: 23 declined and 2 withdrew, 25/502.

Rate of participation as per centre

The rate of participation varied with individual sites and was higher if the patients were approached at the time of their routine face-to-face clinic visit as in Winchester (83%), or a single person tried to contact them by telephone as in Royal Free Hospital (RFH)/Whittington or Dundee (62% and 64%). However, the low rate at University College

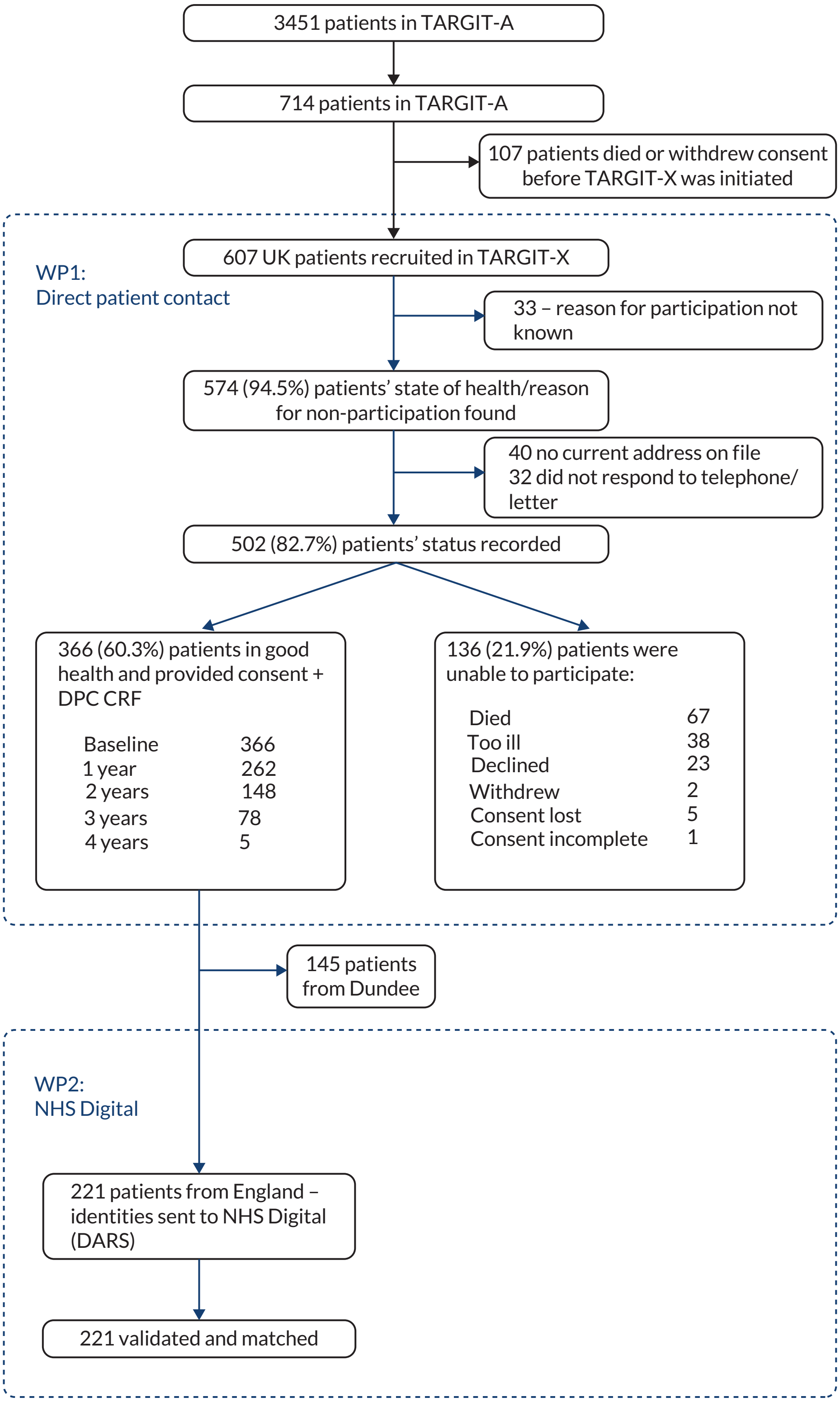

FIGURE 2 Patient flow and overview of results. Note: Both the trials of immediate TARGIT-IORT vs. EBRT (n = 2298) and delayed TARGIT-IORT vs. EBRT (n = 1153) = total 3451 are included in this study. Data from Dundee (Scottish NHS Digital service) could not be retrieved. WP1, work package 1; WP2, work package 2.

London Hospitals (UCLH) could be attributed to the fact that many more patients from UCLH were too unwell to be approached, or had died (39/146, 27%) when compared with rest of the UK (63/461, 14%), $p < 0.0001$. This might possibly be a reflection of the fact that patients from UCLH who were recruited several years before rest of the country, so were much older. The details of patient status at the time of first approach from individual centres are shown in *Table 2*.

TABLE 2 Accrual and detailed patient status from individual centres

	001 UCLH	004 Dundee	018 RFH/ Whittington	024 Winchester	028 Guy's	Total
Total in TARGIT-A	189	270	115	115	22	714[a]
Not eligible for TARGIT-X	43	44	1	14	2	107[a]
Initially eligible for TARGIT-X	**146**	**226**	**114**	**101**	**20**	**607**
Consented	59 (40%)	145 (64%)	68 (60%)	84 (83%)	10 (50%)	**366 (60%)**
Not eligible (too unwell)	15 (10%)	13 (6%)	6 (5%)	3 (3%)	1 (5%)	**38 (6%)**
Died	24 (16%)	29 (13%)	9 (8%)	3 (3%)	2 (10%)	**67 (11%)**
Not contactable	20 (15%)	19 (8%)	26 (23%)	7 (7%)	0 (0%)	**72 (12%)**
Declined	4 (3%)	11 (5%)	5 (4%)	2 (2%)	1 (5%)	**23 (4%)**
Withdrawn	0	0	0	2 (2%)	0	**2 (0.33%)**
Lost consent	0	5 (2%)	0	0	0	**5 (0.8%)**
Incomplete consent	0	1 (0.5%)	0	0	0	**1 (0.2%)**
Unknown	24 (16%)	3 (1%)	0	0	6 (30%)	**33 (5.4%)**

a Includes three patients from St John and St Elizabeth hospital (038 HJE), a private hospital which did not participate because the local PI had passed away.

Note

Percentage use 607 as denominator.
Bold values indicate the numbers who were eligible for TARGIT-X.

Overall accrual

Across the whole study, accrual was steady until early 2020 when research activities of hospital site staff were affected by the pandemic. Accrual picked up again in late 2021, mainly due to the work of a research nurse (JL) in the hospital site in Dundee, Scotland. NB: 45 of the consent forms initially received from Dundee had to be reconsented in 2024 as described elsewhere. The accrual from 2018 to 2022 is shown in *Figure 3*.

Age

Median age at the time of randomisation in TARGIT-A was 63 years [interquartile range (IQR) 55–69] and, if eligible for TARGIT-X, 73 years (IQR 66–79) and, if participated, 71.7 years (IQR 65–78).

This graph (*Figure 4*) shows the age distribution of patients who consented for TARGIT-X compared with their ages when they were randomised in the TARGIT-A trial.

Those who participated were younger (71.95 years, 95% CI 71.1 to 72.8) compared with those who could not (74.7 years, 95% CI 73.5 to 75.9), $p = 0.0001$ [as many of those could not participate had died or were too unwell ($n = 102$), 17% of cases].

Follow-up forms received directly from patients

The number of follow-up forms received was high in the first 2 years and declined later on, which is likely to be a reflection of the duration in the study as well as increasing age and illness in the ageing population as shown in *Table 3*.

