

<b>Institution:</b> University of Sheffield		
<b>Unit of Assessment:</b> A-01 Clinical Medicine		
<b>Title of case study:</b> Adjuvant bisphosphonates – cost effective treatment saves 1,000 UK lives per year		
<b>Period when the underpinning research was undertaken:</b> 2000–2020		
<b>Details of staff conducting the underpinning research from the submitting unit:</b>		
<b>Name(s):</b>	<b>Role(s) (e.g. job title):</b>	<b>Period(s) employed by submitting HEI:</b>
Rob Coleman	Professor of Medical Oncology	1990–2017
Ingunn Holen	Professor of Bone Oncology	1995–present
Janet Brown	Professor of Translational Medical Oncology	1999-06–2010-present
Penny Ottewell	Senior Lecturer in Bone Biology	2005–present
Matt Winter	Honorary Reader & Consultant in Breast cancer	2006-09 & 2011–present
Caroline Wilson	Consultant/Honorary Senior Lecturer in Breast Cancer	2011–present
<b>Period when the claimed impact occurred:</b> Aug 2013–2020		
<b>Is this case study continued from a case study submitted in 2014?</b> N		
<b>1. Summary of the impact</b> (indicative maximum 100 words)		
<p>One in eight women develop breast cancer in the UK. For a significant proportion, the cancer will spread to other organs (metastasis) and cause death. Sheffield work over 20 years has produced greater understanding of the biological/clinical mechanisms underlying adjuvant bisphosphonate (BP) drug therapy which has underpinned changes to national and international clinical guidelines and practice regarding the use of adjuvant BPs to treat postmenopausal patients with breast cancer. These changes have resulted in reduction in bone metastatic disease, saving approximately 1,000 UK lives per year and approximately £50 million per annum for the NHS.</p>		
<b>2. Underpinning research</b> (indicative maximum 500 words)		
<p>Despite major advances in treatment, the number of women dying from breast cancer remains high (11,563 in the UK in 2016), and the great majority of these deaths are associated with incurable distant metastatic disease – in particular, 70% of patients with advanced breast cancer develop skeletal metastasis. The prevention or reduction of metastasis is therefore a key clinical goal. Though BPs are highly effective in long-term palliation of bone metastases, their use in this advanced setting has not improved survival from breast cancer. In the last 15 years, our clinical (Coleman, Brown) and pre-clinical (Holen, Ottewell) research programs have investigated the effects of BPs on the complex process of metastasis [R1, R2] and have led to the development of <b>BPs to prevent bone metastasis</b> and improve survival for women with <b>early breast cancer</b> and to reduce the effects of <b>advanced breast cancer</b> once bone metastasis is established.</p> <p>The international AZURE trial (NCT00072020, ISCRTN-79831382, 2003-2011) was sponsored by the University of Sheffield (CI: Coleman) and funded (&gt;£6m) by Novartis in partnership with the NIHR. Patient recruitment was completed in 2006; 3,360 patients with stage II/III breast cancer were included from 174 centres in seven countries. This was randomised to 5 years of the BP zoledronic acid (ZOL) plus standard therapy or standard therapy alone. The trial provided the first demonstration of significant improvement in both breast cancer relapse rates and overall</p>		

survival in postmenopausal women with early breast cancer receiving adjuvant ZOL [R3, R4]. Moreover, these benefits persisted at 10 years' follow-up [R5], meaning that the 75% of breast cancer patients who are postmenopausal might benefit from this treatment.

Following the AZURE study, Coleman was the clinical lead for the Early Breast Cancer Clinical Trials Collaborative Group (EBCTCG) worldwide individual patient meta-analysis of 18,766 patients included in randomised clinical trials of adjuvant BPs for early breast cancer. This meta-analysis found a 28% reduction in bone recurrence, 18% reduction in cancer mortality and 3.3% absolute reduction in mortality at 10 years [R6]. These outcomes confirmed the benefits of BP treatment for postmenopausal women seen in the AZURE trial [R3].

### 3. References to the research (indicative maximum of six references)

Since 2000, Sheffield researchers have published more than 200 high-quality papers on breast cancer and bone-targeted agents in international scientific journals. Sheffield researchers are in bold.

