Institution: University of Glasgow (UofG)

Unit of Assessment: UoA1 (Clinical Medicine)

Title of case study: A new standard of adjuvant care in colorectal cancer: reduced treatment burden and healthcare costs.

Period when the underpinning research was undertaken: 2007–present

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) Prof. Jim Cassidy	(1) Professor of Oncology	(1) Feb 2002–Jun 2011
(2) Dr Kathleen Boyd	(2) Senior Lecturer	(2) 2007–present
(3) Prof Andrew Briggs	(3) Chair in Health Economics	(3) 2005–2019
(4) Jim Paul	(4) Senior Research Fellow	(4) 1988–Sept 2019
(5) Dr Jose Robles-Zurita	(5) Research Associate	(5) 2016–present

Period when the claimed impact occurred: 2017–present

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Six months of post-operative chemotherapy with an oxaliplatin-containing therapy had been the current standard treatment for stage III colorectal cancer (CRC). Although effective, this treatment caused considerable and durable side effects, reducing patient quality of life. The SCOT trial, initiated and led by UofG, was the largest contributor to research showing that three months is as effective as six months of treatment, preserving treatment outcomes while significantly reducing side effects. The change in practice saves an estimated GBP42 million in healthcare costs over two years in the UK NHS alone. Since 2018, these findings form the basis of recommendations in leading international clinical guidelines, changing practice among 99% of UK clinicians.

2. Underpinning research

Over 40,000 people are diagnosed with colorectal cancer (CRC) in the UK each year, and 1.8 million globally. Since 2004, the standard of care had been surgery, followed by 6 months of chemotherapeutic treatment with an oxaliplatin-containing regimen for patients with stage III CRC. However, while of proven benefit, these therapies can cause cumulative dose- and duration-dependent peripheral nerve damage, which can cause permanent numbness, loss of function and pain.

One way to potentially address the toxicity and cost of these therapies is to halve treatment duration to 3 months, but it was unclear whether this might compromise treatment efficacy. In 2007, Prof. Jim Cassidy and Jim Paul conceived and initiated the Short Course Oncology Treatment (SCOT) study to address this question, with Prof. Andrew Briggs leading a health-economic study component to provide robust evidence on the cost-effectiveness of reducing the duration of adjuvant therapy (little investigated at the time) and the impact on toxicity. UofG researchers were ideally placed given the expertise of the UofG's Cancer Research UK Clinical Trials Unit (CTU) and UofG's pivotal role in establishing a leading oxaliplatin regimen (CAPOX, also known as XELOX, a doublet therapy of capecitabine and oxaliplatin) as a first-line treatment for metastatic CRC, which was the subject of a REF2014 case study. The UofG led and sponsored the international SCOT trial via the CTU, which comprises statisticians, trial managers, medical and IT staff, who contributed to the trial's design and protocols, co-ordinated international recruitment, undertook all randomisation processes and data collection for all patients, conducted analyses and pharmacovigilance, and interpreted the clinical outcome data [3.1].

The innovative SCOT study

SCOT was an independent, international, randomised, phase 3 trial, with embedded health economic analysis, to establish whether a three-month oxaliplatin-based regimen (either CAPOX or FOLFOX—5-fluorouracil, leucovorin, and oxaliplatin) is non-inferior to a six-month regimen, with respect to disease-free survival in patients with CRC. Having secured a GBP2.7 million grant to UofG from the Medical Research Council (PI: Cassidy, 2007–2010), the trial recruited 6,088 patients in 244 centres (UK, Denmark, Spain, Sweden, Australia and New Zealand) between 2008 and 2013, who had high-risk stage II or stage III colon or rectal cancer

and were followed up for 5-year disease-free survival and overall survival. SCOT is the largest randomized study to date investigating short course adjuvant therapy for CRC. Published in April 2018, SCOT showed that 3 months of treatment was non-inferior to 6 months, with no detrimental impact on patient survival, and with substantially less neuropathy (both acute and long-term) [3.2]. The accompanying health economic analysis showed that the 3-month was less costly than the 6-month regimen, saving the NHS GBP4,881 per patient per year, with no significant detriment to quality-of-life years (QALY) [3.3], and highlighting that a 3-month treatment strategy should be considered a new standard of care.