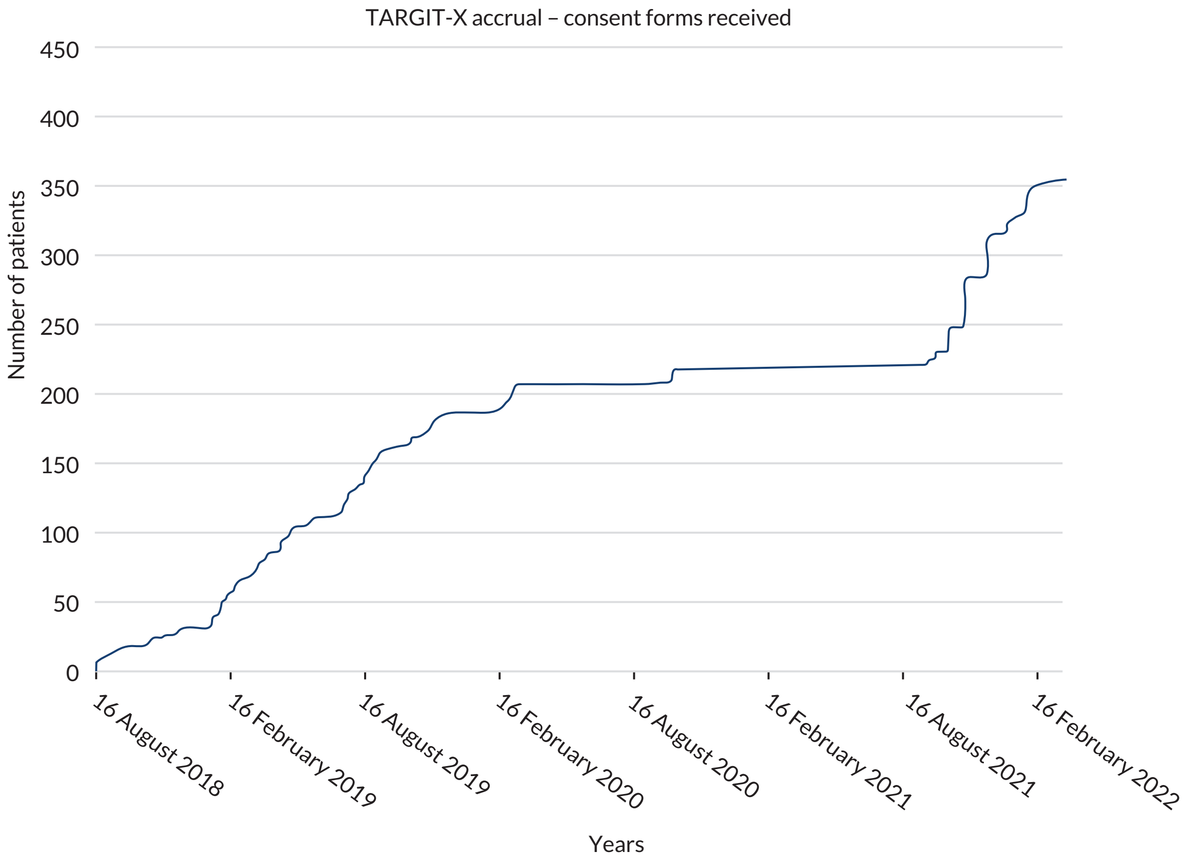

FIGURE 3 Accrual to TARGIT-X study. *X*-axis is the timeline and *y*-axis is the number of patients.

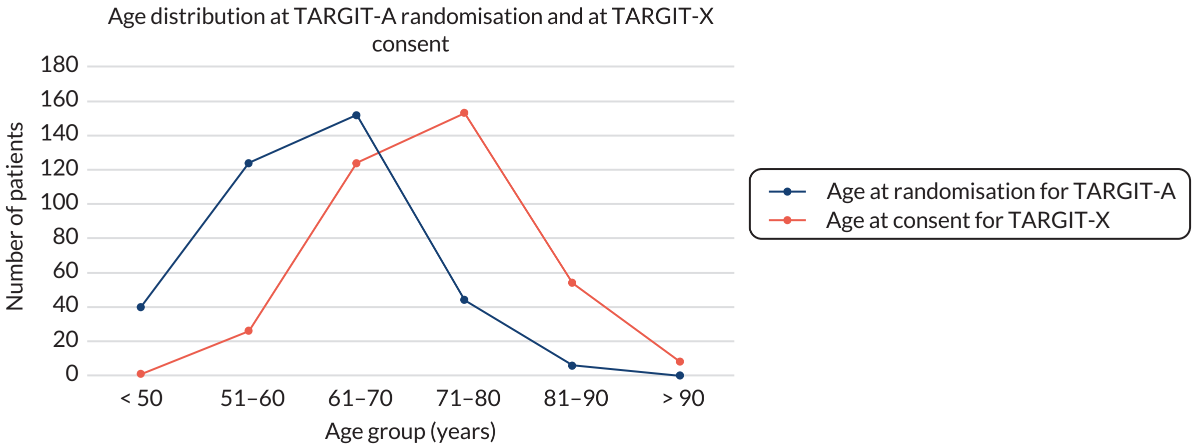

FIGURE 4 The figures show how the age of patients in this long-term follow-up study is about 10 years older than the age at the time of their randomisation. *X*-axis shows the age groups and *y*-axis shows the number of patients.

Data quality

Out of 1470 forms received in total, we found just one discrepancy in date recorded. The patient signed the consent form in August 2019, but the accompanying CRF recorded 'today's date' the same date in August, but the year was recorded as 2017 by the patient. This gives us an error rate of 1/1470 total forms = 0.068%.

TABLE 3 Number of forms returned for each follow-up year

Site	Baseline	1 year	2 years	3 years	4 years	Total
001 (UCL)	59	48	32	8		147
004 (Dundee)	150	70	1			221
018 (RFH)	67	58	41	18		184
024 (Winchester)	84	77	68	49	5	283
028 (Guy's)	10	9	6	3		28
Total	*370*	*262*	*148*	*78*	*5*	*863*

Additional follow-up due to TARGIT-X

The TARGIT-X was funded for 7 years. During these 7 years, we achieved an additional 6.1 years of follow-up for those patients who participated in the study.

Additional years of follow-up due to TARGIT-X (median years) was 6.1 years (IQR 3.4–6.2) for those who consented and 3.2 (IQR 0.45–6.2) overall, as shown in *Figure 5*.

Knowledge about additional deaths

- Two hundred and three additional deaths were recorded during the course of the study.
- Thirty-seven of these were included in the 137 that were reported in the publication of the 2020–1 TARGIT-A outcomes.
- Forty additional deaths were reported by the site PIs.
- Twenty-six deaths were known only because of DARS. The overall survival is shown in *Figure 6*.

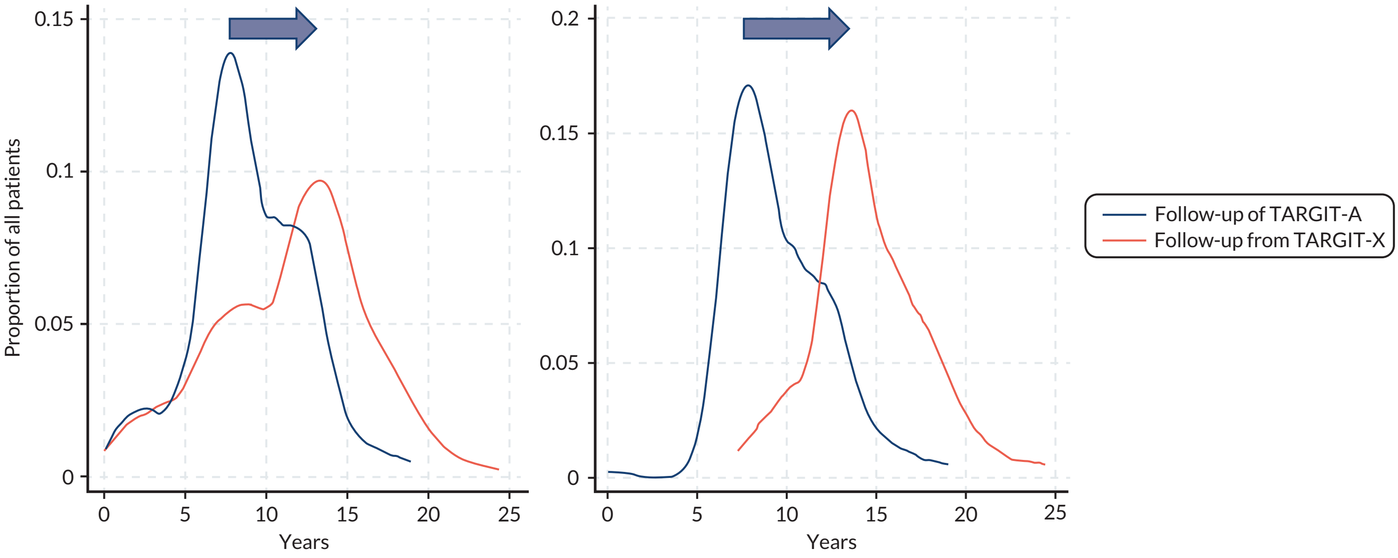

FIGURE 5 Additional follow-up provided by TARGIT-X study: left-hand graph shows the additional follow-up in the whole cohort of UK patients in the TARGIT-A trial, and the right-hand graph for those patients who signed the consent form, showing that there was a substantial increase in the length of follow-up as indicated by the blue arrows. The *x*-axis shows the number of years and the *y*-axis shows proportion of all patients.

