

Impact case study (REF3)

Institution: University of Leicester		
Unit of Assessment: UoA2		
Title of case study: Providing Reliable Foundations for Health Policy Decisions		
Period when the underpinning research was undertaken: 2000–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) Keith Abrams	1) Professor of Medical Statistics	1) 1994-Present
2) Sylwia Bujkiewicz	2) Professor of Biostatistics	2) 2011-Present
3) Nicola Cooper	3) Professor of Healthcare Evaluation Research	3) 2000-Present
4) Michael Crowther	4) Associate Professor of Biostatistics	4) 2010-Present
5) Paul Lambert	5) Professor of Biostatistics	5) 1992-Present
6) Mark Rutherford	6) Associate Professor of Biostatistics	6) 2011-Present
7) Alex Sutton	7) Professor of Medical Statistics	7) 1996-Present
8) Rhiannon Owen	8) Associate Professor of Biostatistics	8) 2011-Present
Period when the claimed impact occurred: 2013–Present		
Is this case study continued from a case study submitted in 2014? N		
1. Summary of the impact		
<p>For over 20 years, the University of Leicester Biostatistics Groups (LBG) has made significant impacts on healthcare guidance. LBG research underpins the process of evidence generation, consideration and synthesis on which the National Institute for Health and Care Excellence (NICE) base their decisions (known as Health Technology Assessments (HTA)). NICE have completed hundreds of HTAs utilising the Leicester methods. Beyond NICE, LBG methods are routinely used by pharmaceutical and health technology companies seeking product approval both in the UK and globally via international HTA agencies including in the USA and CADTH (Canada).</p>		
2. Underpinning research		
<p>Over the past 20 years, LBG researchers have undertaken pioneering work in the interlinked fields of Evidence Synthesis and Decision Modelling Methodology and in Survival Analysis Methodology. These fields are critical to timely and robust decision making by NICE during HTA.</p>		
Evidence Synthesis and Decision Modelling		
<p>In HTA, the evidence on clinical effectiveness is often disparate and heterogeneous in both source and nature. It is therefore necessary to utilise flexible analysis methods though these are often necessarily complex. Members of LBG have been at the forefront of developing evidence synthesis methodologies capable of meeting the criteria of a wide variety of assessments, products and parties; as demonstrated by the diverse funding streams and demand for their work from collaborators ranging from the EU[G3] to the UK Government[G4] and from research councils[G1] to pharmaceutical companies.[G3]</p>		
<p>Evidence syntheses are often undertaken to inform either a clinical net benefit model or an economic decision model, and it is important that uncertainty and correlation derived from the same source informing multiple model inputs are properly accounted for. LBG research has created methodologies capable of allowing and compensating for different evidence types within a generalised evidence synthesis framework,[R2,R3] identifying and adjusting for publication bias[R5] and improved methods for undertaking both multivariate[R3] and network meta-</p>		

analyses.[R2,R4] The solutions to many of these issues were founded upon Bayesian methods which allow for synthesis of heterogeneous evidence and complex structures whilst enabling appropriate inputs into decision models to be obtained.[G1]

Survival Analysis

The Cox proportional hazards model is one of the most widely used methods in medical research in a variety of clinical settings where the time to an event is the main outcome, e.g., mortality, discharge, disease recurrence. However, the model makes a number of strong assumptions that may not be appropriate; this hinders the complexity of data that can be modelled thereby limiting the clinical questions that can be answered. Extension of these regression-based survival models to accommodate more realistic aspects of the data is a key component of LBG research,[R5] which frequently utilises flexible parametric models (FPM). LBG expertise in FPM development was demonstrated following their original proposal for the use in relative survival models allowing for estimation of loss in life expectancy. This model was developed, validated and shown to be applicable across 4 types of cancer using user-friendly software developed by LBG.[R1]

In HTA, interest often focuses on differences in overall survival for decision-making, however, this is frequently problematic when patients switch from the randomised treatment assigned in RCTs. LBG research has focussed on the evaluation of a variety of different methods for accurate adjustment of RCTs to account for treatment switching [R5]. In both HTA and wider healthcare policy contexts, appropriate long-term patient outcome prediction (including death) is vital for both evaluating health technologies and patient service planning. LBG methodologies using flexible parametric models are uniquely adept at modelling this complex survival data and providing improved long-term predictions.[R1]