SCOT contributes to international meta-analysis

In parallel to SCOT, the IDEA collaboration was set up as a prospective, pre-planned, pooled analysis of six, phase-3 trials worldwide, to address the short course question. IDEA focussed on stage III colon cancer only, across two adjuvant regimens (CAPOX and FOLFOX). While SCOT was designed as a stand-alone international study, Prof. Cassidy agreed to contribute data from SCOT to the IDEA analysis. Thereafter, Cassidy (until 2011) and Paul (throughout) were IDEA steering committee members. SCOT contributed 3,893 stage III colon cancer patients to the total 12,834 patients in the main IDEA analysis—the largest contribution from any single trial. Across the entire population of patients, IDEA confirmed the non-inferiority of a shorter course of CAPOX, but not of FOLFOX. However, an exploratory analysis combining both regimens within newly established risk subgroups, low risk (patients with T1–3/N1 disease) and high-risk (patients with T4/N2 disease), confirmed the shorter courses to be non-inferior in the low-risk group; whereas for the high-risk patient sub-group, 6 months was superior. IDEA thus concluded that 3 months of treatment with CAPOX was as effective as 6 months with regard to 3-year, disease-free survival (particularly in low-risk patients) and offered a significant three-fold reduction in neuropathy [3.4]. SCOT was the only trial (out of six) which recruited patients with rectal cancer. Rectal cancer patients are often under-represented in adjuvant trials and their management is more complex because pre-operative treatment such as radiotherapy/chemotherapy are often given. SCOT suggested that clinical practice for rectal cancer patients who hadn't received pre-operative chemotherapy or long-course chemoradiation need not differ from patients with stage III colon cancer [3.2].

In a further prospective, pre-planned sub-group analysis, which ran parallel to the IDEA study, the IDEA steering group investigated whether 3 months of CAPOX was non-inferior to 6 months' treatment in high-risk stage II CRC patients. This study pooled data from 3,273 stage II colon cancer patients from SCOT and three other IDEA studies that included stage II patients. In this more heterogenous group, significantly less grade 3–5 toxicity occurred following 3 months of treatment, although with a reduction in 5-year, disease-free progression compared to 6 months of treatment (80.7% v 83.9%, respectively) [3.5].

3. References to the research

1. **Paul, J.**, **Boyd, K.**, **Briggs, A.**, **Cassidy, J.**, Harkin, A. and Iveson, T. (2019) The 'Short Course Oncology Treatment' (SCOT) trial. [Data Collection and trial framework], University of Glasgow CRUK Clinical Trials Unit, Glasgow (doi: 10.5525/gla.researchdata.819)
2. Iveson, T. J., Kerr, R. S., Saunders, M. P., **Cassidy, J.**, Hollander, N. H., Tabernero, J., … **Paul, J**. (2018). 3 versus 6 months of adjuvant oxaliplatin-fluoropyrimidine combination therapy for colorectal cancer (SCOT): an international, randomised, phase 3, non-inferiority trial. *Lancet Oncol. 19*(4):562–578. (doi: 10.1016/S1470-2045(18)30093-7)
3. **Robles-Zurita, J**; **Boyd, K.A**; **Briggs, A.H**. *et al*. (2018) SCOT: A comparison of cost-effectiveness from a large randomised phase III trial of two durations of adjuvant oxaliplatin combination chemotherapy for colorectal cancer. *Br J Cancer.* 119:1332–1338 (doi:10.1038/s41416-018-0319-z)
4. Grothey, A., Sobrero, A.F., Shields, A.F., Yoshino, T., **Paul, J**. *et al*. (2018) Duration of Adjuvant Chemotherapy for Stage III Colon Cancer. *N Engl J Med.* 378:1177-1188 (doi: 10.1056/NEJMoa1713709) [Citations: 250; Field-Weighted Citation Impact: 53.64 (Scopus)]
5. Iveson T *et al*. […] **Paul, J** (2019) Prospective pooled analysis of four randomized trials investigating duration of adjuvant (adj) oxaliplatin-based therapy (3 vs 6 months {m}) for patients (pts) with high-risk stage II colorectal cancer (CC). ASCO abstract 3501.