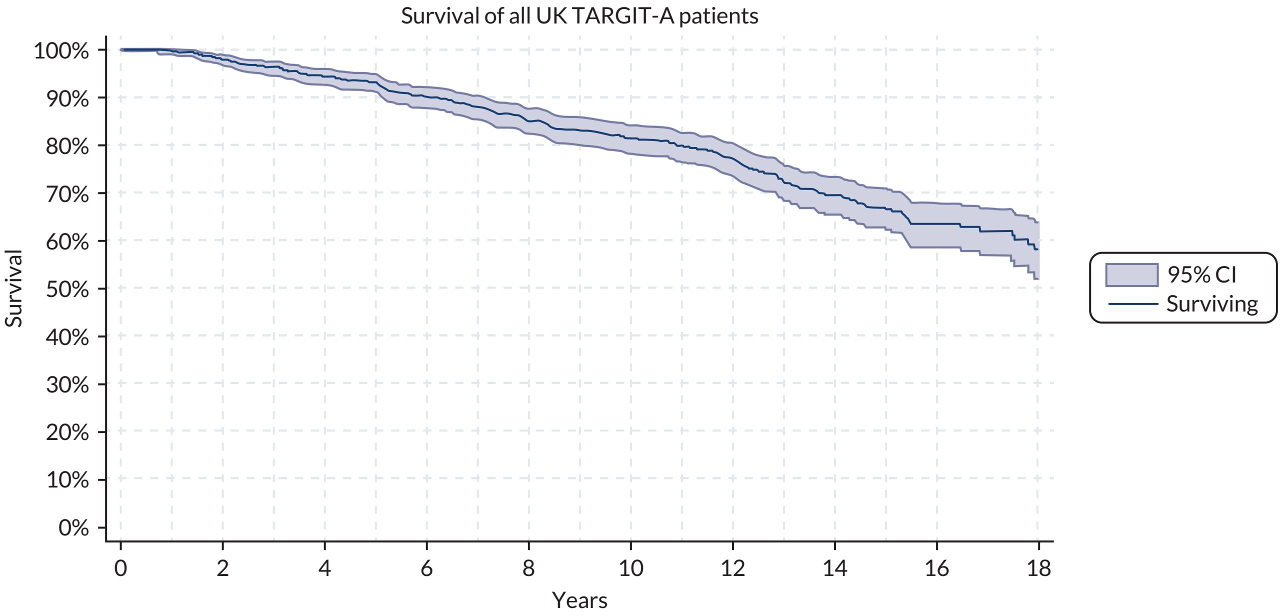

FIGURE 6 Overall survival and 95% CIs of UK patients in TARGIT-X.

We separately report significantly more lung cancer diagnoses with EBRT compared with TARGIT-IORT, HR 3.3 (95% CI 1.1 to 10.2), *p* = 0.0266; 16-year incidence of lung cancer: EBRT: 7.2% vs. TARGIT: 1.8% The increase starts after 9 years of follow up and at 16 years, the reduction in lung cancer incidence with TARGIT-IORT is 5.4% (95% CI 0.3% to 10.5%).[102–104]

In the TARGIT-A trial, patients were randomised at a median age of 63 years, and at 17 years of follow-up, 62% (95% CI 57 to 67) of patients, which means that for those at a median age of 63 years, more than nearly two-thirds of patients can expect to survive beyond 80 years of age.

Low cost of gathering long-term follow-up

In terms of cost, a large proportion of the funding was used for administration of the research part of the trial. The actual cost was approximately 210,000 = 33,000 per year – for 6 years of follow-up of 600 patients, which amounts to about £57.6 per patient, the annual cost for long-term follow-up of breast cancer patients. We believe this is a good value for money and a fraction of the cost in a traditional clinical trial.

Summary of linked data obtained from NHS England

Hospital Episode Statistics: admitted patient care

Year	Episodes	Study IDs
2017	99	49
2018	140	62
2019	135	66
2020	138	52
2021	160	62
2022	176	61
2023	171	66
Total	*1019*	*167*

Hospital Episode Statistics: critical care

Year	Episodes	Study IDs
2017	1	1
2018	8	3
2019	1	1
2020	9	5
2021	2	2
2022	7	6
2023	4	3
Total	*32*	*20*

Hospital Episode Statistics: outpatients

Year	Episodes	Study IDs
2017	1391	196
2018	1602	194
2019	1324	176
2020	952	159
2021	1053	146
2022	1446	140
2023	1552	152
Total	*1019*	*167*

Cancer

Year	Episodes	Study IDs
1983–2024	211	295

Mortality

Year	Episodes	Study IDs
2020–4	26	26

Analysis of admitted patient care data

Hospital admitted patient care (APC) activity

Finished Consultant Episodes (FCE)

Finished Admission Episodes (FAE)

Finished Admission Episodes by emergency admission (FAEem)

Year	Episodes	Study IDs	APC max[a]	FCE max[b]	FAE max[c]	FAEem max[d]
2017	99	49	13	6	6	3
2018	140	62	16	16	8	4
2019	135	66	13	11	5	5
2020	138	52	18	18	8	8
2021	160	62	12	11	11	4
2022	176	61	26	18	15	12
2023	171	66	15	10	9	3
Total	*1019*	*167*	*52*	*27*	*26*	*14*

a Maximum number of APCs per participant per year, and maximum across all 7 years.
b Maximum number of FCEs per participant per year, and maximum across all 7 years.
c Maximum number of FAEs per participant per year, and maximum across all 7 years.
d Maximum number of FAEms per participant per year, and maximum across all 7 years.

Chapter 4 Discussion

Principal findings

We aimed to assess whether use of Direct Patient Contact and NHS Digital data can enable continuing follow-up clinical trials that need long-term follow-up despite the disruptions caused by the COVID-19 pandemic which erupted in the midst of the trial (2017–24).

The proportion of patients for whom data could be made available was relatively high. We could ascertain the state of health or reason for non-participation of 94.5% of eligible patients; 87% of these patients' status could be determined. Of these 502 patients, 73% (n = 366, 60.3% of the total) were found to be in good health, were willing to participate and had a valid signed consent form.

One hundred and thirty-six (22%) patients did not sign a consent for continuing follow-up. In the process of setting up the trial, we were able to ascertain the reasons for this: the large majority (105/136, 77%) were too unwell or had died already; 23 declined and 2 withdrew, and in 6 patients, the consent was either incomplete or the physical form could not be traced.

The TARGIT-X study enabled us to record about 6.1 additional years of follow-up. We could record an additional 103 deaths, the most important outcome in a trial of breast cancer – 63 from work package 1, and 26 from work package 2. Of these, 30 and 4, respectively, were known at the time of the 2019 TARGIT-A data lock. This is a substantial increase – more than doubling the number from the 100 deaths that were recorded before TARGIT-X. We separately report 16-year lung cancer incidence of 7.2% with whole breast radiotherapy vs 1.8% with TARGIT-IORT.

We found that, in this cohort of patients (median age at potential participation was 73 years), older patients were less likely able to participate. Interestingly, there was a larger proportion of patients from UCLH (vs. rest of the country) that were found to be too unwell or had died before they could be approached, likely to be attributable to their older age (recruited many years before the rest of the country). We believe that for these older (11 years older than when randomised) patients, the direct contact method might have been less onerous than going to the clinic for a follow-up, especially when they are otherwise well. We found that if the disease had relapsed, there was a lower chance of participation.

We were impressed by the data quality of the follow-up CRFs sent by the patients. The patient made an error (wrong year recorded – 2017 instead of 2019) in only one case, giving a very low error rate of < 0.1% (1/1470, 0.068%).

We found that using this new approach of Direct Patient Contact, follow-up needs some but not very onerous engagement from the local clinical team. The funding for the highly intelligent, committed and empathetic senior breast care nurse (JL) enabled us to get the high level of completion of data from Dundee. The lack of PIs for some duration at RFH/Whittington, and UCLH reduced the level of completion.

In terms of cost, a large proportion of the funding was used for administration of the research part of the trial. Despite this, it cost < £60 per patient per year of additional (long-term follow-up). We believe this is good value for money and a fraction of the cost spent in a traditional clinical trial.

We found that the contribution of the important outcome data from NHS Digital is considerable and increases the number of important events and lengthens the available follow-up substantially.

