Institution: Queen Mary University of London		
Unit of Assessment: 1		
Title of case study: Approval of Tamoxifen for Breast Cancer Prevention		
Period when the underpinning research was undertaken: 2006-2017		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role (s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
1) Jack Cuzick	1) Director, Wolfson Institute	1) 12/2002-present
2) Ivana Sestak	2) Reader in Medical Studies	2) 07/2007-present
3) Sam Smith	3) Honorary Senior Research Fellow	3) 11/2016-10/2019
4) Adam Brentnall	4) Lecturer in Biostatistics	4) 03/2009-present
5) Caroline Reuter	5) Laboratory Manager	5) 09/2011-01/2020
Period when the claimed impact occurred: August 2013-2019		
Is this case study continued from a case study submitted in 2014? N		

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

Queen Mary's follow up results of the IBIS-I trial, published in 2007 and 2015, demonstrated that for women at increased breast cancer risk, taking tamoxifen for five years has a 20-year preventive effect. Thus, since August 2013, the US Preventive Services Task Force, the American Cancer Society, and the US National Comprehensive Cancer Network have recommended prophylactic tamoxifen for women at increased breast cancer risk, numbering over 7,000,000. In Australia, tamoxifen was licenced for breast cancer prevention in 2016, and was added to the Australian Government's pharmaceutical benefits scheme, as a result of which an estimated 250,000 women will directly benefit. In April 2018, the UK Medicines and Healthcare Products Regulatory Agency approved the use of tamoxifen in the primary prevention of breast cancer in women at moderate or high risk. In England and Wales this amounts to approximately 500,000 women. A five-year preventive treatment course of tamoxifen costs approximately GBP130. By contrast, the treatment for breast cancer per patient can cost GBP12,000 per year.

2. Underpinning research (indicative maximum 500 words)

As the incidence of breast cancer continues to rise (an estimated 1,600,000 cases now occur worldwide each year), research is focussing on prevention for women at increased risk. Prior to 2002, several studies of the prophylactic utility of the selective oestrogen receptor modulator (SERM) drug, tamoxifen, had produced mixed results, and opinion was divided on the risk to benefit ratio. In the two follow up studies to the Queen Mary led the International Breast Cancer Intervention Study (IBIS-I) trial, published in 2007 and 2015, Prof. Cuzick, as lead investigator in the IBIS-I, demonstrated that for women at increased risk, tamoxifen taken for five years has a continuing preventive effect for 20 years.

In the original IBIS-I double-blind randomised placebo controlled trial of tamoxifen, 7,154 women considered to be at increased risk of breast cancer were allocated to five years of either tamoxifen, or placebo. The first published results in 2002 showed that after a median follow-up of 50 months, there was an observed 32% risk reduction, but the overall risk to benefit ratio remained unclear. At median eight years of follow-up, the long term results reported in 2007 [3.1] showed that the risk reducing effects of tamoxifen appeared to persist for at least ten years. This study also presented the first randomised evidence that while the benefits of tamoxifen extend beyond the treatment period, the side effects largely did not.

A 2013 meta-analysis of all SERM prevention trials [3.2] confirmed the preventive efficacy of these drugs. In the extended long term IBIS-I follow up (median 16 years) published in 2015 [3.3], it was found that the preventive effect of five years of tamoxifen treatment remained similar, and persisted, throughout the 20-year period. Reductions were recorded for invasive oestrogen receptor positive cancers and ductal carcinoma in situ, but not for invasive oestrogen receptor negative cases. Tamoxifen was shown to offer a very long period of protection after treatment cessation, and therefore the benefit to harm ratio of tamoxifen for breast cancer prevention was substantially improved.

Cuzick and his team have subsequently published additional research on tamoxifen in breast cancer prevention, including:

- An assessment of uptake [3.4]
- A comparison of results with a second trial to help identify more women who would benefit from the treatment and to investigate the effect of adding a polygenic risk score to refine the risk models [3.5]
- And a study of attitudes among general practitioners to prescribing tamoxifen for breast cancer prevention and the potential benefit of initiating prescriptions for preventive therapy in secondary rather than primary care [3.6].

Thus, Queen Mary's research has demonstrated that for women at increased breast cancer risk, taking tamoxifen for five years has a 20-year preventive effect and that tamoxifen should, therefore, be considered for long-term preventive treatment.

