Institution: University of Sheffield		
Unit of Assessment: C-17 Business and Management Studies		
Title of case study: The SF-6D: An internationally adopted measure for assessing the cost-effectiveness of healthcare interventions		
Period when the underpinning research was undertaken: 1999–2008		
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:**
Jennifer Roberts	Professor of Economics	1993–2010, 2011–2019
Period when the claimed impact occurred: August 2013–July 2020		
Is this case study continued from a case study submitted in 2014? Y		

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

Deciding which health care interventions to fund is a complex and emotive question. Objective analyses of cost-effectiveness are a crucial aid to decision making. The Short Form 6 Dimension (SF-6D) algorithm, developed by University of Sheffield researchers, is used around the world to inform these decisions. It enables the calculation of 'quality adjusted life years' (QALYs), which allow calculation of the cost-effectiveness of healthcare interventions given ever increasing demands on scarce resources. The SF-6D is one of only three such algorithms in general use globally, and has major advantages over the other two due to its greater sensitivity to detect changes in health. Public policy and social welfare benefits arise from its use by health reimbursement agencies globally to facilitate more efficient use of funds. Commercial benefits arise from licensing the SF-6D to pharmaceutical companies and other private sector users, to enable them to assess the cost effectiveness of their products. Since August 2013, 1,568 commercial licences have been purchased globally generating more than $2.2 million in royalty income. The SF-6D is also freely available to non-commercial bodies for use in research and policymaking.

2. Underpinning research (indicative maximum 500 words)

Estimating the cost effectiveness of healthcare interventions requires a generic measure of health benefit to allow comparison across treatments for different conditions. The standard accepted measure is the QALY; this combines benefits to both quantity and quality of life (QoL). The SF-6D is used to calculate 'Q' - the change in QoL arising from an intervention. For example, if a hip replacement enables patients to move without pain, the SF-6D is used to estimate how much that QoL improvement is worth. In a healthcare system, it is used to compare the benefits arising from say, statins for high cholesterol to different treatments for dementia, or diabetes, or cancer, or a myriad of other conditions.

Roberts was a key member of the 3-person team (with Brazier and Deverill of Sheffield's School for Health and Related Research - ScHARR) which developed the original SF-6D project funded by GlaxoSmithKline (GSK) in 1999-2001. Roberts' main contributions included development of the methodology behind the entire project, and the econometric modelling underpinning the SF-6D algorithm. Following data collection in 2000, the main models were developed in 2001, with extensions to research and modelling up to 2008. Impact arises from the whole body of work.

The main research involved three steps:

(i) Deriving the SF-6D from an existing healthcare measure used in clinical studies worldwide, the SF-36, using a pioneering psychometric approach. The SF-36 is not suitable for use in economic evaluation because it is not 'preference based'; it measures only the amount of limitation, it does not show how people 'trade' between different dimensions of health (e.g. pain vs. physical functioning), or between quality and length of life. The research reduced the SF-36 to the simpler SF-6D classification, which defines 18,000 different health states.

(ii) Obtaining population preferences for a sample of the health states from a large sample of the UK population, using the theoretically grounded standard gamble stated preference method.

(iii) Using econometric modelling to estimate preferences (utilities) for all possible SF-6D states, from the sample data. The resulting SF-6D algorithm generates an index, from 0 (equivalent to being dead), to 1 (full-health). It quantifies how much value people place on different health limitations, and how they trade between them; e.g. how much vitality they would sacrifice for a reduction in pain. This index is the 'Q' value used to calculate QALYs.

The main SF-6D research output was published in 2002 and has been cited more than 1,800 times **[R1].** Four main extensions to the research led to findings that increased the impact in this submission period: (i) in 2005 we developed a second algorithm for the SF-12 **[R2]** a reduced version of the SF-36, also in common clinical use. (ii) we developed an improved Bayesian algorithm in 2007 **[R3],** enabling decision makers to take better account of differences across patients. (iii) The Sheffield team pioneered the development of the SF-6D, and since then studies using this method have been replicated in 8 additional countries (Australia, Brazil, China, Indonesia, Japan **[R4],** Portugal, Singapore and Spain) to obtain local population preferences. (iv) We have extended reach to a broader set of health problems by developing algorithms for some conditions where the SF-6D is not appropriate; for example, in urinary incontinence where the SF-6D may neglect important effects on sleep quality **[R5].**

The SF-6D has three key advantages over its main competitor (the EQ-5D): (i) It is a richer descriptive system (18,000 states cf. 243), so is more sensitive to changes in health **[R6]**. (ii) Preferences are obtained using a theoretically superior method. Standard gamble is realistic because it involves making a risky choice; i.e. "would you choose to live the remainder of your life in less than perfect health, or take a risk on a treatment that could restore perfect health but could also leave you in a worse health state". In contrast, the EQ-5D uses a riskless valuation approach. (iii) The SF-6D can be derived from the SF-36 or SF-12, the most widely used generic outcome measures already included in clinical trials around the world; thus it imposes no additional resource burden on the trial.