Contribution to existing knowledge

We have shown that Direct Patient Contact is an effective method of collecting follow-up information from patients with breast cancer. We found patients with previously diagnosed breast cancer remain well for lengthy periods of time and willing to share their follow-up information. We have recorded a higher number of important events (lung cancer and deaths) in this cohort of patients. We found with extended follow-up, lung cancer incidence is more than 3 times higher in those randomised to EBRT compared with TARGIT-IORT.

Strengths and limitations

Strengths

TARGIT-A was the first clinical trial to compare IORT versus conventional whole-breast EBRT. Breast cancer has a long natural history and excellent prognosis. Therefore, assessments of the long-term benefits and harms of treatments are crucially important. The strength of our protocol is that we were able to establish direct contact with the patients while they are alive as well as gathered data from the national registries about their hospital episodes/new diagnoses and checked if they had died. Another strength is that despite the study management being considerably disrupted due to the COVID-19 pandemic from March 2020, which erupted in the midst of the study (2017–24), we believe that we have shown that the approach is an effective means of continuing follow-up in the UK.

Limitations

The initial consent from the patient requires the site PIs to contact the patient, but this is just once. Our approach relies on having adequate patient contact details, which were available at the treating hospitals and were confirmed by the patient when they sent us the consent form. Continuing contact from the trial centre requires research funding, while the usual hospital follow-up would simply have been absorbed within the patients' routine care. However, routine follow-up now frequently stops much sooner (≤ 3 years) rather than the much longer follow-up carried out previously (10 years). The COVID-19 pandemic limited the number of annual follow-up cycles that could be undertaken by the clinical trials unit. If consenting for Direct Patient Contact and data collection from national registries is included in the initial trial set-up, then our approach will enable very long-term follow-up of clinical trials.

Take-home message

Breast cancer patients can look forward to a long life. In the UK, it is feasible and cost-effective to roll out Direct Patient Contact as a method of continuing follow-up of patients with long-term health conditions. It leads to substantial increase in the length of follow-up and number of events, at a low cost. If the bureaucracy of NHS Digital can be reduced, it can provide additional and important information about deaths and relevant diagnoses (e.g., more than three times higher incidence of lung cancer with whole breast radiotherapy compared with more focussed targeted intraoperative radiotherapy).

Challenges faced

We faced the challenge of the COVID-19 pandemic well and ensured continued trial participation.

We found that obtaining data from NHS Digital was extremely difficult and without persistent efforts, well-nigh impossible. Twenty years ago, obtaining data from ONS only required a phone call and an e-mail, and it was supplied free of charge.[105] During this project, despite starting to work towards it from 2018, they sent us the data only in 2024. The reasons for this delay were multiple – change in administration, change of name, restructuring, repeated change of case worker, repeated changes in the regulations, multiple changes in the method of pricing, leading to a substantial increase in the cost, and of course, the COVID-19 pandemic. As of March 2025, NHS England has been dissolved, with a promise of reduction in bureaucracy. We hope that future researchers are not as disappointed as we are. If the bureaucracy of NHS Digital could be reduced, this could then provide additional and important information about deaths, as well as relevant data about the patient's health problems, in a much more accessible and timely manner.

Public and patient involvement

A patient (Ms Marcelle Bernstein) has been involved from the outset. She has consulted with other patients to gain a wider perspective. She was involved in study design, monitoring, data interpretation and contributed to the manuscript.

Another patient (Ms Anne Millman) was involved in oversight of the study as an independent member of the Trial Steering Committee.

Both patients contributed by giving the patients' perspective in designing the initial letter to the patient requesting their consent as well as the follow-up CRF.

Equality, diversity and inclusion

All attempts were made to be inclusive. We believe that the results of work package 1–DPC as a means of continuing follow-up of patients are generalisable internationally. The key element is the rapport between the local clinical team and the patient. Once that is present, and with the usual concern of all patients with long-term health conditions for continuing monitoring, especially when they have participated in a randomised clinical trial, our approach is a recipe for excellent response rates from patients to supply the trials unit with annual single-page health status CRF.

Implications for decision-makers

Clinical scientists and funding bodies should recognise that using Direct Patient Contact (DPC) is a highly cost-effective approach to follow-up patients in clinical trials. Provision should be made during set-up of clinical trials, and the mechanisms of DPC should be set up at the outset during the consent process. The process can be much easier today than 10 years ago, as the access to electronic systems is much more widespread.

Policy-makers should recognise the difficulties and the high cost of engaging with NHS Digital. NHS Digital has a treasure of data, which should be more easily available to scientists, researchers and general public to whom it actually belongs. The many obstacles currently in place, despite excellent ground staff, should be removed.

Chapter 5 Research recommendations and future directions

1. Study of using electronic secure systems for Direct Patient Contact from the outset of a clinical trial to collect both the trial-specific outcome measures as well as patient-reported outcomes for quality of life.
2. Investigate the organisational and systemic bottlenecks in NHS Digital services with a view to reducing bureaucracy and cost.
3. Investigate why results of large, international, well-conducted randomised trials (e.g. TARGIT-A), that have been shown to be beneficial to patients and cost-effective to the health system, are not widely adopted in the UK[106], while they are included in almost every other country's clinical practice guideline and get widely adopted worldwide. Is this personal prejudice or professional or economical conflicts of interest? Or does it demand potential improvements in NICE processes?

Chapter 6 Conclusions

Patients diagnosed with breast cancer during the last two decades can now look forward to a lengthy survival. They appreciate being monitored and mostly respond very positively to requests for collection their health status data. We found that they report their personal data accurately. In the UK, it is both feasible and cost-effective to roll out DPC as a method of continuing follow-up of patients with long-term health conditions. Such an approach leads to substantial increase in the length of follow-up and number of relevant events (e.g. greatly reduced incidence of lung cancer with targeted intraoperative radiotherapy compared with whole breast radiotherapy), at a low cost. Our new approach could be adopted as an efficient method of obtaining long-term follow-up data from patients in randomised clinical trials.

Additional information

CRediT contribution statement

Jayant S Vaidya (https://orcid.org/0000-0003-1760-1278): Conceptualisation, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualisation, Writing – reviewing and editing.

Norman R Williams (https://orcid.org/0000-0001-6496-312X): Conceptualisation, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualisation, Writing – reviewing and editing.

Max Bulsara (https://orcid.org/0000-0002-8033-6123): Conceptualisation, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Methodology, Resources, Software, Supervision, Validation, Visualisation, Writing – reviewing and editing.

Chris Brew-Graves (https://orcid.org/0000-0002-0266-0315): Conceptualisation, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Methodology, Project administration, Resources, Supervision, Writing – reviewing and editing.

Ingrid Potyka (https://orcid.org/0009-0004-6924-0886): Conceptualisation, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Methodology, Project administration, Resources, Supervision, Writing – reviewing and editing.

Nicholas Roberts (https://orcid.org/0000-0002-7985-5153): Data curation, Investigation, Project administration, Project administration, Resources, Writing – reviewing and editing.

Julie Lindsay (https://orcid.org/0009-0004-1959-5654): Data curation, Investigation, Resources, Writing – reviewing and editing.

Siobhan Laws (https://orcid.org/0000-0002-1815-8928): Data curation, Investigation, Resources, Writing – reviewing and editing.

Sanjay Raj (https://orcid.org/0000-0003-2502-0246): Data curation, Investigation, Resources, Writing – reviewing and editing.

Michael Douek (https://orcid.org/0000-0003-2872-8514): Data curation, Investigation, Resources, Writing – reviewing and editing.

Mary Falzon (https://orcid.org/0009-0006-6210-4376): Data curation, Investigation, Resources, Writing – reviewing and editing.

Gloria Petralia (https://orcid.org/0000-0002-3731-6637): Data curation, Investigation, Resources, Writing – reviewing and editing.

Sarah Needleman (https://orcid.org/0000-0001-6137-9075): Data curation, Investigation, Resources, Writing – reviewing and editing.

Anu Malhotra (https://orcid.org/0009-0007-7778-9854): Data curation, Investigation, Resources, Writing – reviewing and editing.

Marcelle Bernstein (https://orcid.org/0009-0008-5011-3755): Writing – reviewing and editing.

Jeffrey S Tobias (https://orcid.org/0000-0001-6989-4450): Conceptualisation, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Methodology, Project administration, Resources, Supervision, Validation, Writing – reviewing and editing.

Acknowledgements

We gratefully thank the participants, PIs, research nurses, multidisciplinary team co-ordinators, data managers and other site staff who have been responsible for setting up, recruiting participants and collecting the data for the trial.

We are grateful for the trial oversight provided by the sponsor, and the members of the Trial Steering Committee (TSC).

