Institution: University of Leeds

Unit of Assessment: 3

Title of case study: Self-reporting of symptoms and well-being improves cancer patients' care, quality of life and survival

Period when the underpinning research was undertaken: 2000-2019

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:
Galina Velikova	Professor Psychosocial and Medical Oncology	2003-present
Adam Glaser	Professor Paediatric Oncology and Late Effects	2013-present
Daniel Stark	Professor Teenage & Young Adult Cancer Research	2003-present
Peter Selby	Professor of Cancer Medicine	1989-2019 (retired)
Penny Wright	Associate Professor	1996-2019 (retired)
Kate Absolom	University Academic Fellow	2013-present

Period when the claimed impact occurred: 2014-2020

Is this case study continued from a case study submitted in 2014? Y

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

In 2004, we identified that collection of patient-reported outcome measures (PROMs) improves quality of life. The work has been cited and expanded on international clinical trials showing further benefits of lengthened overall survival in advanced cancers.
Since 2014, we have built on our knowledge of implementing cancer PROMs to successfully:
a) Develop further and evaluate the online technology for adoption in routine patient care to monitor symptoms, improve care and patient self-efficacy during and after cancer treatment.
b) Deliver the largest whole population PROMs studies in the world, to facilitate identification of unmet needs that health services can now address. Results have directly influenced national health policy and international activities.
c) Use PROMs to identify toxicities and quality of life issues in cancer clinical trials. Results have directly informed cancer treatment guidelines nationally/internationally in the evaluation of novel pharmaceutical agents.

2. Underpinning research (indicative maximum 500 words)

In our REF2014 impact case study, we reported the design and development of new approaches and technologies for cancer patients to self-report their symptoms and quality of life. The work focused on electronic methods for collecting PROMs. We have built on this work to: (i) Develop methodologies to enable direct use of PROMs to self-report problems in innovative patient-centred care models, (ii) Enhance clinical implementation to improve efficiency and quality of care during and following cancer treatment, (iii) Deliver large whole population-based research to describe unmet needs and inform NHS policy and practice, and (iv) Lead quality of life sub-studies in world leading cancer clinical trials.

Methodologies and technical development
Since 2014, the secure web-based platform (QTool) for collecting PROMs from patients has been further developed to facilitate direct implementation in patient care. **Wright & Velikova** linked PROMs data with national cancer registration systems, supporting epidemiological outcome assessments [grant a]. The eRAPID (electronic patient self-Reporting of Adverse-events: Patient Information and aDvice) programme developed a web-application for secure real-time display of self-reported data within the individual electronic patient records across three sites (Leeds, Manchester, Bristol), so oncologists can immediately use the information to improve care. The new

QTool platform enabled the inclusion of a bespoke clinical algorithm using symptom severity and medical risk to provide immediate advice to patients. This is a unique innovative feature, designed to improve patient education and confidence in safely managing cancer symptoms [grant b] (1,2). In 2018, **Velikova & Absolom** led the development of a web-application, PROMPT, that supports clinical pathways by scheduling both PROMs and clinical events (appointments, blood tests) [grants c,d]. PROMPT significantly enhances the use of PROMs in post-treatment follow-up.

Enhanced clinical implementation

From 2015 to 2019, **Velikova & Absolom** led the evaluation of the eRAPID platform in chemotherapy, radiotherapy and surgery across three cancer centres [grant b]. To the best of our knowledge, eRAPID intervention is one of the first internationally to include severity-stratified advice to patients about how to self-manage mild/moderate symptoms and when to contact their medical team. A randomised controlled trial in Leeds recruited 508 participants, during systemic treatment, with breast, colorectal or gynaecological cancers. Results demonstrated benefit for patients: improved symptom-control, physical wellbeing and increased confidence in self-managing treatment-related side-effects, without increasing the NHS costs. Benefit was particularly observed in patients with early stage cancers, given chemotherapy with curative intent (2). This is the first large trial internationally showing benefits in this patient population. Pilot studies in pelvic radiotherapy (167 participants) and during recovery after major cancer-related upper gastrointestinal surgery (40 patients) also suggested better symptom control (NIHR monograph Sept 2019, in peer review). Another innovative part of eRAPID was the eLearning programme for professionals to get trained and evaluated in the use of PROMs, following research in 2015-2016.

PROMs survey data in large scale population-based studies

Glaser & Wright led the collection of the largest international PROMs datasets at population level. Analysis and interpretation of findings from these population surveys are being used to inform national policy and planning of cancer services. **Glaser** developed the methodology for linked population-based national cancer PROMs collections and led: the NHS England colorectal cancer survivors survey team (>21,000 participants) (3); UK-wide prostate cancer PROMs programme (>35,000 participants) “,Life After Prostate Cancer” [grant e] (4); ongoing bladder cancer quality of survival studies across Yorkshire & Humber [grant f]. Ovarian, breast and colorectal cancer data were collected on 795 cancer survivors and 1,140 matched control patients from Leeds Teaching Hospitals NHS Trust and linked with primary care data (**Glaser, Wright, Absolom, Velikova**) [grant g].