3. References to the research

PUBLICATIONS

R1) Andersson TM, Dickman PW, Eloranta S, Lambe M, Lambert PC. Estimating the loss in expectation of life due to cancer using flexible parametric survival models. *Stat Med*. 2013 Dec 30;32(30):5286-300. doi: 10.1002/sim.5943. **Part CRUK-funded.**

R2) Tan SH, Cooper NJ, Bujkiewicz S, Welton NJ, Caldwell DM, Sutton AJ. Novel presentational approaches were developed for reporting network meta-analysis. *J Clin Epidemiol*. 2014 Jun;67(6):672-80. doi: 10.1016/j.jclinepi.2013.11.006. **Part Industry-funded.**

R3) Bujkiewicz S, Thompson JR, Sutton AJ, Cooper NJ, Harrison MJ, Symmons DP, Abrams KR. Use of Bayesian multivariate meta-analysis to estimate the HAQ for mapping onto the EQ-5D questionnaire in rheumatoid arthritis. *Value Health*. 2014 Jan-Feb;17(1):109-15. doi: 10.1016/j.jval.2013.11.005. **MRC-funded.**

R4) Achana FA, Cooper NJ, Bujkiewicz S, Hubbard SJ, Kendrick D, Jones DR, Sutton AJ. Network meta-analysis of multiple outcome measures accounting for borrowing of information across outcomes. *BMC Med Res Methodol*. 2014 Jul 21;14:92. doi: 10.1186/1471-2288-14-92. **NIHR-funded.**

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R5) Latimer NR, [Abrams K](#), [Lambert P](#), [Crowther M](#), Wailoo A, Morden J, Akehurst R, Campbell M. Adjusting for treatment switching in randomised controlled trials - A simulation study and a simplified two-stage method.

Stat Methods Med Res. 2014 Nov 21. DOI: 10.1177/0962280214557578. **NIHR & Industry-funded.**

GRANTS

G1) £340K MRC/NIHR 2008 (3 years)

[Sutton AJ](#), [Cooper NJ](#), [Abrams KR](#), Spiegelhalter DJ.

Evaluating Use of Bayesian Methods in HTA.

G2) £1M Department of Health/NICE 2012 (5 years)

Wailoo A, Tappenden P, Akehurst R, Palmer S, Claxton K, Sculpher M, [Abrams K](#).

National Institute for Health & Clinical Excellence (NICE) Decision Support Unit (DSU)

G3) €16M European Union/European Federation of Pharmaceutical Industries and Associations (EFPIA). 2013 (3.5 years)

C Chinn, E Godber, [K Abrams](#), [S Bujkiewicz](#), [P Dequen](#), et al.,

Innovative Medicines Initiative (IMI) – GetReal.

G4) £2M NIHR 2015 (5 Years)

Wu O, Hawkins N, [Cooper NJ](#), [Sutton AJ](#), Langhorne P, Quinn T, Govan L, Stott D, Grieve R, MacKenzie M, Thomson H, [Abrams KR](#).

NIHR Complex Reviews Support Unit

4. Details of the impact

Over the last 20 years, LBG research has changed healthcare decision and policy making across the world. Individually and collectively, their expertise is in demand, providing pivotal input into processes with fundamental impacts on healthcare. Their influence is due to continuing world-leading research and novel methodology creation that guides, defines and underpins health policy decisions.

The impact of LBG research is best summarised in two main areas:

Enabling Health Policy Decision Makers to Utilise Appropriate, Rigorous and Standardised Methodologies for Health Technology Assessments

In the UK, responsibility for making timely, equitable and accurate decisions regarding appropriate use of health technologies within the NHS lies with NICE. Since establishment, NICE has fundamentally changed the assessment and appraisal process of health technologies using evidence of both cost and clinical effectiveness. The evidence required for these decisions is identified, collated and synthesised by commissioned academic groups, health technology manufacturers and finally by an independent technology appraisal committee at NICE. Since 2006, this committee has always contained at least one LBG member, providing input and guidance on >493 HTAs.