- R1. Ottewell, P. D., Monkkonen, H., Jones, M., Lefley, D. V., Coleman, R. E., & Holen, I.** (2008). Antitumor Effects of Doxorubicin Followed by Zoledronic Acid in a Mouse Model of Breast Cancer. *JNCI Journal of the National Cancer Institute*, 100(16), 1167–1178. <https://doi.org/10.1093/jnci/djn240>
- R2. Coleman, R. E., Major, P., Lipton, A., Brown, J. E., Lee, K.-A., Smith, M., Saad, F., Zheng, M., Hei, Y. J., Seaman, J., & Cook, R.** (2005). Predictive Value of Bone Resorption and Formation Markers in Cancer Patients With Bone Metastases Receiving the Bisphosphonate Zoledronic Acid. *Journal of Clinical Oncology*, 23(22), 4925–4935. <https://doi.org/10.1200/jco.2005.06.091>
- R3. Coleman, R. E., Marshall, H., Cameron, D., Dodwell, D., Burkinshaw, R., Keane, M., Gil, M., Houston, S. J., Grieve, R. J., Barrett-Lee, P. J., Ritchie, D., Pugh, J., Gaunt, C., Rea, U., Peterson, J., Davies, C., Hiley, V., Gregory, W., & Bell, R.** (2011). Breast-Cancer Adjuvant Therapy with Zoledronic Acid. *New England Journal of Medicine*, 365(15), 1396–1405. <https://doi.org/10.1056/nejmoa1105195>
- R4. Coleman, R., Cameron, D., Dodwell, D., Bell, R., Wilson, C., Rathbone, E., et al.** (2014) Adjuvant zoledronic acid in patients with early breast cancer: final efficacy analysis of the AZURE (BIG 01/04) randomised open-label phase 3 trial. *The Lancet Oncology*, 15(9), 997–1006. [https://doi.org/10.1016/s1470-2045\(14\)70302-x](https://doi.org/10.1016/s1470-2045(14)70302-x)
- R5. Coleman R.E., Brown J.E., Wilson C.** et al (2018) Benefits and risks of adjuvant treatment with zoledronic acid in stage II/III breast cancer. 10 years follow-up of the AZURE randomized clinical trial (BIG 01/04). *Journal of Bone Oncology*, 13, 123–135. <https://doi.org/10.1016/j.jbo.2018.09.008>
- R6. EBCTCG (Coleman RE, Powles T, Paterson A et al).** (2015) Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *The Lancet*, 386(10001), 1353–1361. [https://doi.org/10.1016/s0140-6736\(15\)60908-4](https://doi.org/10.1016/s0140-6736(15)60908-4)

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

Sheffield research provided rigorous evidence that led to the introduction of adjuvant BPs into routine clinical practice and changes in national and international clinical guidelines and practice for the treatment of postmenopausal patients with early breast cancer. This resulted in reductions in bone metastatic disease, substantial cost savings for the NHS, and increased public awareness.

### Changes to national and international guidelines regarding the clinical implementation of adjuvant BPs

The AZURE trial and EBCTCG meta-analysis underpinned changes in key national and international clinical guidance to include the use of adjuvant BPs in early breast cancer. Informed by Sheffield research, in November 2015 the UK Breast Cancer Group (UKBCG) endorsed adjuvant BPs as an urgent priority for implementation, recommending in their clinical guidance that “*adjuvant bisphosphonates should be considered for all postmenopausal breast cancer patients*” [S1]. In addition, the Sheffield team developed guidelines on patient selection and prescribing, a patient information sheet, and a business case with financial modelling for Sheffield/South Yorkshire/North Derbyshire, which were also shared nationally and led to the adoption by centres across the UK [S2].

Drawing on [R2-R4] and [R6], the research team wrote 2 of 3 published international consensus papers on the clinical implementation of adjuvant BPs. The 2016 European consensus guidance recommended “*bisphosphonates as routine clinical practice in the prevention of metastases in patients with low levels of female sex hormones - age 55 and over and/or postmenopausal*” [S3].