Leading PROMs sub-studies in cancer clinical trials

Velikova led the analysis and publication of quality of life data from a commercial clinical trial comparing use of eribulin for advanced breast cancer versus capecitabine (5). The results showed that despite more side-effects, patient functioning and overall quality of life during eribulin treatment were similar to capecitabine (known as a well-tolerated chemotherapy), with a survival advantage of 3 months. These results contributed to the subsequent NICE approval of eribulin as a 3rd line treatment for advanced breast cancer.

Stark led the quality of life sub-study of the international ICON 7 trial demonstrating a small detriment to quality of life from Bevacizumab (6). Results contributed significantly to NICE decision against recommending Bevacizumab for advanced ovarian cancer.

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

1. Holch P, Warrington L, Bamforth LCA, **Absolom K**, **Velikova G** *et al*. Development of an integrated electronic platform for patient self-report and management of adverse events during cancer treatment. *Ann Oncol*. 2017;28(9):2305-11. DOI: 10.1093/annonc/mdx317.

2. **Velikova G**, **Absolom K** *et al*. Phase III randomised controlled trial of eRAPID (electronic patient self-Reporting of Adverse-events: Patient Information & aDvice)- an eHealth intervention during chemotherapy (oral presentation). American Society for Clinical Oncology Annual Meeting 2020 (ASCO20), Chicago, IL, United States. *J Clin Oncol*. 2020;38 (supple abstr 7002) DOI 10.1200/JCO.2020.38.15_suppl.7002. Full paper was published on 08.01.2021

3. Downing A, Morris EJ, Richards M, Corner J, **Wright P**, Sebag-Montefiore D, **Glaser AW.** Health-related quality of life after colorectal cancer in England: A patient-reported outcomes study

of individuals 12 to 36 months after diagnosis. *J Clin Oncol*. 2015;33(6):616-24. DOI: 10.1200/JCO.2014.56.6539
4. Downing A, **Wright P,** Hounsome L, **Selby P, Velikova G**, McCaughan E, **Glaser AW** *et al*. Quality of life in men living with advanced and localised prostate cancer in the UK: a population-based study. *Lancet Oncol*. 2019;20(3):436-447. DOI: 10.1016/S1470-2045(18)30780-0
5. Cortes J, Hudgens S, Twelves C, **Velikova G** et al. Health-related quality of life in patients with locally advanced or metastatic breast cancer treated with eribulin mesylate or capecitabine in an open-label randomized phase 3 trial. *Breast Cancer Res Treat*. 2015;154(3):509-20. DOI: 10.1007/s10549-015-3633-7
6. **Stark D**, Nankivell M, Pujade-Lauraine E, Kristensen G, **Velikova G** *et al*. Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phase 3 randomised trial. *Lancet Oncol*. 2013;14(3):236-43. DOI: 10.1016/S1470-2045(12)70567-3

Research grants
a) **Wright P, Velikova G**. Macmillan Cancer Support. Survivors of adult cancer: a feasibility cohort study 2010-2012. GBP409,000.
b) **Velikova G**. National Institute for Health Research (NIHR) programme grant for applied research. Electronic patient self-Reporting of Adverse-events: Patient Information and aDvice (eRAPID) 2013-2019, ~GBP2,000,000 (Development 2010-2012 GBP100,000).
c) **Velikova G**. Yorkshire Cancer Research. Electronic Patient reported outcomes to improve patient management and experiences (ePRIME). 2016-2020, GBP500,000
d) **Velikova G.** Yorkshire Cancer Research. Patient-centred models for surveillance and support of cancer survivors with bowel & breast cancer. 2019-2023, GBP790,000
e) **Glaser A,** Gavin A, **Selby, Wright**. Prostate Cancer UK. Life after prostate cancer diagnosis. 2014-2019, GBP2,000,000.
f) Catto J, **Glaser A**, **Wright/Absolom**. Yorkshire Cancer Research. The Yorkshire Cancer Research Bladder Cancer Patient Reported Outcomes Survey. 2015-2019, GBP377,000.
g) **Glaser A**, Hall G, **Velikova G, Wright P**. Macmillan Cancer Support. Comprehensive Patient Records for Cancer Outcomes: to define the impact of cancer, co-morbidities and late-effects on individuals and health service. 2015-2019, GBP689,000.