Grants:

- SCOT- Short Course Oncology Therapy - A study of Adjuvant Chemotherapy in colorectal ca by the CACTUS & QUASAR 3 Groups. Medical Research Council, 2007–2010, £2,707,635, grant no. G0601705. PI: J. Cassidy; Co-Is: Jim Paul (UofG), Claire Kelly (UofG), Andrew Briggs (UofG), Timothy Iveson (Southampton) and David Kerr (Oxford)
- Cancer Research UK Clinical Trials Unit - Core Programme Funding, Cancer Research UK (2010–present), funding ref: C6716/A9894
- Extension of Follow-Up for High Risk Stage II Patients (additional 3 years) and Stage III Patients (up to year 3 follow-up) in the SCOT study. National Institute for Health Research, 2015-2018, £274,695, funder ref. 14/140/84 (PI: J. Paul; Co-Is: A.H Briggs, K.A. Boyd).

4. Details of the impact

The SCOT and the IDEA trials have been highlighted through international guidelines and within the professional community as a landmark moment for oncologists and their patients. The studies demonstrated the effectiveness of 3 months of adjuvant chemotherapy for some patients with CRC (with reduced side effects) and the economic benefits of a shorter regimen. The clinical findings reported by these trials have led to a new global standard for most patients who are suitable to treat with CAPOX, particularly those with low-risk stage 3 disease; this new standard balances the efficacy of a chemotherapy regimen with toxicity and quality of life, depending on patients' tolerance and attitude to their disease.

Dissemination and discussion in the clinical community

In 2017, the SCOT and IDEA trial results were presented at the American Society for Clinical Oncology (ASCO) conference, a leading forum for oncologists worldwide consisting of 35,000 medical professionals, and at the 2017 European Society for Medical Oncology (ESMO) congress, which brings together over 15,000 medical professionals. At ESMO, a Special Session debate brought together the SCOT and IDEA trial leads with external experts and a clinical audience to clarify the potential impact of these results on clinical practice and to achieve a more meaningful interpretation of the results. The panel agreed on the value of CAPOX for 3 versus 6 months in low-risk stage III patients, given the increased quality of life [5.A]. Given that 92% of oncologists in a recent survey identified conferences as a key influence in their practice, the presentation of the SCOT and IDEA trial findings at these conferences likely stimulated discussion and considerations of practice within the CRC community [5.B]. An important and unanticipated piece of knowledge generated from post-hoc studies within both SCOT and IDEA is stage III risk stratification (into 'low' and 'high') which didn't exist before. Many clinicians have adopted this risk stratification into their practice [5.B].

Impact on clinical guidelines now reflect a short-course treatment option

Updates to the preeminent clinical guidelines used by UK and international clinicians provide new options for treating low- and high-risk stage III CRC. We know that from a recent survey of this clinical community that 87% of clinicians treating CRC patients in the adjuvant setting use guidelines to inform treatment decisions, citing ESMO, ASCO, NCCN and NICE as preeminent in this regard [5.B].

- In September 2019, **ESMO** issued an eUpdate to their 2013 early colon cancer guidelines, citing IDEA data to recommend that duration of oxaliplatin-based adjuvant treatment for stage III colon cancer may be tailored to 3 months for CAPOX (for patients with low risk T1–3 N1 disease), level II B [5.C]. They also recommended, for the first time, that oncologists consider using a 3-month CAPOX regimen for high-risk, stage II colon cancer, based on the pre-planned sub-group analysis of IDEA data that drew heavily from SCOT trial data [3.5]. This is an important consideration given the benefits that oxaliplatin therapy can have for patients with high-risk stage II CRC, and addresses uncertainty among oncologists—25% of survey respondents were unsure whether 3-month CAPOX could be considered.
- In June 2019, **ASCO** published a clinical practice guideline to specifically address the duration of oxaliplatin-containing adjuvant therapy [5.D]. This guideline offers three recommendations: 1) that high-risk (T4 and/or N2) stage III CRC patients are offered a 6-month therapy; 2) that low-risk patients (those with T1-3 and N1 stage tumours) are given a choice of 3-month or 6-month therapy; and 3) that a shared decision-making approach with

patients should be used that reflects patient characteristics and preferences, and the risks and benefits of treatment duration.

