Institution: University of Brighton		
Unit of Assessment: A3 – Allied Health Professions, Dentistry, Nursing and Pharmacy		
Title of case study: Improving early HER2-positive breast cancer management based on patient choice and preferences		
Period when the underpinning research was undertaken: 2011 – 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:**
Professor Dame Lesley Fallowfield	SHORE-C Director	2001 – to date
Professor Val Jenkins	SHORE-C Deputy Director	2001 – to date
Dr Susan Catt	Research Fellow	2001 – to date
Ms Kathryn Monson	Trial Coordinator	2009 – to date
Period when the claimed impact occurred: 2013 – 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Brighton and Sussex Medical School (BSMS) researchers designed, conducted and analysed study-specific patient interview schedules used in the international clinical trial, PrefHER, to measure patient preference for subcutaneous or intravenous HER2 positive (HER2+) breast cancer treatment. The findings of the PrefHER study were pivotal to the regulatory approval of trastuzumab subcutaneous by the Australian Therapeutic Goods Administration in 2015 and the US Federal Drug Administration in 2019, thus opening the route to market in these countries. PrefHER patients' preference data also allowed the [text removed for publication] - to expand on their range of cancer drugs delivered closer to the patients' home, in accordance with the NHS England Five Year Forward View (2014).

2. Underpinning research

Approximately 1 in 5 patients diagnosed with breast cancer worldwide will have HER2-positive (HER2+) breast cancer, a particularly aggressive form of the disease. HER2+ breast cancer patients require treatment via the targeted anti-HER2 monoclonal antibody agent, trastuzumab following surgery, chemotherapy and radiotherapy. This demands hospital attendance for intravenous administration via a cannula, an *in situ* port, or line, 3 times weekly for 12 months. Intravenous administration is inconvenient and can take several hours exerting a considerable physical and emotional burden, limiting patients' ability to resume normal life. In 2013 NICE approved a new subcutaneous formulation of trastuzumab with similar efficacy and safety as its intravenous counterpart, but with an administration time of just 5 minutes. In the wider clinical context patient preference is a key factor when drugs or administration methods have similar efficacy and safety properties. Taking patient preference into account helps to ensure optimal treatment adherence and improves the patient experience and satisfaction with treatment. Professor Dame Lesley Fallowfield and colleagues at the Sussex Health Outcomes Research and Education in Cancer Centre (SHORE-C) have pioneered a body of research on Psycho-Oncology with a particular focus on patient preference and health professionals' communication skills with patients, especially those with cancer. The team is also leading the field in assessing patients' quality of life in cancer trials including the MRC/NIHR funded UK Collaborative Trial of Ovarian Cancer Screening (April 2001 – December 2014 Main Trial: January 2017 – June 2021 Long term impact of screening on ovarian cancer mortality in the UKCTOCS).

In 2011, the international, open label randomised PrefHER study examined preferences of patients with HER2+ primary breast cancer for either intravenous or subcutaneous delivery of trastuzumab. This prospective, crossover design was conducted in 10 European countries, together with Turkey and Canada and recruited 488 patients randomised in 2 cohorts. In both cohorts, patients had the trastuzumab administered first subcutaneously and then switched to intravenous, or vice-versa. The clinical element of the trial including the safety, efficacy and

pharmacokinetics was led by Professor Pivot [references 3.4, 3.5]. Fallowfield and colleagues at SHORE-C led the development, optimisation and implementation of the study-specific patient interviews in each participating country. The SHORE-C team trained all health professionals at PrefHER investigative sites prior to commencement of the trial. For this purpose, the team produced professional-quality educational DVDs, available in 10 different languages, and adapted to the needs of all the foreign language interviewers [3.1, 3.2, 3.3]. The SHORE-C team also completed the analyses/coding of all the interviews conducted. Two sets of interviews were carried out, one before patient randomization, and one after the treatment cycles. Results for both cohorts showed an overwhelming and strong preference for the subcutaneous route of administration (89% for Cohort 1 and 91.5% for Cohort 2) [3.1, 3.2]. The primary reasons for the preference for the subcutaneous route (415/467) were the time saved and less pain and discomfort experienced. Fallowfield and SHORE-C colleagues conducted a more extensive exploratory analysis of patient experience with intravenous and subcutaneous trastuzumab administration, and the implications these may have for nurse training and future patient management [3.3]. This study revealed that if given the choice, 60% of patients preferred subcutaneous trastuzumab administration at home.