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

Changes in practice
Change in health outcomes (cancer survival). Velikova's RCT (2004) was the first internationally to demonstrate improved patient well-being from routine PROMs assessments during cancer treatment. The results encouraged and directly influenced subsequent international randomised trials. Basch *et al*. (2016) in the USA evaluated patient monitoring using web-based PROMs, confirming our findings of improved symptom control and quality of life, whilst demonstrating survival improvements in patients with metastatic cancer. This finding was replicated in France (Denis *et al*, 2017) in advanced lung cancer (A).

Adoption of online PROMs in clinical practice. The improved technology allowing immediate display of self-reports within the individual patient electronic records was adopted in routine NHS follow-up care by Leeds Cancer Centre, led by **Stark**. Since 2016, 330 patients with germ cell tumours in remission (>30% of eligible patients) chose shared community care based on QTool/PROMs, rather than traditional hospital aftercare, allowing them to maintain normal work/study, and significantly reducing the need for hospital attendance. QTool delivered more timely scheduled clinical assessments without delaying the diagnosis of cancer relapse. Patient satisfaction was unaffected. Shared community follow-up reduced personal and health service costs (B). The presentation of these data won an award at the Teenagers & Young Adults with Cancer national research meeting (2017) and was selected for plenary presentation at the Global Adolescent & Young Adults with Cancer Congress (Sydney 2018).
COVID19 pandemic precipitated a rapid shift to technology-enabled care to reduce hospital visits. Our secure delivery platform speeded up the adoption of PROMs for continued safe delivery of cancer care.

Velikova provided professional advice and shared our training toolkit on interpretation and use of PROMs in oncology practice with the Cancer Care Ontario, Canada team leading the Improving Patient Experiences and Health Outcomes Collaborative project (iPEHOC). This province-wide program captured over 30,000 patient reports monthly since 2015. Recent evaluations demonstrated reduction in healthcare utilisation and survival advantage (C).

The Life after Prostate Cancer Diagnosis programme (35,823 participants) (**Glaser, Wright, Selby, Velikova**) identified significant variation in quality of survival across the UK with novel findings of the importance of non-cancer issues in outcomes, including co-morbidities, age and carer responsibilities. Failure of services to identify and support late effects, such as sexual dysfunction, have been highlighted (experienced by 80% of men after prostate cancer). "*More than half of British men treated for prostate cancer were abandoned without support, study finds*", Daily Mail (D). Results were used to produce a public-facing toolkit with information for men with prostate cancer (MenLikeMe app; promoted internationally by Movember Foundation), and to generate hospital, regional and national level toolkits to identify quality of survival and drive service improvements.

Change in Health policy

Glaser was Clinical Director, National Cancer Survivor Initiative (NCSI), Department of Health England and National Clinical Lead for Cancer at NHS Improvement (2009-2013). He established and led the National Cancer PROMs Programme to generate the evidence to improve cancer aftercare and support for the 2 million people living with and beyond cancer across the UK. The national cancer PROMs pilot (4,992 participants) and national colorectal PROMs programmes (21,802 participants) (**Glaser, Wright, Velikova**) directly influenced changes to national health policy (E-i). *The Achieving World Class Cancer Outcomes: A Strategy for England 2015-2020 (2015) and NHS long Term Plan (2019)* mandated PROMs data collection in all cancer patients 1 year after diagnosis (300,000 patients diagnosed each year) (E-ii). It is known that 25% cancer patients report unmet needs at the end of treatment. The national PROMs data collection will identify unmet needs and support service quality improvement.

Since 2016, **Velikova & Glaser** had leading roles in the implementation of the above policy, working on NHS England project "Cancer Quality of Life metric". **Velikova** was the academic lead (following a national competition) of 1st pilot phase with Ipsos MORI. After stakeholders' interviews/literature review, Quality of Life instruments and data collection approaches were recommended. These have been evaluated in pilots across five NHS cancer alliances (Internal NHS England Report 2016). **Velikova & Glaser** won the bid to lead the independent evaluation of the five pilots, producing essential recommendations for the last pilot phase in 2020, prior to national rollout (E-i). **Glaser** was involved in the commissioning of the provider for national delivery of the programme (2019). Both are currently members of the NHS England Quality of Life metric Steering Group. The national rollout successfully started in September 2020 http://www.cancerqol.england.nhs.uk/, with initial pilot aiming for 10% of eligible cancer survivors (~900) and full rollout planned December 2020 for all breast, prostate and colorectal cancer survivors. The national project expects to collect quality-of-life data on ~50,000 survivors in year 1, and ~180,000 in year 2.

Contributing to PROMs guidelines internationally

The Leeds research has influenced guidelines and practices internationally. The Life After Prostate Cancer Diagnosis methodology has been modified and adopted in Norway and Victoria, Australia to support quality improvement activities. We have worked with the International Health Outcomes Consortium (ICHOM) to develop standardised data collection methodologies for prostate cancer (**Glaser**) and digital collection of PROMs **(Glaser & Wright**). The guidance is used internationally to standardise data collection and service evaluation whilst shifting the focus of healthcare to measurement of health outcomes that matter most to patients.