- In 2018, the National Comprehensive Cancer Network (**NCCN**) —a consortium of 23 US centres of clinical excellence in cancer care— updated its colon cancer guidelines to recommend that the preferred treatment for low-risk stage III CRC include CAPOX for 3 months or FOLFOX for 3–6 months; and for high-risk CRC, CAPOX (3–6 months) or FOLFOX (6 months) [5.E].
- In January 2020, **NICE** published a new guideline (NG151 Colorectal cancer) that specifically addressed the optimal duration of adjuvant chemotherapy for CRC [5.F]. Drawing on the SCOT and IDEA trials, the committee recommended 3 months of CAPOX chemotherapy for both low- and high-risk CRC patients. The review concluded there was strong cost-effectiveness evidence to support the recommendation, citing the UofG study [3.3] as being directly applicable and of high quality. NICE also recommended FOLFOX for 3 to 6 months, with duration determined through individual consultation with those patients not suitable for 3 months of CAPOX, taking into account the benefits and short- and long-term harms of each option. On the basis of the SCOT trial, which was the only study to recruit a significant number of patients with rectal cancer, the committee also extended these recommendations to those rectal cancer patients who had not received preoperative, long-course chemotherapy.

Impact on clinical practice

Around 64% of all stage-III CRC patients are eligible for chemotherapy. In the UK, this equates to ~6,300 patients, with an equal split between low-risk (T1–3/N1) and high-risk (T4/N2) disease. In April 2019, 95% of international clinicians and 99% of UK clinicians who provide adjuvant doublet chemotherapy to CRC patients reported being aware of clinical trials on optimising chemotherapy duration in this setting, citing either SCOT (more common in UK) or IDEA. Around 92% self-reported changing their practice in line with these studies' findings, with 98% of these clinicians doing so specifically when treating 'low risk' stage III disease [5.B]. Of UK clinicians surveyed (n=141), 92% treat patients with rectal cancer and 58% use the same treatment strategy as for CRC [5.B]. Practice change is also evident within the Beatson West of Scotland Cancer Care Centre, which serves 60% of Scotland's population. The proportion of patients within this region receiving more than 3 months of CAPOX treatment decreased substantially since the SCOT trial results were reported (from 84% pre-SCOT to 20% post-SCOT) with a clear change in trend from June 2017 onwards, reflecting rapid translation of trial evidence into practice [5.G]. This change to a 3-month treatment duration is also apparent in prescribing data from across Scotland [5.G].

The National Cancer Research Institute (NCRI) Colorectal Cancer Clinical Studies Group (CRC-CSG) comprises senior clinicians and patient representatives with a broad overview of UK practice in CRC. They stated, '*there has been a nationwide shift in prescribing a shorter duration of adjuvant doublet chemotherapy (CAPOX) for patients with low-risk stage III colon cancer. Using a shorter duration of treatment (3 months versus 6 months) for these patients has also had an immediate capacity impact at oncology outpatient departments and chemotherapy units across the UK, allowing appointments and chair time to be made available for treatment of other patients. For those patients with colorectal cancer who receive a shorter duration of treatment, a reduction in toxicity, especially peripheral neurotoxicity, has already been seen*' [5.H]. The CRC-CSG also acknowledged that, '*a shorter duration of doublet treatment (CAPOX) will likely be included as a new standard treatment for many patients receiving adjuvant treatment for CRC in future trials*'. A reduction in toxicity also makes it possible to include additional combination therapies (e.g. immunotherapies) concurrently, increasing their curative potential [5.H].

Impact on patient quality of life

Neuropathy is the primary, long-term adverse effect of chemotherapy that has a significant negative impact on patients' lives. However, peripheral sensory neuropathy is measurably reduced in patients receiving a shorter duration of treatment. In the UK, if ~3,630 patients per year agreed to a 3-month treatment regimen for stage III disease, 1,198 fewer patients are

likely to experience grade 2 (moderate) or more severe neuropathy. These levels of neuropathy impede daily life (preparing meals, shopping, managing money) and work, and can persist for up to 5 years. A shorter course of chemotherapy also means less diarrhoea (a 40% reduced incidence has been reported in a 3-month therapy population [3.2]), as well as a lower incidence of fatigue, neutropenia, thrombocytopenia, nausea and hand-foot syndrome, fewer doctor appointments, blood draws and less time away from work/social interactions.