We thank the trial steering and data committee members: The TSC members were (* independent, ** non-independent):

Professor Fred Hamdy (TSC Chair) FH*, Professor Ian Fentiman (Surgeon) – IF*, Professor Martin Bland (Statistician), Dr Mangesh Thorat (MTHo*), Dr David Dommett (Radiotherapy Physics)*, Ms Caroline Murphy (King's CTU)*, Ms Anne Millman (PPI)*, Dr David Morgan (Radiation Oncologist)*, Professor Max Bulsara (Trial Statistician)** and Professor Jayant S Vaidya (Chief Investigator) – JSV**.

The Chairmanship by Prof Hamdy was taken over by Prof Fentiman in 2022. Ms Caroline Murphy, Prof Martin Bland were replaced by Mr Sankaran Narayanan and by Mr Risikesh Parmeshwar in 2024.

The study funding was reviewed by the UCL/UCLH Research Office and deemed sufficient to cover the requirements of the study. NHS costs will be supported via UCLH and/or the local Clinical Research Network. The research costs for the study have been supported by the NIHR HTA programme.

Sponsor

University College London, Ref 17/0774.

DARS-NIC-126676-G1X4M-v1: DSA signed on 11 October 2024.

Database

MACRO 20 January 2021 and then REDCap. Database lock 10 December 2024.

Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives. You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

We obtained ethics approval to collect follow-up data directly from patients already recruited in the TARGIT-A trial. The method described below was approved by the ethics committee. If it worked it could be a cost-effective approach to obtaining long-term data for clinical trials and audits for diseases such as breast cancer that have a long natural history. REC and HRA approval were obtained in March 2018 (REC reference: 18/LO/0181). The first site was opened in September 2018. IRAS ref 236431, Fulham REC 10 November 2017–17 December 2024. LCRN North Thames CPMS 37219.

Information governance statement

All information governance regulations of the sponsor have been followed. UCL is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under Data Protection legislation, University College London (UCL) is the Data Processor and the Data Controller, and we process personal data in accordance with their instructions. You can find more information here (www.ucl.ac.uk/joint-research-office/about-us/data-protection-statement).

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJJV2820.

Primary conflicts of interest: Jayant S Vaidya, Norman R Williams, Max Bulsara, Ingrid Potyka, Chris Brew-Graves, Nicholas Roberts and Jeffrey S Tobias receive funding from HTA, NIHR, Department of Health and Social Care for some activities related to the TARGIT trials. Jayant S Vaidya has received a research grant from Photoelectron Corporation and Carl Zeiss for supporting data management at the University of Dundee (Dundee, UK, 2004–8) and has received honorariums. Jayant S Vaidya and Michael Douek are president and immediate past-president of British Association of Surgical Oncology ~ Association for Cancer Surgery (BASO~ACS). Jayant S Vaidya is a member of the Data Monitoring Committee of the ENDONET trial. Carl Zeiss has sponsored some of the travel and accommodation for some meetings for Jayant S Vaidya, Norman R Williams, Max Bulsara, Marcelle Bernstein and Jeffrey S Tobias. Julie Lindsay, Siobhan Laws, Sanjay Raj, Michael Douek, Mary Falzon, Gloria Petralia, Sarah Needleman and Anu Malhotra declare that they have no competing interests.

Disclaimer

Every effort has been made to obtain the necessary permissions for reproduction, to credit original sources appropriately and to respect copyright requirements. However, despite our diligence, we acknowledge the possibility of unintentional omissions or errors and we welcome notifications of any concerns regarding copyright or permissions.

References

1 Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024;**74**:229–63.

2 Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Pineros M, *et al*. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 2019;**144**:1941–53.

3 Wojtyla C, Bertuccio P, Giermaziak W, Santucci C, Odone A, Ciebiera M, *et al*. European trends in ovarian cancer mortality, 1990–2020 and predictions to 2025. *Eur J Cancer* 2023;**194**:113350.

4 Peto R. Mortality from breast cancer in UK has decreased suddenly. *BMJ* 1998;**317**:476–7.

5 Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20–69 years. *Lancet* 2000;**355**:1822.

6 Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mittra I. Multicentricity of breast cancer: whole-organ analysis and clinical implications. *Br J Cancer* 1996;**74**:820–4.

7 Vaidya JS, Baum M, Tobias JS, D'Souza DP, Naidu SV, Morgan S, *et al*. Targeted intra-operative radiotherapy (TARGIT): an innovative method of treatment for early breast cancer. *Ann Oncol* 2001;**12**:1075–80.

8 Vaidya JS, Baum M, Tobias JS, Morgan S, D'Souza D. The novel technique of delivering targeted intraoperative radiotherapy (TARGIT) for early breast cancer. *Eur J Surg Oncol* 2002;**28**:447–54.

9 Bagga SK, Swiderska N, Hooker C, Royle J, Ennis-O'Connor M, Freeney S, *et al*. Qualitative exploration of patients' experiences with Intrabeam TARGeted Intraoperative radioTherapy (TARGIT-IORT) and External-Beam RadioTherapy Treatment (EBRT) for breast cancer. *BMJ Open* 2024;**14**:e081222. https://doi.org/10.1136/bmjopen-2023-081222

10 Vaidya A, Vaidya P, Both B, Brew-Graves C, Bulsara M, Vaidya JS. Health economics of targeted intraoperative radiotherapy (TARGIT- IORT) for early breast cancer: a cost- effectiveness analysis in the United Kingdom. *BMJ Open* 2017;**7**:e014944. https://doi.org/10.1136/bmjopen-2016-014944

11 Coombs NJ, Coombs JM, Vaidya UJ, Singer J, Bulsara M, Tobias JS, *et al*. Environmental and social benefits of the targeted intraoperative radiotherapy for breast cancer: data from UK TARGIT-A trial centres and two UK NHS hospitals offering TARGIT IORT. *BMJ Open* 2016;**6**:e010703. https://doi.org/10.1136/bmjopen-2015-010703

12 Vaidya JS, Bulsara M, Baum M, Wenz F, Massarut S, Pigorsch S, *et al*. New clinical and biological insights from the international TARGIT-A randomised trial of targeted intraoperative radiotherapy during lumpectomy for breast cancer. *Br J Cancer* 2021;**125**:380–9. https://doi.org/10.1038/s41416-021-01440-8

13 Vaidya JS, Bulsara M, Wenz F, Sperk E, Massarut S, Alvarado M, *et al*. The TARGIT-A randomized trial. *Int J Radiat Oncol Biol Phys* 2023;**115**:256–9.

14 Vaidya JS, Bulsara M, Wenz F, Sperk E, Massarut S, Alvarado M, *et al*.; TARGIT-A authors. The TARGIT-A randomized trial: TARGIT-IORT versus whole breast radiation therapy: long-term local control and survival. *Int J Radiat Oncol Biol Phys* 2023;**115**:77–82. https://doi.org/10.1016/j.ijrobp.2022.08.029

15 Vaidya JS, Bulsara M, Baum M, Wenz F, Massarut S, Pigorsch S, *et al*. Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial. *BMJ* 2020;**370**:m2836. https://doi.org/10.1136/bmj.m2836

16 Vaidya JS, Bulsara M, Saunders C, Flyger H, Tobias JS, Corica T, *et al*. Effect of delayed targeted intraoperative radiotherapy vs whole-breast radiotherapy on local recurrence and survival: long-term results from the TARGIT-A randomized clinical trial in early breast cancer. *JAMA Oncol* 2020;**6**:e200249. https://doi.org/doi:10.1001/jamaoncol.2020.0249

17 Vaidya JS. Intraoperative radiotherapy for early breast cancer – authors' reply. *Lancet* 2010;**376**:1143–4.

18 Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph D, Keshtgar M, *et al*. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2014;**383**:603–13. https://doi.org/10.1016/S0140-6736(13)61950-9

19 Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph D, Baum M. Radiotherapy for breast cancer, the TARGIT-A trial – authors' reply. *Lancet* 2014;**383**:1719–20.

20 Vaidya JS, Bulsara M, Baum M, Tobias JS; TARGIT-A trial authors. Single-dose intraoperative radiotherapy during lumpectomy for breast cancer: an innovative patient-centred treatment. *Br J Cancer* 2021;**124**:1469–74. https://doi.org/10.1038/s41416-020-01233-5

21 Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, *et al*. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* 2010;**376**:91–102.

22 Williams NW, Keshtgar M, Corica T, Saunders C, Joseph D. Significantly better cosmetic outcome after intra-operative radiotherapy compared with external beam radiotherapy for early breast cancer: objective assessment of patients from a randomized controlled trial. *Eur J Cancer Suppl* 2010;**8**:129.