The PrefHER study was global and yet, irrespective of culture, the primary outcome was the same, with patients expressing a strong and compelling preference for subcutaneous delivery. In addition to providing further evidence in support of subcutaneous trastuzumab's use in breast cancer, it also '*introduces a new direction into clinical research oncology'*, as explained by Professor Melichar in the Lancet Oncology Editorial where the results of PrefHER cohort 1 were published (September 2013).

3. References to the research

[3.1] Pivot, X., Gligorov, J., Müller, V., Barrett-Lee, P., Verma, S., Knoop, A., Curigliano, G., Semiglazov, V., López-Vivanco, G., Jenkins, V., Scotto, N., Osborne, S., Fallowfield, L., and the PrefHer Study Group. (2013). Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): An open-label randomised study. *The Lancet. Oncology*, *14*(10), 962–970. https://doi.org/10.1016/S1470-2045(13)70383-8 [Quality validation: leading peer-reviewed journal].

[3.2] Pivot, X., Gligorov, J., Müller, V., Curigliano, G., Knoop, A., Verma, S., Jenkins, V., Scotto, N., Osborne, S., Fallowfield, L., and the PrefHer Study Group. (2014). Patients' preferences for subcutaneous trastuzumab versus conventional intravenous infusion for the adjuvant treatment of HER2-positive early breast cancer: Final analysis of 488 patients in the international, randomized, two-cohort PrefHer study. *Annals of Oncology: Official Journal of the European Society for Medical Oncology*, *25*(10), 1979–1987. https://doi.org/10.1093/annonc/mdu364 [Quality validation: leading peer-reviewed journal].

[3.3] Fallowfield, L., Osborne, S., Langridge, C., Monson, K., Kilkerr, J., and Jenkins, V. (2015). Implications of subcutaneous or intravenous delivery of trastuzumab; further insight from patient interviews in the PrefHer study. *Breast (Edinburgh, Scotland)*, *24*(2), 166–170. https://doi.org/10.1016/j.breast.2015.01.002 [Quality validation: leading peer-reviewed journal].

[3.4] Gligorov, J., Curigliano, G., Müller, V., Knoop, A., Jenkins, V., Verma, S., Osborne, S., Lauer, S., Machackova, Z., Fallowfield, L., Pivot, X. (2017). Switching between intravenous and subcutaneous trastuzumab: Safety results from the PrefHer trial. *Breast (Edinburgh, Scotland)*, *34*, 89–95. https://doi.org/10.1016/j.breast.2017.05.004 [Quality validation: leading peer-reviewed journal].

[3.5] Pivot, X., Verma, S., Fallowfield, L., Müller, V., Lichinitser, M., Jenkins, V., Sánchez Muñoz, A., Machackova, Z., Osborne, S., Gligorov, J., and the PrefHer Study Group. (2017). Efficacy and safety of subcutaneous trastuzumab and intravenous trastuzumab as part of adjuvant therapy for HER2-positive early breast cancer: Final analysis of the randomised, two-cohort PrefHer study. *European Journal of Cancer (Oxford, England: 1990)*, *86*, 82–90. https://doi.org/10.1016/j.ejca.2017.08.019 [Quality validation: leading peer-reviewed journal].

Key research grants

[3.1] Dame Lesley Fallowfield [PI], Roche Product Limited, 2010-2019, Roche PrefHER Phase 1 and Phase 2, GBP1,206,054.

4. Details of the impact

Patient preference studies such as PrefHER can serve as a powerful tool to engage patients and their communities. Moreover, it can quantify the patient voice across different stages of clinical drug development, drug regulatory approval and care management to support patient-centric, healthcare decision-making. By measuring patient preference for either formulation of trastuzumab, PrefHER revealed an overwhelming preference for its subcutaneous route of administration. This finding contributed to the market approval of trastuzumab subcutaneous by the US Food and Drug Administration (FDA) and its Australian counterpart. In practice, it also provided the research evidence to support the delivery of cancer treatments closer to the patient's home – a central tenet of the NHS Five Year Forward plan for improvement in outcomes for cancer patients.

4.1 Market approval of subcutaneous trastuzumab by the US Federal Drug Administration and the Australian Department of Health

The submission of patient preference information (PPI) to the US Federal Drug Administration (FDA) is voluntary. However, the FDA recommends applicants to collect and submit such information for certain premarket approval when patient decisions are 'preference sensitive' [source 5.1]. Patient decisions regarding treatment options are preference sensitive when multiple treatment options exist and there is no option that is clearly superior for all patients.