Impacts on healthcare and societal costs

The treatment costs accrued during the first year of a CRC diagnosis are greater than those accrued for other common cancers, such as breast, lung, and prostate. The total economic burden of CRC in the USA alone is estimated to be around USD39 billion. A shorter treatment duration will, on average, halve drug costs, as well as reducing administrative costs and the costs of treating adverse effects. The estimated costs saved in the UK ultimately depend on treatment choice, but the UofG health economic analysis put NHS cost savings at GBP4,881 per patient per year (or GBP3,853 for CAPOX and GBP6,481 for FOLFOX, with two-thirds of patients treated with CAPOX) [3.3]. A budget impact analysis calculated NHS savings over two years at GBP42 million [5.I]. This assumes that 64% stage III CRC patients receive adjuvant chemotherapy and 55% practice change across the whole stage III population who get chemotherapy. The budget impact analysis over a 5-year basis performed for SCOT-participant countries amounts to savings of around USD151 million: Australia (USD25 million), Denmark (USD7 million), New Zealand (USD4 million), Spain (USD44 million), Sweden (USD10 million) and UK (USD61 million) [5.I]. Furthermore, there are substantial potential savings in societal costs—defined as productivity loss from time away from work during chemotherapy treatment in patients of working age, plus the travel costs incurred by patients. During year 1 of treatment, extended over a 5-year basis, societal savings are nearly equal to the healthcare savings [5.I].

5. Sources to corroborate the impact [PDFs provided unless otherwise indicated]

A. Sobrero A. *et al*. (2018) The hard road to data interpretation: 3 or 6 months of adjuvant chemotherapy for patients with stage III colon cancer? *Ann Oncol*. 29(5):1099-1107. doi: 10.1093/annonc/mdy064
B. Clinical practice survey: (1) Hanna *et al*. (2020) Do clinical trials change practice? A longitudinal, international assessment of colorectal cancer prescribing practices [submitted to ESMO Open]. *A survey of 265 clinicians (141 UK, 124 international) conducted in 2019 and 2020 who provide adjuvant chemotherapy for patients with CRC*; (2) The 2019 survey was also published as a poster: #P-335, EMSO Gastrointestinal Cancer Conference 2020.
C. ESMO 2019 eUpdate - Early Colon Cancer Treatment Recommendations, 23 September 2019 (cites [3.4] as ref 4; also, [3.5] on stage II CRC)
D. ASCO Clinical Practice Guideline 2019 - Duration of oxaliplatin-containing adjuvant therapy for stage III colon cancer. (p.1437, cites [3.4])
E. NCCN v.1.2020 colon cancer guideline, p.COL-3 (footnote 'u') cites [3.4]
F. NICE guidance: (1) NICE NG151 Colorectal cancer (recommendation 1.3.14, p.13 and p.30; see also rationale for recommendation, p.31); (2) The NICE guidance cites the clinical evidence summary (Optimal duration of adjuvant chemotherapy for colorectal cancer), which refers to the SCOT and IDEA studies throughout.
G. Change in prescribing: (1) Hanna *et al*. (2020) Real-life implementation of the SCOT trial findings: An interrupted time series analysis. *J Clin Oncol*. 38(15 suppl): e19341 (doi: 10.1200/JCO.2020.38.15_suppl.e19341) [*ASCO 2020 presentation*]; (2) Hanna,C. UofG PhD chapter 8: Impact on national practice (see Section 1.2.5.1, p.11; and Fig. 9a, p.21)
H. Testimony from the NCRI Clinical Studies Group
I. Hanna,C. UofG PhD chapter 7: The cost-effectiveness of shorter adjuvant treatment for patients with CRC and budget impact of implementation of the SCOT trial findings [See section 1.2.2, p.20; Table 6, p.22/23 (5-year budget impact); Table 8, p.26 (2-year UK budget impact); and Table 9, p.28 (societal costs)].