23 Welzel G, Hofmann F, Blank E, Kraus-Tiefenbacher U, Hermann B, Sutterlin M, Wenz F. Health-related quality of life after breast-conserving surgery and intraoperative radiotherapy for breast cancer using low-kilovoltage X-rays. *Ann Surg Oncol* 2010;**17**:359–67.

24 Keshtgar M, Williams N, Corica T, Saunders C, Joseph D. Cosmetic outcome one, two and three years after intra-operative radiotherapy compared with external beam radiotherapy for early breast cancer: an objective assessment of patients from a randomised controlled trial. *Eur J Surg Oncol* 2010;**36**:1105.

25 Corica T, Nowak A, Saunders C, Bulsara M, Joseph D. Patient preferences for adjuvant radiotherapy in early breast cancer – an Australian sub-study of the international TARGIT trial. *Eur J Cancer* 2012;**48**:S187.

26 Andersen KG, Gartner R, Kroman N, Flyger H, Kehlet H. Persistent pain after targeted intraoperative radiotherapy (TARGIT) or external breast radiotherapy for breast cancer: a randomized trial. *Breast* 2012;**21**:46–9.

27 Welzel G, Boch A, Sperk E, Hofmann F, Kraus-Tiefenbacher U, Gerhardt A, *et al*. Radiation-related quality of life parameters after targeted intraoperative radiotherapy versus whole breast radiotherapy in patients with breast cancer: results from the randomized phase III trial TARGIT-A. *Radiat Oncol* 2013;**8**:9.

28 Keshtgar MR, Williams NR, Bulsara M, Saunders C, Flyger H, Cardoso JS, *et al*. Objective assessment of cosmetic outcome after targeted intraoperative radiotherapy in breast cancer: results from a randomised controlled trial. *Breast Cancer Res Treat* 2013;**140**:519–25.

29 Alvarado MD, Mohan AJ, Esserman LJ, Park CC, Harrison BL, Howe RJ, *et al*. Cost-effectiveness analysis of intraoperative radiation therapy for early-stage breast cancer. *Ann Surg Oncol* 2013;**20**:2873–80.

30 Alvarado MD, Conolly J, Park C, Sakata T, Mohan AJ, Harrison BL, *et al*. Patient preferences regarding intra-operative versus external beam radiotherapy following breast-conserving surgery. *Breast Cancer Res Treat* 2014;**143**:135–40.

31 Vaidya A, Vaidya P, Both B, Brew-Graves C, Vaidya J. Cost effectiveness analysis of targeted intraoperative radiotherapy alone (TARGIT-A) in early breast cancer patients. *Value Health* 2014;**17**:A640.

32 Corica T, Joseph D, Saunders C, Bulsara M, Nowak AK. Intraoperative radiotherapy for early breast cancer: do health professionals choose convenience or risk? *Radiat Oncol* 2014;**9**:33.

33 Corica T, Nowak AK, Saunders CM, Bulsara M, Taylor M, Vaidya JS, *et al*. Cosmesis and breast-related quality of life outcomes after intraoperative radiation therapy for early breast cancer: a substudy of the TARGIT-A trial. *Int J Radiat Oncol Biol Phys* 2016;**96**:55–64.

34 Corica T, Nowak AK, Saunders CM, Bulsara MK, Taylor M, Williams NR, *et al*. Cosmetic outcome as rated by patients, doctors, nurses and BCCT.core software assessed over 5 years in a subset of patients in the TARGIT-A Trial. *Radiat Oncol* 2018;**13**:68.

35 Corica T, Saunders CM, Bulsara MK, Taylor M, Joseph DJ, Nowak AK. Patient preferences for adjuvant radiotherapy in early breast cancer are strongly influenced by treatment received through random assignment. *Eur J Cancer Care (Engl)* 2019;**28**:e12985.

36 Spaich S, Krickeberg S, Hetjens S, Wenz F, Gerhardt A, Sutterlin M. Patient preferences regarding intraoperative versus external beam radiotherapy for early breast cancer and the impact of socio-demographic factors. *Arch Gynecol Obstet* 2019;**299**:1121–30.

37 Tang A, Cohan CM, Beattie G, Cureton EL, Svahn JD, Lyon LL, *et al*. Patients older 65 years with early breast cancer prefer intraoperative radiation as a locoregional treatment choice. *Ann Surg Oncol* 2021;**28**:5158–63. https://doi.org/10.1245/s10434-021-09618-3

38 Vaidya JS. Principles of cancer treatment by radiotherapy. *Surgery (Oxford)* 2024;**39**:193–201.

39 Vaidya JS, Vaidya UJ, Baum M, Bulsara MK, Joseph D, Tobias JS. Global adoption of single-shot targeted intraoperative radiotherapy (TARGIT-IORT) for breast cancer-better for patients, better for healthcare systems. *Front Oncol* 2022;**12**:786515. https://doi.org/10.3389/fonc.2022.786515

40 TARGIT_IORT_Website_https://bit.ly/TARGIT-IORT-Bibliography. *Scientific Papers About TARGIT-IORT for Breast Cancer*. URL: https://bit.ly/TARGIT-IORT-Bibliography (accessed 14 July 2025).

41 Bhimani F, McEvoy M, Chen Y, Gupta A, Pastoriza J, Fruchter S, *et al*. Case report: IORT as an alternative treatment option for breast cancer patients with difficulty staying still. *Front Oncol* 2024;**14**:1429326.

42 De la Mata D, Santiago-Concha BG, Bargalló-Rocha JE, Robles-Vidal CD, Gómez-Pue D, Castorena-Rojí G, *et al*. Outcomes from real-world data on intraoperative electronic radiotherapy for the treatment of early-stage breast cancer: long-term recurrence and survival outcomes from a single center. *Int J Breast Cancer* 2024;**2024**:6207762.

43 Yang HY, Tsang YW, Tu CW, Hsu YC. Guiding sole intraoperative radiotherapy in breast cancer according to ASTRO guidelines: mitigating adverse outcomes in a Taiwan single-center. *Cancer Med* 2025;**14**:e70537.

44 Sperk E, Lemanski C, Zahn J, Neumaier C, Siefert V, Völker R, *et al*. 1201 Intraoperative radiotherapy in elderly patients with breast cancer: long-term follow-up results of the prospective phase II trial TARGIT-E. *Radiother Oncol* 2025;**206**:S474–5.

45 García-Cabrera L, Pinar-Sedeño B, Cabezón-Pons MA, Rodriguez-Ibarria N, Dominguez-Dominguez A, Aguiar-Santana D, *et al*. Long-term results of a prospective multicenter trial of APBI with photon IORT. *Cancers* 2025;**17**:1762.

46 Palacios-Eito A, Moreno-Manzanaro MC, Espinosa-Calvo M, Ginés-Santiago F, Camús-Martínez JA, Calvo-Tudela A, *et al*. IORT for early-stage, low-risk breast cancer: outcomes from a prospective, observational study. *Clin Transl Radiat Oncol* 2025;**54**:100998.

47 Vinante L, Vaidya JS, Caroli A, Mileto M, Piccoli E, Avanzo M, *et al*. Real world clinical outcomes from targeted intraoperative radiotherapy (TARGIT-IORT) during lumpectomy for breast cancer: data from a large cohort at a national cancer institute. *Front Oncol* 2024;**14**:1424630.

48 Goerdt L, Schnaubelt R, Kraus-Tiefenbacher U, Bruck V, Bauer L, Dinges S, *et al*. Acute and long-term toxicity after planned intraoperative boost and whole breast irradiation in high-risk patients with breast cancer-results from the targeted intraoperative radiotherapy boost quality registry (TARGIT BQR). *Cancers (Basel)* 2024;**16**:2067.

49 Goerdt L, Poemsl J, Spaich S, Welzel G, Abo-Madyan Y, Ehmann M, *et al*. Longitudinal cosmetic outcome after planned IORT boost with low kV X-rays-monocentric results from the TARGIT BQR registry. *Transl Cancer Res* 2023;**12**:1715–26.

50 Nevo H, von Loggereneberg D, Benn C. Intraoperative radiotherapy & oncoplastic breast surgery – safe, feasible, and better. *Eur J Surg Oncol* 2024;**50**:107452.

51 Baek SH, Bae SJ, Kook Y, Cho Y, Ahn SG, Kim JW, *et al*. Long-term oncologic outcome of intraoperative radiotherapy (IORT) with low-energy X-rays as a tumor-bed boost in Korean patients with breast cancer. *Cancer Treat Res Commun* 2025;**43**:100925.