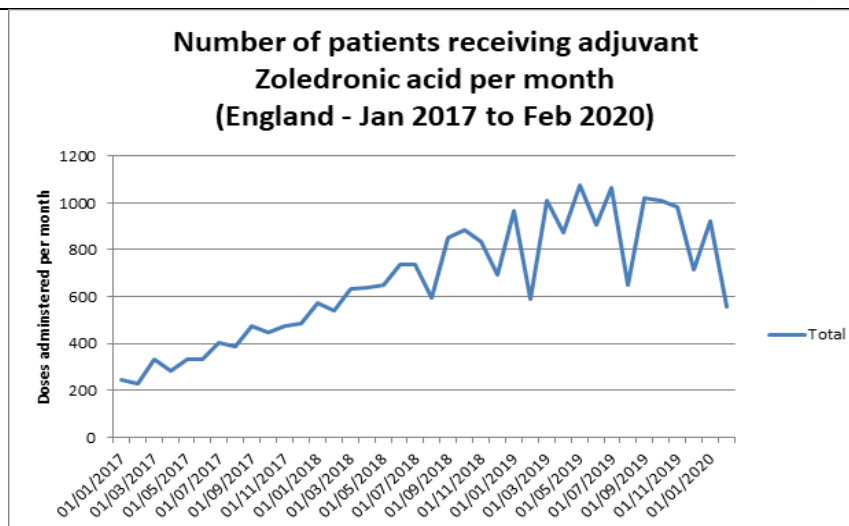
Sheffield researchers have a long-standing collaboration with Breast Cancer Now (BCN, the largest UK breast cancer charity) to carry out health economics assessments and to employ the underpinning research [R3-R6] in lobbying the Department of Health to make BPs available for the prevention of secondary breast cancer [S4, S5].

The UK National Breast Clinical Reference Group guidance, the open letters to the Department of Health [S5] and presentation of the research to NICE by Coleman, were used to provide evidence on the use of adjunct (adjuvant) bisphosphonates to NICE [S6]. In 2018, *Nice Guidance (NG101): Early and locally advanced breast cancer: diagnosis and management* recommended offering bisphosphonates (ZOL or sodium clodronate) as adjuvant therapy to postmenopausal women with node-positive invasive breast cancer, and considering adjuvant BP therapy for postmenopausal women with node-negative invasive breast cancer and a high risk of recurrence [S6].

In North America, the Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline recommends that, “*if available, zoledronic acid (4 mg intravenously every 6 months) or clodronate (1,600 mg/d orally) be considered as adjuvant therapy for postmenopausal patients with breast cancer who are deemed candidates for adjuvant systemic therapy*” [S7].

### Impact on the use of adjuvant BPs in regional and national routine oncology practice in the UK

Prior to 2016, routine commissioning for the use of adjuvant BPs was not available nationally, and in *Sheffield/South Yorkshire/North Derbyshire*, no postmenopausal early breast cancer patients received adjuvant BPs as the standard of care. Following the research team’s regional health economic modelling, the NHS commissioning of adjuvant BPs was agreed upon [S6], and the use of BPs was embedded into clinical practice across the whole of the NHS. As a result, by the end of 2016, **24%** of UK oncologists were using adjuvant BPs [S4]. Following the publication of international clinical guidelines informed by Sheffield research [S1, S3, S7, S8] and the sharing of the Sheffield guidelines [S9] for adjuvant BPs, this percentage increased to **>70%** in 2018 [S9]. Nationally (in England), the use of adjuvant zoledronic acid increased 4-fold from 1<sup>st</sup> January 2017 to February 2020 [S10].



In the Sheffield/South Yorkshire/North Derbyshire population, the number of patients treated with adjuvant BPs increased from zero prior to November 2016 to 572 in 2017, with continued increases to the end of the submission period [S11].

Currently, the strategy is to routinely provide adjuvant BPs to all patients with an adverse prognostic factor of a >12% 10-year risk of cancer death. BCN determined that 94% of UK NHS Trusts are now routinely using adjuvant BPs. Furthermore, a Sheffield-led national UK survey completed in March 2019 (**Brown, Wilson, Holen**) demonstrated that **99%** of UK centres are now using adjuvant BPs [S9].

### Health and economic impacts

BPs were found to be acceptable and well-tolerated as adjuvant treatment [S2], and the introduction of adjuvant BPs has resulted in cost savings for the NHS and reduced mortality in South Yorkshire [S2] and across the UK. Calculations within the business case for Sheffield/South Yorkshire [S9], which has been shared nationally, show that the costs of adjuvant BP treatment range from £325-£561/patient depending on the BP and scheduling.

**Fewer DEXA scans:** Routine bone density monitoring (done by DEXA scanning) is expensive but is not required for patients on adjuvant BPs, amounting to a UK savings of £6.8 million with the European Consensus guidelines or £4.5m with the South Yorkshire guidelines [S9].