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

[3.1] Cuzick, J., Forbes, J. F., Sestak, I., Cawthorn, S., Hamed, H., Holli, K. & Howell, A. (2007). International Breast Cancer Intervention Study I Investigators. Long-term results of tamoxifen prophylaxis for breast cancer—96-month follow-up of the randomized IBIS-I trial. *Journal of the National Cancer Institute, 99* (4), 272-82. https://doi.org/10.1093/jnci/djk049

[3.2] Cuzick, J., Sestak, I., Bonanni, B., Costantino, J. P., Cummings, S., DeCensi, A., Dowsett, M., Forbes, J. F., Ford, L., LaCroix, A. Z., Mershon, J., Mitlak, B. H., Powles, T., Veronesi, U., Vogel, V. & Wickerham, D. L. (2013). SERM Chemoprevention of Breast Cancer Overview Group. Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. *The Lancet, 381* (9880), 1827-1834. https://doi.org/10.1016/S0140-6736(13)60140-3

[3.3] Cuzick, J., Sestak, I., Cawthorn, S., Hamed, H., Holli, K., Howell, A. & Forbes, J. F. (2015). IBIS-I Investigators. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. *The Lancet Oncology, 16* (1), 67-75. http://dx.doi.org/10.1016/S1470-2045(14)71171-4

[3.4] Smith, S. G., Sestak, I., Forster, A., Partridge, A., Side, L., Wolf, M. S., Horne, R., Wardle, J. & Cuzick, J. (2016). Factors affecting uptake and adherence to breast cancer chemoprevention: a systematic review and meta-analysis. *Annals of Oncology, 27* (4), 575-590. https://doi.org/10.1093/annonc/mdv590

[3.5] Cuzick, J., Brentnall, A. R., Segal, C., Byers, H., Reuter, C., Detre, S., Lopez-Knowles, E., Sestak, I., Howell, A., Powles, T. J., Newman, W. G. & Dowsett, M. (2017). Impact of a Panel of 88 Single Nucleotide Polymorphisms on the Risk of Breast Cancer in High-Risk Women: Results From Two Randomized Tamoxifen Prevention Trials. *Journal of Clinical Oncology, 35* (7), 743-750. https://doi.org/10.1200/JCO.2016.69.8944

[3.6] Smith, S. G., Foy, R., McGowan, J. A., Kobayashi, L. C., DeCensi, A., Brown, K., Side, L. & Cuzick, J. (2017). Prescribing tamoxifen in primary care for the prevention of breast cancer: a national online survey of GPs' attitudes. *British Journal of General Practice, 67* (659), e414-e427. https://doi.org/10.3399/bjgp17X689377

Evidence of the quality of the research

[EQR.1] Cuzick, J. (01/04/2004-31/03/2009). Epidemiology, Maths and Statistics Unit [C569/A5030]. *Cancer Research UK*. Programme Grant. GBP3,387,222.

[EQR.2] Cuzick, J. (01/04/2009-31/03/2014). Prevention of Hormone Related Cancers [C569/A10404]. *Cancer Research UK*. Programme Grant. GBP5,309,642.

[EQR.3] Cuzick, J. (01/04/2014-31/03/2019). Cancer Prevention [C569/A16891]. *Cancer Research UK*. Programme Grant. GBP5,519.109.

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

Queen Mary's research has enabled access to tamoxifen as a long-term preventive treatment for breast cancer for women at increased risk. This has been achieved through influencing international clinical guidelines and providing evidence that has facilitated approval for this new use of tamoxifen.

Informing clinical guidelines in the US

Over 7,000,000 women in the US (approximately 10% of the female population aged 35 or older) fall into the 'high risk' category for breast cancer. Using tamoxifen to prevent breast

cancer among women aged 55 and younger with a 5-year risk of ≥1.66% will prevent 29 cases and 9 breast cancer deaths, and save USD47,580 per 1,000 women treated [5.1].

Recommendations regarding tamoxifen for preventive use changed after publication of the IBIS-I long term follow up results [3.1, 3.2]. The US Preventive Services Task Force, in September 2013, reviewed IBIS-I [3.1] as part of the evidence for offering risk reducing SERMs such as tamoxifen and recommended offering them to asymptomatic women aged 35 or older without a prior diagnosis of breast cancer, ductal carcinoma in situ, or lobular carcinoma in situ, but who are at increased risk of breast cancer [5.2]. The American Cancer Society also altered its guidelines, referencing [3.2] to note that tamoxifen has been shown to lower breast cancer risk [5.3]. The National Comprehensive Cancer Network (NCCN) guidelines of 2017 referenced Prof. Cuzick's work on chemoprevention [3.2] and recommend that women with a strong family history of breast cancer should be evaluated for preventive treatment [5.4]. The NCCN used Cuzick's work [3.1, 3.3] as part of the evidence base for their recommendation that tamoxifen is used as an option for pre- and post-menopausal women aged 35 or older with a life expectancy of 10 years or more, who are at increased risk for breast cancer (generally those with ≥1.7% 5-year risk for breast cancer using the Gail model) [5.5].

Informing clinical guidelines in Australia

Based on the IBIS-I and other clinical trials, in April 2016, Nolvadex [5.6] (tamoxifen) was approved with an "extension of indication" by the Australian Government's Department of Health Therapeutic Goods Administration. It announced that Nolvadex was now indicated for the primary reduction of breast cancer risk in women either at moderately increased risk (lifetime breast cancer risk 1.5 to 3 times the population average) or high risk (lifetime breast cancer risk greater than 3 times the population average) [5.7]. Tamoxifen for women at increased risk of breast cancer was then added to the Australian Government's Pharmaceutical Benefits Scheme (PBS) [5.8]. The National Breast Cancer Foundation's press coverage of this development noted that this change in policy was a result of the IBIS-I trial evidence, which it was "proud" to have funded [5.9].