In the case of trastuzumab subcutaneous, both HannaH and SafeHER trials had shown the subcutaneous formulation to be of the same efficacy and safety as its intravenous counterpart. PrefHER trial findings were the only research-based evidence revealing an overwhelming preference by patients for the subcutaneous drug delivery. In May 2018, these findings – alongside the efficacy and safety data – were included in Roche's Biologics Licence Application to the FDA for permission to deliver trastuzumab subcutaneous to the US market [5.2]. As part of its multi-disciplinary review and evaluation of the application, the FDA commented on the robustness of the SHORE-C led interview methods stating:

'The methods used to conduct the telephone interviews appear to be consistent with best practices of survey research (eg the Applicant [Roche] sought expert opinion [SHORE-C] and patient input for item generation of the interview guide, translated the interview guide using forward and backward translation, and pilot tested the interview guide)' [5.2]. The FDA concluded its benefit-risk assessment with the following:

'Results from the patient preference study (PrefHER) suggest patients preferred the SC route due to time. In conclusion, the efficacy and safety of SC trastuzumab was comparable to IV trastuzumab and offers a new route of administration for patients with HER2-positive breast cancer' [5.2]. In February 2019, the FDA approved trastuzumab for subcutaneous injection for the treatment of eligible patients with HER2+ early breast cancer [5.3]. The FDA approved product labelling refers to the PrefHER trial data to support the Patient Experience subsection in the prescribing information [5.2, 5.4]. In its news announcement, Roche highlighted the importance of this approval, especially concerning the consideration of patient preference in treatment choice. As explained by Roche's Chief Medical Officer and Head of Global Product Development at the time, Sandra Horning: '*The approval of Herceptin Hylecta [ie trastuzumab subcutaneous] gives physicians and patients in the United States a new option to select treatment based on individual needs and preferences'* [5.3].

[text removed for publication] [5.5, 5.6]. [text removed for publication] [5.5]. With these validated tools, Roche evaluated the patient preference for Perjeta (pertuzumab) and Herceptin (trastuzumab) IV vs PHESGO – Roche's first example of combining Perjeta and Herceptin for administration via single SC injection [5.6]. As per PrefHER, the PHranceSCa study showed that 85% (136/160) of people showed a strong preference for PHESGO in comparison to IV Perjeta and Herceptin due to less time in the clinic and more comfortable treatment administration [5.6]. In June 2020 PHESGO was approved by the FDA [5.7].

In addition, PrefHER's main finding relating to patient preference for subcutaneous trastuzumab has been used by its manufacturer, Roche, in its application to the Australian Therapeutic Goods Administration (TGA), part of the Australian Government Department of Health responsible for the regulation of new therapeutic drugs. In its August 2015 evaluation report [5.8], prepared in

collaboration with Roche, the TGA cites the PrefHER study and more specifically the overwhelming patient preference for the trastuzumab subcutaneous administration as one of the new formulation benefits. Following this evaluation by the TGA, the Australian Government Department of Health approved the registration of trastuzumab subcutaneous for supply to the Australian market.

4.2 Provided the research-based evidence on patient preference to improve trastuzumab delivery in clinical practices

Several studies have used data from the PrefHER study to determine the timesaving benefits of the subcutaneous compared with the intravenous formulation of trastuzumab. A prospective observational time-and-motion study in 8 countries (n = 488) involved in the PrefHER trial quantified patient time in the infusion chair and active health practitioner's time [5.9]. Results showed that on average 55 minutes of patient chair time was saved with the subcutaneous formulation. In addition, active health practitioners' time was reduced on average by 15 minutes per session with the subcutaneous formulation [5.9]. Results from this observational time-and-motion study showed that listening to the patient's preference for treatment results in substantial reduction in active health practitioners' time, patient chair and unit time, thus increasing capacity within very limited existing resources. This is particularly significant in the overall context with more than 2,000,000 patients worldwide with breast cancer being treated with trastuzumab (2019); and approximately 80,000 of them via the subcutaneous formulation [5.10].

Results from PrefHER supported practitioners in their recommendations to patients regarding their trastuzumab treatment. [text removed for publication] [5.11]. In practice, this translated into a significant increase in trastuzumab subcutaneous prescription rates from 2014 (one-year following the publication of PrefHER clinical trial results) onwards in England, with the subcutaneous administration route becoming the treatment mode of choice for HER2 positive breast cancer. [text removed for publication] [5.12]. This increased trend in trastuzumab subcutaneous prescription rate was replicated in other Trusts in the England with the subcutaneous formulation of trastuzumab being on average administered 14 times more than its intravenous form [5.13].