Velikova provided ongoing professional advice and expertise through invited membership of international consortia, publishing guidelines that influence international PROMs strategy beyond oncology (F). Examples include: 2016-USA Patient-Centered-Outcomes-Research-Institute (PCORI) Users' Guide to Integrating Patient-Reported Outcomes in Electronic Health Records;

2017-Consensus group Guidelines for Inclusion of Patient-Reported-Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension JAMA, 2018; 2017-Invited Co-author Lancet Haematology Commissioned issue "Beyond Maximum Grade: Modernizing Adverse-Event Reporting in Haematologic Malignancies"; 2016-Consortium on Setting International Standards in Analyzing Patient-Reported Outcomes & Quality of Life (SISAQOL), Lancet Oncology 2019.

Changes in clinical practice guidelines

The quality of life study of the clinical trial comparing eribulin with capecitabine, published by **Velikova** significantly contributed to NICE decision in 2016 to support eribulin (Halaven) for the management of advanced breast cancer, making it the first chemotherapy for this type to be approved in the last 15 years. In NICE online news 3.11.2016 director of the centre for health technology evaluation said: "*For this appraisal we've been able to consider updated results from the trial used in the original guidance (2012) that show women taking eribulin lived on average 3 months longer… We've also been able to take into account the results for health-related quality-of-life from another trial that compared eribulin with capecitabine. This new evidence…enabled the appraisal committee to conclude that eribulin represents good value for money.*" (G). Since January 2017, 6,155 patients were treated with eribulin (~300 more/year compared to pre-2016 approval) (G).

Stark's work on the quality of life of patients receiving bevacizumab for advanced ovarian cancer directly influenced NICE guidance to not recommend its use. The guidance points: *"One large (n=1,528), open-label, randomised controlled trial (ICON7) that assessed the efficacy and safety of bevacizumab 7.5 mg/kg for treating ovarian cancer was identified; quality of life outcomes from this study were also reported separately (Stark et al. 2013)."* (6) (H).

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

A. References in Basch E, Deal AM, Kris MG, *et al*. Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. *J Clin Oncol*. 2016;34(6):557-565. Replicated by Denis F, Lethrosne C, Pourel N et al. Randomized trial comparing a web-mediated follow-up with routine surveillance in lung cancer patients. *J Natl Cancer Inst*, 2017;109(9). DOI: 10.1200/JCO.2015.63.0830 and DOI: 10.1093/jnci/djx029

B. Lindner OC, Boon IS, Joffe J, **Stark D**. Evaluation of the "Shared Community Follow-up" after a germ cell tumour-A novel initiative for remote cancer follow-up enhanced by online patient-reported outcome measures. *Eur J Cancer C*are (Engl) 2020;29(5):e13264. DOI: 10.1111/ecc.13264.

C. Testimonial letter from Emeritus Scientist, Princess Margaret Cancer Centre Research Centre and their Cancer Care Ontario publications

D. Daily Mail article 2nd February 2019. https://www.dailymail.co.uk/health/article-6659671/More-half-British-men-treated-prostate-cancer-abandoned-without-support.html

E-i. Testimonial letter from Senior Programme Manager for Cancer Quality of Life NHS England and Improvement and Chair of Cancer Quality of Life Steering Group.

E-ii. National Cancer Transformation Programme Progress Report 2016-2017 (page 42); Achieving World-Class Cancer Outcomes: Taking the strategy forward (May 2016); and NHS long-term plan 2019.

F. Contributions to PROMS guidelines internationally: 2016-USA Patient-Centered-Outcomes-Research-Institute (PCORI) Users' Guide to Integrating Patient-Reported Outcomes in Electronic Health Records; 2017-Consensus group Guidelines for Inclusion of Patient-Reported-Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension, JAMA, 2018; 2017-Invited Co-author Lancet Haematology Commissioned issue "Beyond Maximum Grade: Modernizing Adverse-Event Reporting in Haematologic Malignancies"; 2016-Consortium on Setting International Standards in Analyzing Patient-Reported Outcomes & Quality of Life (SISAQOL), Lancet Oncology, 2019.

G. NICE approval of eribulin as 3rd line chemotherapy for advanced breast cancer. Number of patients treated with eribulin (Halaven) from EMEA Medical Information, Eisai Europe Limited. NICE online news 3 Nov 2016.

H. NICE decision on bevacizumab in advanced ovarian cancer and resulted summary: https://www.nice.org.uk/advice/esuom21/chapter/Evidence-review-efficacy#quality-of-life https://www.nice.org.uk/advice/esuom21/ifp/chapter/Summary-of-possible-benefits-and-harms