With the approval of tamoxifen as a preventive measure on PBS, an estimated 250,000 women with a family history or a genetic predisposition to breast cancer will benefit. Australian women deemed at moderate-to-high high risk of developing breast cancer have access to subsidised tamoxifen (AUD36 per script) to reduce their lifetime risk of developing breast cancer, which will, in turn, reduce costs to the health system [5.9].

Facilitating approval for preventive use of tamoxifen in the UK

In April 2018, the Medicines and Healthcare Products Regulatory Agency approved the use of tamoxifen in the primary prevention of breast cancer in women at moderate or high risk in the UK and the Cuzick team's meta-analysis and IBIS-I papers [3.1-3.3] were the "pivotal" publications for the clinical efficacy conclusions made [5.10].

In the UK, around 3.7% of the female population aged 35-74 have a moderate or high risk [5.11]. In England and Wales this is around 500,000 women. A five-year preventive treatment course of tamoxifen costs about GBP130. By contrast, the treatment of breast cancer per patient can cost GBP12,000 per year [5.12].

The NHS Accelerated Access Collaborative has named tamoxifen, as a provision to women at risk of developing breast cancer, as one of four new innovations to be addressed in its 2020-21 Rapid Uptake Product Programme. The programme supports stronger adoption and spread of proven innovations for products that support the key clinical priorities of the NHS Long Term Plan, and will work to improve patient care and outcomes by more effectively providing tamoxifen to women who are at risk [5.13].

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

[5.1] Noah-Vanhoucke, J., Green, L. E., Dinh, T. A., Alperin, P. & Smith, R. A. (2011). Cost-Effectiveness of Chemoprevention of Breast Cancer Using Tamoxifen in a Postmenopausal

US Population. *Cancer, 117* (15), 3322-3331. https://doi.org/10.1002/cncr.25926

[5.2] Moyer, V. M., on behalf of the US Preventive Services Task Force. (2013). Medications for risk reduction of primary breast cancer in women. US Preventive Services Task Force recommendation statement. *Annals of Internal Medicine*, *159*, 698-708. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/breast-cancer-medications-for-risk-reduction-2013

[5.3] American Cancer Society. (2017). *Tamoxifen and raloxifene for breast cancer prevention.* https://www.cancer.org/cancer/breast-cancer/risk-and-prevention/tamoxifen-and-raloxifene-for-breast-cancer-prevention.html

[5.4] National Comprehensive Cancer Network (2017). *NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast and Ovarian (V 1.2018)*.

[5.5] National Comprehensive Cancer Network (2016). *NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Risk Reduction (V 1.2017).*

[5.6] AstraZeneca. (2020). *Australian product information: Nolvadex (Doc ID-002078899 v13)*. https://apps.medicines.org.au/files/appnolva.pdf

[5.7] Department of Health, Therapeutic Goods Administration, Australian Government. (2017, 31 July). *Prescription medicines: new or extended uses, or new combinations of registered medicines, 2016*.

[5.8] Breast Cancer Network Australia (2016, 2 May). *Submission to Pharmaceutical Benefits Advisory Committee on tamoxifen for women at increased risk of breast cancer*. https://www.bcna.org.au/about-us/advocacy/submissions-and-reviews/submission-to-pharmaceutical-benefits-advisory-committee-on-tamoxifen-for-women-at-increased-risk-of-breast-cancer/

[5.9] National Breast Cancer Foundation (2016, 28 April). *NBCF funding leads to Australia's first breast cancer prevention treatment listed on PBS*. https://nbcf.org.au/news/nbcf-funding-leads-to-australias-first-breast-cancer-prevention-treatment-listed-on-pbs/

[5.10] Medicines and Healthcare products Regulatory Agency, UK Government. (2018). *Public Assessment Report, Nolvadex 10mg, Nolvadex D, UK License No: PL 17901/0033 & 0034, AstraZeneca UK Limited.*

[5.11] Curtis, H. J., Walker, A. J. & Goldacre, B. (2018). Impact of NICE guidance on tamoxifen prescribing in England 2011–2017: an interrupted time series analysis. *British Journal of Cancer, 118*, 1268-1275. https://doi.org/10.1038/s41416-018-0065-2

[5.12] Abderrahman, B. & Jordan V. C. (2017). Chemoprevention in British women is inadequate. *Clinical Pharmacist, 9* (4). DOI: 10.1211/PJ.2017.20202378 https://pharmaceutical-journal.com/article/letters/chemoprevention-in-british-women-is-inadequate

[5.13] NHS. (2020). *NHS Accelerated Access Collaborative: Rapid uptake products*. https://www.england.nhs.uk/aac/what-we-do/what-innovations-do-we-support/rapid-uptake-products/. Accessed 22 January 2021.