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

R1. Brazier, J., Roberts, J., & Deverill, M. (2002). The estimation of a preference-based measure of health from the SF-36. *Journal of Health Economics*, *21*(2), 271–292. https://doi.org/10.1016/s0167-6296(01)00130-8. **[1855]** Awarded 2002 *International Soc. for Quality of Life* prize for "outstanding contribution to study of health related quality of life".

R2. Brazier, J. E., & Roberts, J. (2004). The Estimation of a Preference-Based Measure of Health From the SF-12. *Medical Care*, *42*(9), 851–859. https://doi.org/10.1097/01.mlr.0000135827.18610.0d. **[766]**

R3. Kharroubi, S. A., Brazier, J. E., Roberts, J., & O'Hagan, A. (2007). Modelling SF-6D health state preference data using a nonparametric Bayesian method. *Journal of Health Economics*, *26*(3), 597–612. https://doi.org/10.1016/j.jhealeco.2006.09.002. **[125]**

R4. Brazier, J. E., Fukuhara, S., Roberts, J., Kharroubi, S., Yamamoto, Y., Ikeda, S., Doherty, J., & Kurokawa, K. (2009). Estimating a preference-based index from the Japanese SF-36. *Journal of Clinical Epidemiology*, *62*(12), 1323–1331. https://doi.org/10.1016/j.jclinepi.2009.01.022. **[40]**

R5. Brazier, J., Czoski-Murray, C., Roberts, J., Brown, M., Symonds, T., & Kelleher, C. (2007). Estimation of a Preference-Based Index from a Condition-Specific Measure: The King's Health Questionnaire. *Medical Decision Making*, *28*(1), 113–126. https://doi.org/10.1177/0272989x07301820. **[80]**

R6. Brazier, J., Roberts, J., Tsuchiya, A., & Busschbach, J. (2004). A comparison of the EQ-5D and SF-6D across seven patient groups. *Health Economics*, *13*(9), 873–884. https://doi.org/10.1002/hec.866. **[509]**

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

Pathways to impact. The original research was funded by the global pharma company GSK, giving the SF-6D a high profile in this important industry. GSK freely uses the algorithm to calculate the cost-effectiveness of their products; other companies have to purchase licences to

gain the same capability. Early dissemination was aided by targeted presentations to pharma companies and other key health decision makers. Ongoing dissemination since August 2013 includes: coverage in ScHARR's annual 2-day course on *Utility Data for Health Technology Assessment*, as well as in the free *Measuring and Valuing Health* Massive Open Online Course (MOOC), completed by 3,730 learners globally since it started in 2015; and promotion at the annual *International Society for Pharmacoeconomics and Outcomes Research* (ISPOR) conference. ISPOR has more than 20,000 members in 110+ countries. To optimise access, the algorithm is supplied via easy-to-use software, including Excel, SPSS, and SAS, and the SF-6D website provides full guidance.

Reach of the SF-6D is illustrated by the range and number of beneficiaries.

International commercial organisations

The main commercial beneficiaries are pharma companies. A standard measure administered in their clinical trial (SF-36/SF-12) can be easily translated into QALYs via the SF-6D, to demonstrate the cost-effectiveness of their products. Most commercial licence sales are via OptumInsight, a US-based global health innovation company who sell the SF-6D under sub-contract, alongside other related products (SF-36 and SF-12). Further sales are via the University's Licensing Portal.

[Text removed for publication]. Together these companies control over 60% of the $1,200 billion global pharma market. 56% of licence sales are in the US, where other important commercial users include healthcare insurers and providers. Licences have also been purchased in 40 other countries, including Australia, Canada, China, Denmark, France, Germany, India, Japan, Russia, South Korea and the UK **[S1]**. They cover a broad range of disease areas, including, for example; addiction, asthma, diabetes, heart disease, HIV, multiple sclerosis, rheumatoid arthritis, stroke, and a number of different forms of cancer, including those with the highest population prevalence such as bowel, breast and prostate cancer. Reach is increasing over time. Annual sales have increased from 139 licenses in 21 countries in 2014, to 354 in 31 countries in 2019 **[S1]**. This reflects the fact that the companies are under increasing pressure to demonstrate the cost-effectiveness of their products in resource pressured healthcare systems; and more health reimbursement agencies (HRAs) around the world are recommending the use of the SF-6D to generate this evidence (see below).