52 Yang G, Kim JW, Lee IJ, Jeong J, Ahn SG, Bae SJ, *et al*. Feasibility of intraoperative radiotherapy tumor bed boost in patients with breast cancer after neoadjuvant chemotherapy. *Yonsei Med J* 2024;**65**:129–36.

53 Sethi A, Gros S, Brodin P, Ghavidel B, Chai X, Popovic M, *et al*. Intraoperative radiation therapy with 50 kV x-rays: a multi-institutional review. *J Appl Clin Med Phys* 2024;**25**:e14272.

54 Salari K, Glaza A, Lee JS, Sarvepalli N, Dekhne N, Kiran SH, *et al*. Clinical outcomes of breast-conserving surgery with synchronous 50-kV X-ray intraoperative partial breast irradiation in patients aged 64 years or older with low-risk breast cancer. *Breast Cancer (Auckl)* 2024;**18**:11782234231224267.

55 Bhimani F, McEvoy M, Gupta A, Pastoriza J, Shihabi A, Basavatia A, *et al*. Case Report: Bilateral targeted intraoperative radiotherapy: a safe and effective alternative for synchronous bilateral breast cancer. *Front Oncol* 2023;**13**:1276766.

56 Andraos TY, Skalina KA, Feldman S, Mehta K, Tome WA, McEvoy MP, *et al*. Experience with intraoperative radiation therapy in an urban cancer center. *Radiat Oncol* 2023;**18**:123.

57 Sanz-Latiesas J, Ibáñez-Carreras R, Eraso-Urién A, Algara-López M. ¿Se puede realizar la radioterapia intraoperatoria de forma asistencial en el tratamiento del cáncer de mama en estadios iniciales?: Can intraoperative radiation therapy be performed in early-stage breast cancer treatment as standard care? *Revista de Senología y Patología Mamaria* 2023;**36**:100500.

58 Martinez C, Meterissian S, Saidi A, Tremblay F, Meguerditchian AN, Fleiszer D, *et al*. Targeted intraoperative radiation therapy during breast-conserving surgery for patients with early stage breast cancer: a phase II single center prospective trial. *Adv Radiat Oncol* 2023;**8**:101236.

59 Kolberg HC, Loevey G, Akpolat-Basci L, Stephanou M, Fasching PA, Untch M, *et al*. Targeted intraoperative radiotherapy tumour bed boost during breast-conserving surgery after neoadjuvant chemotherapy. *Strahlentherapie und Onkologie* 2017;**193**:62–9.

60 Kolberg HC, Lovey G, Akpolat-Basci L, Stephanou M, Fasching P, Untch M, *et al*. Targeted intraoperative radiotherapy tumour bed boost during breast-conserving surgery after neoadjuvant chemotherapy – a subgroup analysis of hormone receptor-positive HER2-negative breast cancer. *Breast Care (Basel)* 2017;**12**:318–23.

61 Kolberg HC, Niesing H, Vaidya JS, Akpolat-Basci L, Maguz A, Hoffmann O, *et al*. Breast conserving surgery in combination with targeted intraoperative radiotherapy compared to mastectomy for In-breast-tumor-recurrence. *Anticancer Res* 2023;**43**:733–9.

62 Kolberg HC, Loevey G, Akpolat-Basci L, Stephanou M, Fasching PA, Untch M, *et al*. Targeted intraoperative radiotherapy tumour bed boost during breast-conserving surgery after neoadjuvant chemotherapy. *Strahlentherapie und Onkologie* 2016;**193**:62–9.

63 Fehm TN, Stickeler E, Fasching PA, Janni W, Kolberg-Liedtke C, Kolberg HC, *et al*. Update breast cancer 2021 Part 3 – current developments in the treatment of early breast cancer: review and assessment of specialised treatment scenarios by an international expert panel. *Geburtshilfe Frauenheilkd* 2021;**81**:654–65.

64 Kolberg HC, Uhl V, Massarut S, Holmes D, Kolberg-Liedtke C, Kelly EW, *et al*. Targeted intraoperative radiotherapy during breast-conserving surgery for breast cancer in patients after implant augmentation. *Anticancer Res* 2019;**39**:4215–8.

65 Mosiun JA, See MH, Teoh LY, Danaee M, Lai LL, Ng CH, *et al*. Comparison of clinical outcomes between low- and high-risk groups of early breast cancer patients treated with intraoperative radiotherapy in addition to external beam radiation: a multi-centre prospective study. *World J Surg* 2023;**47**:201–8.

66 Refaat T, Gros SE, Small W Jr. The case for risk-stratified IORT for early breast cancer. *Brachytherapy* 2022;**21**:719–22.

67 Giap F, O'Steen L, Liu IC, Spiguel LE, Shaw CM, Morris CG, *et al*. Intraoperative radiation therapy for early-stage breast cancer: a single-institution experience. *Rep Pract Oncol Radiother* 2022;**27**:666–76.

68 Mi Y, Zuo X, Cao Q, He J, Sui X, Li J, *et al*. Intraoperative radiotherapy versus no radiotherapy for early stage low-risk breast cancer patients undergoing breast-conserving surgery: a propensity score matching study based on the SEER database. *Clin Transl Oncol* 2022;**24**:2409–19.

69 Chen Q, Qu L, He Y, Xu J, Deng Y, Zhou Q, *et al*. Prognosis comparison between intraoperative radiotherapy and whole-breast external beam radiotherapy for T1–2 stage breast cancer without lymph node metastasis treated with breast-conserving surgery: a case-control study after propensity score matching. *Front Med (Lausanne)* 2022;**9**:919406.

70 Bhimani F, Johnson K, Brodin NP, Tome WA, Fox J, Mehta K, *et al*. Case report: can targeted intraoperative radiotherapy in patients with breast cancer and pacemakers be the new standard of care? *Front Oncol* 2022;**12**:927174.

71 Falco M, Masojc B, Rolla M, Czekala A, Milchert-Leszczynska M, Pietruszewska J. Accelerated partial breast irradiation with intraoperative radiotherapy is effective in luminal breast cancer patients aged 60 years and older. *J Pers Med* 2022;**12**:1116.

72 Brown A, Buss EJ, Chin C, Liu G, Lee S, Rao R, *et al*. Targeted intraoperative radiotherapy (TARGIT-IORT) for early-stage invasive breast cancer: a single institution experience. *Front Oncol* 2022;**12**:788213.

73 Laplana M, Garcia-Marqueta M, Sanchez-Fernandez JJ, Martinez-Perez E, Perez-Montero H, Martinez-Montesinos I, *et al*. Effectiveness and safety of intraoperative radiotherapy (IORT) with low-energy X-rays (INTRABEAM((R))) for accelerated partial breast irradiation (APBI). *Clin Transl Oncol* 2022;**24**:1732–43.

74 Guillerm SO, Bourstyn E, Itti R, Cahen-Doidy L, Quero L, Labidi M, *et al*. Intraoperative radiotherapy for breast cancer in elderly women. *Clin Breast Cancer* 2022;**22**:e109–13.

75 Ramdas Y, Benn CA, van Heerden M. First intraoperative radiation therapy center in africa: first 2 years in operation, including COVID-19 experiences. *JCO Glob Oncol* 2020;**6**:1696–703. https://doi.org/10.1200/go.20.00258

76 Hu X, He Y, Chen X, Xia T, Cao T, Jia H, Zhang L. Impact of intraoperative radiotherapy on the perioperative period of patients after breast-conserving surgery. *Gland Surg* 2020;**9**:1535–42.

77 Mi Y, Lv P, Wang F, Li L, Zhu M, Wang Y, *et al*. Targeted intraoperative radiotherapy is non-inferior to conventional external beam radiotherapy in Chinese patients with breast cancer: a propensity score matching study. *Front Oncol* 2020;**10**:550327.

78 Ramdas Y, Benn CA, Grubnik A, Mayat Y, Holmes DR. Targeted intraoperative radiotherapy is a safe approach for patients with pacemakers: a case study and literature review. *Case Rep Oncol* 2020;**13**:916–22.

79 Lorenzen AW, Kiriazov B, De Andrade JP, Lizarraga IM, Scott-Conner CE, Sugg SL, *et al*. Intraoperative radiotherapy for breast cancer treatment in a rural community. *Ann Surg Oncol* 2018;**25**:3004–10.

80 Battisti NML, Mislang AR, Cooper L, O'Donovan A, Audisio RA, Cheung KL, *et al*. Adapting care for older cancer patients during the COVID-19 pandemic: recommendations from the international society of geriatric oncology (SIOG) COVID-19 working group. *J Geriatr Oncol* 2020;**11**:1190–8.