[text removed for publication], the significance of PrefHER's findings was not only limited to trastuzumab, but it helped to evolve the concept of delivering other monoclonal antibodies via the subcutaneous route which was shown to be quicker, easier and lent itself to patients having treatment closer to or at home: [text removed for publication] [5.11].

PrefHER's findings on patient preference also affected clinical practice outside the UK. In Germany, a project describing the experiences with trastuzumab subcutaneous outside clinical studies at 7 main cancer centres showed that for 2 centres, the results of the PrefHER study were one of the decisive factors motivating them to introduce trastuzumab subcutaneous in clinical practice [5.14].

5. Sources to corroborate the impact

[5.1] US Department of Health and Human Services FDA Guidance for Industry, Food and Drug Administration Staff and other Stakeholders on Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labelling. August 2016 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications [Accessed 10 March 2021; PDF available]

[5.2] NDA/BLA Multi-Disciplinary Review and Evaluation (761106) Trastuzumab and hyaluronidase for subcutaneous injection. 01 May 2018

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761106Orig1s000MultidisciplineR.pdf [Accessed 16 March 2021; PDF available]

[5.3] Roche Media Announcement of FDA Approval for Herceptin SC (dated 28 Feb 2019)

https://www.roche.com/media/releases/med-cor-2019-02-28.htm [Accessed 16 March 2021; PDF available]

[5.4] FDA Prescribing information for Herceptin Hylecta with section 14.3 on patient experience (revised Feb 2019)

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761106s000lbl.pdf [Accessed 16 March 2021; PDF available]

[5.5] Testimonial Statement from [text removed for publication] [PDF available]

[5.6] PhranceSCa results https://www.esmo.org/oncology-news/esmo-breast-cancer-virtual-meeting-2020-results-of-an-interim-analysis-of-the-phrancesca-study [Accessed 16 March 2021; PDF available]

[5.7] FDA approval for Roche PHESGO https://www.fda.gov/news-events/press-announcements/fda-approves-breast-cancer-treatment-can-be-administered-home-health-care-professional Roche Media announcement of PHESGO FDA approval https://www.roche.com/media/releases/med-cor-2020-06-29c.htm [Accessed 16 March 2021; PDF available]

[5.8] Australian Public Assessment Report for Trastuzumab. August 2015 [Accessed 16 March 2021; PDF available]

[5.9] Cock, E. D., Pivot, X., Hauser, N., Verma, S., Kritikou, P., Millar, D., & Knoop, A. (2016). A time and motion study of subcutaneous versus intravenous trastuzumab in patients with HER2-positive early breast cancer. *Cancer Medicine*, *5*(3), 389–397. https://doi.org/10.1002/cam4.573 [PDF available]

[5.10] Dent, S., Ammendolea, C., Christofides, A., Edwards, S., Incekol, D., Pourmirza, B., Kfoury, S., & Poirier, B. (2019). A Multidisciplinary Perspective on the Subcutaneous Administration of Trastuzumab in HER2-Positive Breast Cancer. *Current Oncology*, *26*(1), 70–80. https://doi.org/10.3747/co.26.4220 [PDF available]

[5.11] Testimonial Statement from [text removed for publication] [PDF available]

[5.12] [text removed for publication] [personal communication; PDF available]

[5.13] Records of 5 NHS Trusts response to the FOI request dated April 2017 “In your trust, how many patients with HER2 breast cancer are currently being treated (in the past 3 months available) with the following products: Herceptin (Trastuzumab intravenous), Herceptin (Trastuzumab subcutaneous), Perjeta (Pertuzumab), Kadcyla (Trastuzumab Emtansine), Tyverb (Lapatinib)” [PDF available]

[5.14] Jackisch, C., Müller, V., Dall, P., Neumeister, R., Park-Simon, T.-W., Ruf-Dördelmann, A., Seiler, S., Tesch, H., & Ataseven, B. (2015). Subcutaneous Trastuzumab for HER2-positive Breast Cancer – Evidence and Practical Experience in 7 German Centers. *Geburtshilfe Und Frauenheilkunde*, *75*(6), 566–573. https://doi.org/10.1055/s-0035-1546172 [PDF available]