International health and welfare policy

The SF-6D is accepted for use in economic evaluation by HRAs around the world. HRAs publish mandatory guidance on how pharma companies must provide cost-effectiveness evidence, in order for the HRA to decide whether the product provides good value for money and hence will be provided within the healthcare system. Both reach and significance are evident in the fact that the SF-6D is accepted for this analysis in at least 20 of the 42 HRA guidelines available via ISPOR **[S2]**. 5 countries, including China, were recommending the SF-6D before August 2013 and continue to do so. 11 countries explicitly accept the SF-6D in guidance published since August 2013: Australia (2016), Brazil (2014), Canada (2017) **[S2]**, Egypt (2013), Hungary (2017), Iran (2017), Ireland (2018), Japan (2016), Norway (2017), Spain (2014), United States (2016) **[S2]**. In Finland (2017) no algorithm is explicitly named but the SF-6D is accepted by implication because it meets the necessary stated criteria. Like NICE in the UK, New Zealand (2015) and the Netherlands (2016) both accept the SF-6D in cases where the alternative EQ-5D measure is not appropriate (e.g. due to ceiling effects **[R3]**).

Significance of the SF-6D is illustrated by the importance of the decisions it enables, the type of benefits it generates and the importance of these benefits for economy and society.

Decisions on the provision of cost-effective health care

HRAs have to decide which health care technologies to provide; these complex and emotive questions are aided by objective SF-6D analysis. In the UK, for example, the SF-6D has been used to calculate QALY benefits in important NICE assessments of treatments for hepatitis C **[S3]** and gout **[S3]**. Hepatitis C is a highly contagious disease which can cause liver failure. The drug in question (sofosbuvir) can cure 90% of patients, but it is very expensive; £39,000 for a 12 week course. Over 200,000 people in the UK have hepatitis C so the NHS budget impact is potentially huge. SF-6D analysis demonstrated that the QALY benefits are substantial, so the drug is cost effective despite its large cost. As a result, NICE recommended that sofosbuvir be

made available; the NHS's single biggest new treatment investment in 2017. SF-6D analysis has also been key to drug appraisals in other countries. For example, in Canada, it was used to estimate the cost-effectiveness of drug treatments for hypertension, and epilepsy, as well as hepatitis C.

The use of the SF-6D in these decisions is also significant because users generally have a choice between the 3 existing health valuation algorithms. The SF-6D has key advantages over the EQ-5D, its main competitor (see Research section). In the sofosbuvir decision for example, the HRA states *"the SF-6D was used in preference to the EQ-5D because the conversion method is well validated and that EQ-5D utilities are less certain"* **[S3**: p79]. Similar arguments are made to explain the use of the SF-6D in decisions for treatments for gout **[S3].** This has also been the case internationally. For example, the appraisal of rifaximin for end-stage liver disease in the Netherlands preferred the SF-6D analysis on the grounds that the direct conversion of the SF-36 to SF-6D was more accurate than the indirect EQ-5D analysis **[S3].**

As well as single technology decisions, SF-6D evidence is also key to some of NICE's influential care pathway guidelines. Low back pain (LBP) affects 10.5 million people in the UK and is a major cause of lost workdays. SF-6D evidence is cited throughout the LBP guideline and is key to the recommendations not to recommend acupuncture or epidural steroids as routine treatment, because they are not cost effective **[S3].** SF-6D evidence was also used in the US Institute for Clinical and Economic Review assessment of LBP therapies **[S3].** This concluded that evidence on acupuncture was inconclusive, hence it is rarely covered by US public health insurance. Other NICE guidelines with key recommendations relying on the SF-6D include: age-related macular degeneration, a deterioration in sight affecting 5% of the over 65s; kidney stones, which affect 9% of the population; and chronic obstructive pulmonary disease which affects 5.5 million people and where SF-6D evidence was key to recommending opportunistic case detection in primary care.

Health outcome in clinical trials

Between them, the two main SF-6D studies (R1 & R2) have been cited over 2,600 times (1,280 since 2014). The vast majority of these report the use of the SF-6D in clinical trials and economic evaluations around the world; providing clear evidence of its significance for healthcare decision-making. For example, **[S4]** is a large German trial to establish the cost-effectiveness of a program to optimise dementia care via early diagnosis and care in the community. Dementia affects 47 million people worldwide at a cost of around $818 billion; prevalence is increasing over time. SF-6D analysis showed the program to be cost–effective; QoL was improved (and costs reduced) by supporting people to live with dementia at home rather than be hospitalised. **[S4]** is the cost effectiveness analysis of the large multi-centre US trial of Look AHEAD; an intensive lifestyle intervention for type 2 diabetes (a chronic disease that affects around 10% of the US adult population and accounts for 24% of all US health spending). SF-6D analysis showed that this was not a cost-effective intervention; the QoL gains were not worth the increased costs compared to standard care, so health budgets could be wasted if this program was rolled out.