81 Tallet A, Racadot S, Boher JM, Cohen M, Barrou J, Houvenaeghel G, *et al*. The actual benefit of intraoperative radiation therapy using 50 kV x-rays in early breast cancer: a retrospective study of 676 patients. *Breast J* 2020;**26**:2145–50. https://doi.org/10.1111/tbj.13827

82 Lemanski C, Bourgier C, Draghici R, Thezenas S, Morel A, Rouanet P, *et al*. Intraoperative partial irradiation for highly selected patients with breast cancer: results of the INTRAOBS prospective study. *Cancer Radiother* 2020;**24**:114–9.

83 Moini N, Akbari ME, Mirzaei H, Hosseini Daghigh SM, Zayeri F, Hajizadeh N, *et al*. Intraoperative boost radiotherapy with 50 kV X-Rays versus external radiotherapy in breast cancer: single-center experiences. *Int J Cancer Manag* 2020;**13**:e98561.

84 Freitas NMA, Freitas P. Patient profile with early stage breast cancer submitted to intraoperative radiotherapy in tertiary service in Goiânia. *Mastology* 2019;**29**:97.

85 Chin C, Hirji S, Onishi M, Ha R, Taback B, Horowitz DP, Connolly EP. A Single-Institution experience in the preoperative selection of DCIS patients for IORT using the ASTRO consensus guidelines. *Adv Radiat Oncol* 2019;**4**:253–60.

86 Hernando E, Casamayor MC, Ibáñez R, Palomares A, Rodrigo V, Cruz S, *et al*. Cirugía oncoplástica y radioterapia intraoperatoria en el cáncer de mama. *Revista de Senología y Patología Mamaria* 2019;**32**:12–6.

87 Banks A, Coronado G, Zimmerman R, Iyengar G, Holmes DR. Breast conserving surgery with targeted intraoperative radiotherapy for the management of ductal carcinoma in situ. *J Surg Oncol* 2019;**119**:409–20.

88 Barrou J, Tallet A, Cohen M, Bannier M, Buttarelli M, Gonzague L, *et al*. Contribution of intraoperative radiotherapy (IORT) for therapeutic de-escalation in early breast cancer: report of a single institution's experience. *Breast J* 2018;**24**:715–23.

89 Thangarajah F, Heilmann J, Malter W, Kunze S, Marnitz S, Mallmann P, *et al*. Breast conserving surgery in combination with intraoperative radiotherapy after previous external beam therapy: an option to avoid mastectomy. *Breast Cancer Res Treat* 2018;**168**:739–44.

90 Aninditha KP, Baumbach S, Ellethy T, Klumpp G, Golle A, Kuhn S, *et al* Intraoperative radiation therapy for brain metastasis in a pregnant patient: a case report. *Strahlentherapie und Onkologie* 2024;**200**:1088–92.

91 Eraso A, Sanz J, Ibáñez R, Alonso LM, Calín A, Casamayor MC, *et al*. Primer consenso español sobre el uso de la radioterapia intraoperatoria en el cáncer de mama. Conclusiones del panel de expertos. *Revista de Senología y Patología Mamaria* 2023;**36**:100502.

92 Pinar Sedeño MB, Calín Lorca A, García Cabrera L. Can breast cancer be reirradiated? *Revista de Senología y Patología Mamaria* 2023;**36**:100497.

93 Bargallo-Rocha JE, Soto-Perez-de-Celis E, Pico-Guzman FJ, Quintero-Rodriguez CE, Almog D, Santiago-Concha G, *et al*. The impact of the use of intraoperative radiotherapy on costs, travel time and distance for women with breast cancer in the Mexico City Metropolitan Area. *J Surg Oncol* 2017;**116**:683–9.

94 Muñoz GH, Hany RP, Cosson A, Gonzalez C, Rasquií JH, Rodriguez I, *et al*. Intraoperative radiation therapy (INTRABEAM) experience at the mastology unit leopoldo aguerrevere clinic. *J Cancer Ther* 2015;**6**:932–42.

95 Abbott AM, Dossett LA, Loftus L, Sun W, Fulp W, Sokol GH, Laronga C. Intraoperative radiotherapy for early breast cancer and age: clinical characteristics and outcomes. *Am J Surg* 2015;**210**:624–8.

96 Malter W, Kirn V, Richters L, Fridrich C, Markiefka B, Bongartz R, *et al*. Intraoperative boost radiotherapy during targeted oncoplastic breast surgery: overview and single center experiences. *Int J Breast Cancer* 2014;**2014**:1–6.

97 Keshtgar MR, Eaton DJ, Reynolds C, Pigott K, Davidson T, Gauter-Fleckenstein B, Wenz F. Pacemaker and radiotherapy in breast cancer: is targeted intraoperative radiotherapy the answer in this setting? *Radiat Oncol* 2012;**7**:128.

98 Kraus-Tiefenbacher U, Blank E, Wenz F. Intraoperative radiotherapy during a second breast-conserving procedure for relapsed breast cancer after previous external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 2011;**80**:1279–80.

99 Keshtgar MR, Vaidya JS, Tobias JS, Wenz F, Joseph D, Stacey C, *et al*. Targeted intraoperative radiotherapy for breast cancer in patients in whom external beam radiation is not possible. *Int J Radiat Oncol Biol Phys* 2011;**80**:31–8.

100. Das A, Abdulkarim K, Banerjee S, Kurmude R, Tan JK, Prusty L, *et al*. The evolution of targeted intra operative radiotherapy in early breast cancer. *Journal of Cancer Research and Clinical Oncology* 2025;**151**. https://doi.org/10.1007/s00432-025-06294-8.

101. National Institute for Health and Care Research. *Five Amazing Health Research Breakthroughs in the Last 12 Months*. 2021. URL: https://bepartofresearch.nihr.ac.uk/news-and-features/breakthroughs-2020-to-2021 (accessed 14 July 2025).

102. Vaidya JS Williams NR, Bulsara M Baum M Brew-Graves C, Potyka I, *et al*. Long-term incidence of lung cancer in the TARGIT-A randomised trial of targeted intraoperative radiotherapy for breast cancer. *Presented at: 44th European Society of Surgical Oncology Annual Congress, Gothenburg, Sweden. Eur J Surg Oncol 2025;***51**(Suppl 2):110790. https://doi.org/10.1016/j.ejso.2025.110790

103. Vaidya JS, Williams NR, Bulsara M Baum M Brew-Graves C Potyka I, *et al*. Substantially lower lung cancer incidence with TARGIT-IORT (targeted intraoperative radiotherapy) compared with whole breast radiotherapy in the TARGIT-A randomised trial for breast cancer: 25-year update Presented at: 87th British Association of Surgical Oncology ~ Association for Cancer Surgery, Annual Congress, London, UK. Eur J Surg Oncol 2026;**52**(suppl 1):111235. http://doi.org/10.1016/j.ejso.2025.111235

104. Vaidya JS, Williams NR, Bulsara M, Baum M, Brew-Graves C, Potyka I *et al*. Using targeted intraoperative radiotherapy for early breast cancer reduces the incidence of late-onset lung cancer: 25-year update from the TARGIT-A randomised trial. Preprint at UCL. London: University College London; 2025. http://doi.org/10.14324/000.wp.10218309

105. Vaidya JS. Reduction in HRT use is not associated with a reduction in breast cancer incidence in Scotland. *J Natl Cancer Inst* 2008;**100**:598–9.

106. Hoskin P. Evidence-based practice in oncology, when it suits us?. BMJ Oncology 2023; 2:e000061. https://doi.org/10.1136/bmjonc-2023-000061.

Appendix 1

Site activations

Site 001 – UCLH (*n* = 146), PI: GP, MF.

20 December 2018 – Site opened.

17 January 2019 – First patient recruited.

New site PI received trial handover and started in April 2021.

Site 004 – Dundee (*n* = 226) PI: JL.

6 May 2021 – Site opened.

6 September 2021 – First patient recruited.

Site 018 – Royal Free Hospital (*n* = 114) PI: SN.

18 October 2018 – Site opened.

22 February 2019 – First patient recruited.

Site 024 – Winchester Hospital (*n* = 101) PI: SL.

4 September 2018 – Site opened.

17 October 2018 – First patient recruited.

Site 028 – Guy's Hospital (*n* = 20) PI: MD and AM.

6 March 2019 – Site opened.

23 April 2019 – First patient recruited.

New site PI received trial handover and started in May 2021.

Site 041 – Whittington Hospital (*n* = 29) – PI: JV and MF.

1 August 2018 – Site opened.

16 August 2018 – First patient recruited.

New site PI received trial handover and started in June 2021.

EME
HSDR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library