**Fewer women developing metastatic breast cancer:** The EBCTCG meta-analysis showed a 3.3% absolute reduction in breast cancer mortality at 10 years with the use of adjuvant BPs in postmenopausal women, equivalent to around 1,000 lives saved per year in the UK. According to a large meta-analysis conducted in 2018, the average estimated saving in treatment costs per patient at 2015 prices was \$62,000 (~£50,000) [S12]. This corresponds to £50m per annum for the 1,000 UK lives saved per annum [S12].

### Impact on public awareness

The research on the use of adjuvant BPs to treat early breast cancer received wide media coverage in scientific news media such as *ScienceDaily*, *The ASCO Post* (the newsletter of the American Society of Clinical Oncology) and *CancerNetwork*, as well as in UK news and media such as *The BBC* and *The Guardian* resulting in the communication of the research results to the wider public [S13]. Coverage on the BBC and BCN websites around BP's potential use attracted attention on BCN's patient forum around lobbying the NHS to provide this treatment, with one patient posting 'Looks like I have found my place to campaign!' [S13]. The above and

subsequent media coverage raised awareness amongst patients and highlighted the potential of adjuvant BP treatment to save thousands of lives.

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

- S1.** The National Breast Clinical Reference Group: benefit of adjuvant bisphosphonates in postmenopausal women (<https://bit.ly/3vQelOp>).
- S2.** Wilson, C., et. al. (2019). Compliance and patient reported toxicity from oral adjuvant bisphosphonates in patients with early breast cancer. A cross sectional study. *Journal of Bone Oncology*, 15, 100226. <https://doi.org/10.1016/j.jbo.2019.100226>. The first real-world evidence of patient adherence and toxicity from adjuvant oral BPs in South Yorkshire, reporting good compliance and low prevalence of significant side effects in 413 patients.
- S3.** European Society for Medical Oncology (ESMO) Clinical Practice Guidelines 2020, <https://doi.org/10.1016/j.annonc.2020.07.019>
- S4.** Combined BCN sources: factual statement supporting collaboration, January 2021 (PDF available), accompanied by BCN summary of adjuvant bisphosphonates - UK, 2016 (<https://bit.ly/3tLWPYj>) supporting clinical use of BPs.
- S5.** Combined open letters lobbying the Department of Health and NHS England regarding the availability of BPs for the prevention of secondary breast cancer: (1) to Secretary of State (published in The Times, 14-Nov-2016); (2) follow-up to Department of Health Minister responsible for access to medicines policy, Dec-2016; and (3) to NHS England Chief Executive, 01-Jun-2017.
- S6.** Combined NICE evidence: Early breast cancer (preventing recurrence and improving survival): adjuvant bisphosphonates. NICE Evidence Summary ES15, July 2017 (<https://www.nice.org.uk/advice/es15>); Early and locally advanced breast cancer, NICE guideline NG101, July 2018 (<https://bit.ly/3rfb3px>). Section 1.9 contains recommendations and rationale. Full details in Evidence review G (<https://bit.ly/3IJHifH>).
- S7.** Dhesy-Third, S. et. al. (2017). Use of Adjuvant Bisphosphonates and Other Bone-Modifying Agents in Breast Cancer: A Cancer Care Ontario and American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology*, 35(18), 2062–2081. <https://doi.org/10.1200/jco.2016.70.7257>
- S8.** Breast Cancer Clinical Expert Group, *Clinical Advice to Cancer Alliances for the Provision of Breast Cancer Services*, August 2017 (<https://bit.ly/2PrAhDS>). Summarises current best practice. The impact is in the inclusion of recommendation of adjuvant BPs (Appendix 4).
- S9.** Combined source: South Yorkshire business case for BP use, February 2016; consensus guidance for clinical practice on the use of BP in early breast cancer - Hadji, P et al.. (2016). Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel. *Annals of Oncology*, 27(3), 379–390. <https://doi.org/10.1093/annonc/mdv617>
- S10.** Data taken from the National Systemic Anti-Cancer Therapy Dataset for use of adjuvant zoledronic acid for breast cancer (<http://www.chemodataset.nhs.uk/home>).
- S11.** 2018 survey of NHS trusts determining no. of patients receiving adjuvant BP treatment.
- S12.** Sun, L., Legood, R., dos-Santos-Silva, I., Gaiha, S. M., & Sadique, Z. (2018). Global treatment costs of breast cancer by stage: A systematic review. *PLOS ONE*, 13(11), e0207993. <https://doi.org/10.1371/journal.pone.0207993>
- S13.** Combined media coverage/stakeholder involvement including BBC News, The Guardian, Breast Cancer Now, Cancer Forums, Stakeholders. PDF available.