Measure of patient Quality of Life (QoL)

The SF-6D is also used in medical research to show how health conditions impact patients' QoL. For example **[S5]** details how patients undergoing hip replacement in the US experience notable QoL gains up to 5 years post-surgery. The report cites the lead clinician from the Cleveland Clinic who states, *"The SF-6D is one of the few straightforward, easily obtainable methods that provide clinicians quantifiable insight into a patient's QoL … widely incorporating the SF-6D into future postoperative assessments is straightforward, and having these values readily available may make prospective cost-effectiveness analyses considerably easier."* In another example **[S5]** demonstrates the usefulness of the SF-6D in assessing the burden of Atopic Dermatitis (AD). AD is a chronic inflammatory skin disease affecting 15-20% of children and 1-3% of adults. Previously QoL assessments for this disease were not standardised. Clinicians in a 2019 US study of 3,500 people showed that the SF-6D was a reliable measure of QoL in AD meaning that it could be used as a common metric to compare the burden of AD to that of other diseases.

Public sector and international charities

Licenses are free for public sector and charitable organisations; at least 1,340 have been distributed (668 since August 2013) **[S1].** This is an underestimate of non-commercial usage, since the software is often shared freely. Non-commercial use demonstrates reach and significance through the wide range of different uses around the world. For example, the UK Department for Education used the SF-6D to demonstrate the value of the health benefits arising from the Youth Contract for unemployed young people (around £1 million/year) **[S6].** SF-6D analysis was also central to establishing the cost-effectiveness of the pay-for-performance program for diabetes care under the Taiwan National Health Insurance scheme. **[S6]**

Summary: The SF-6D contributes to *public policy and social welfare* and has substantial *commercial benefits* **[S1]**. It is accepted by HRAs in at least 20 countries **[S2**], is a key outcome in many important health technology appraisals in the UK and internationally **[S3]**, and is commonly used to measure cost-effectiveness in clinical trials **[S4]** and other medical research **[S5**], as well as more broadly in public service provision **[S6].** Ultimately the populations and tax payers of the countries involved are SF-6D's main beneficiaries, since healthcare authorities are able to extract better value for money from limited resources because of the quantitative comparisons of cost-effectiveness that the SF-6D makes possible.

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

S1. SF-6D license sales [Text removed for publication].

S2. SF-6D use in international Health Reimbursement Agencies (HRA) methods guidance. The International Society for Pharmacoeconomics and Outcomes Research provides summaries of the HRA guidance for 50 countries around the world. Of the 42 available via the website, 17 accept the SF-6D as a means of calculating QALYs. For example: 2017 Guidelines of the Canadian Agency for Drugs and Technologies in Health and 2016 US Academy of Managed Care Pharmacy guidelines for Submission of Clinical

S3. SF-6D use in international health technology appraisals (HTAs) and clinical guidelines. TA430 Sofosbovir for hepatitis C. p79; TA506. Lesinurad for treating chronic hyperuricaemia in people with gout. p18; Pharmaco-economic re-evaluation report for rifaximin in the treatment of recurrent episodes of hepatic encephalopathy manifest in patients aged 18 years (Netherlands HTA). NICE guideline 59: Low back pain and sciatica in over 16s see pp 491, 497, 498. US Institute for Clinical and Economic Review Cognitive and Mind-Body Therapies for Chronic Low Back and Neck Pain: Effectiveness and Value. pp 55, 56.

S4. SF-6D use in important clinical trials. Michalowsky et al (2019) Cost-effectiveness of collaborative dementia care management: results of a cluster-randomized controlled trial. Alzheimer's & Dementia 15:1296-308. Section 2.4 for use of SF-6D (SF-12 version) to calculate health utilities. Zhang et al (2016) Impact of Intensive Lifestyle Intervention on Preference-based Quality of Life in Type 2 Diabetes: Results from the Look AHEAD Trial Obesity 24(4):856-864. doi:10.1002/oby.21445

S5. SF-6D use in patient quality of life (QoL) studies: Undergoing hip replacement improves five-year quality of life. ScienceDaily (2017). Short-Form 12 and Short-Form 6-Dimensional May Reliably Assess Atopic Dermatitis Burden on QoL. Dermatology Advisor (2019):

S6. Non-commercial use of SF-6D in UK government evaluation. Use by UK Department for Education to evaluate the Youth Contract for 16- and 17-year-olds not in education, employment, or training. Hsieh, H.-M. et. al. (2015). Cost-Effectiveness of a Diabetes Pay-For-Performance Program in Diabetes Patients with Multiple Chronic Conditions. *PLOS ONE, 10*(7), e0133163. https://doi.org/10.1371/journal.pone.0133163