In addition to academic and industrial submissions, NICE utilises its own Decision Support Unit (DSU) and Technical Support Unit (TSU) to undertake advanced analyses and provide expert methods advice. In both units, LBG has an integral role. Since September 2014, LBG

researchers have provided critical expertise in 4 NICE DSU documents providing support, training and guidance for those involved in NICE technology appraisals covering survival methods, treatment switching and multivariate meta-analysis [E1] as well as integral guidance for the 2020 update of the NICE Methods Guide used by all relevant parties involved in the healthcare sector [E1].

For instance, Abrams' expertise was vital in NICE's decision to cease use of the EQ-5D-5L population valuation set which had been commissioned for use in all future appraisals until expert input identified serious methodological flaws [E2].

Internationally, LBG researchers were commissioned to produce a review on evidence synthesis methods for the Canadian Agency for Drugs and Technologies and Health (CADTH) which underpins the national 'Guidelines for the Economic Evaluation of Health Technologies' [E3]. LBG expertise is also in high demand in America, where Abrams has provided expert guidance to the Green Park Collaborative in formulating methodologies for treatment switching in oncology trials [E4], and is collaborating on the FDA-funded multi-stakeholder Critical Path (C-PATH) initiative which ensures efficient trial design for Duchenne Muscular Dystrophy and other rare diseases [E5]. In both cases, the results are based fundamentally on LBG methodologies.

In the global fight against cancer, LBG research and expertise has been invaluable. Group members have provided extensive methodological guidance worldwide. As members of the Academic Reference Group to the International Cancer Benchmarking Partnership [E6], they have assisted in identification and quantification of factors associated with cancer survival variations via the creation of the SurvMark-2 interactive online tools, now used by the WHO Global Cancer Observatory [E10] as part of the GLOBOCAN initiative [E8] and cancer registries worldwide to inform health policy [E11]. LBG representation on the Expert Advisory Group on Cancer Survival for Public Health England and the Office for National Statistics [E7] has resulted in the development of specific methods for analysis and presentation of cancer survival statistics which are now incorporated in the PHE Annual Cancer Statistics Reports [E9].

Enabling Selection of the Most Cost and Clinically Effective Health Technologies for Public Use

In the UK, >8.5 million people are affected by joint pain attributable to osteoarthritis. In 2014, utilising novel modelling methods and software developed by the LBG team, the Warwick Evidence Review Group was able to complete a full appraisal of hip replacements and arthroplasty for end-stage arthritis thus enabling the drafting and implementation of a new NICE guideline [E12].

LBG have provided expert guidance and individually tailored methodologies for >17 international pharmaceutical companies for example, in 2018, their expert strategic and methodological input enabled Roche to identify and utilise the most effective methods for multiple outcome modelling for Ocrelizumab (a drug for the treatment of relapsing-remitting multiple sclerosis). Their guidance resulted in NICE approval and subsequently significant quality of life improvements for many of the UK's 127,000 sufferers [E13].

In 2019, pioneering LBG research into evidence synthesis methods led to the development and global release of freely available cloud-based software enabling implementation of the Leicester methodologies. The programme, MetaInsight, built on experience gained previously with the team's successful Stata programmes Stgenreg and Stpm2 and is now widely used both in submissions to NICE [E14] and developing nations (20% of total MetaInsight usage).

MetaInsight have recently launched a special COVID 19 version of the NMA App - Network Meta-Analysis of Pharmacological treatments for COVID 19: Tool for exploration, re-analysis,

sensitivity analysis, and interrogation of data from living systematic reviews [E15]

The research of the Biostatistics Group at the University of Leicester has been instrumental in shaping healthcare policy, practice and understanding globally. Pioneering research in methodology, evidence synthesis and decision modelling has ensured that clinical practice, treatment and health policy decisions are made based on the best available evidence thereby guaranteeing improved outcomes for patients.

5. Sources to corroborate the impact

- E1. NICE [Decision Support Unit](#) Website
- E2. NICE [Technology Appraisal Guidance](#)
- E3. CADTH '[Guidelines for the Economic Evaluation of Health Technologies: Canada – 4th Edition](#)', 2017
- E4. Green Park Collaborative '[Best Practices for the Design, Implementation, Analysis and Reporting of Oncology Trials with High Rates of Treatment Switching](#)' 2016
- E5. C-PATH [Project Information Website](#)
- E6. International Cancer Benchmarking Partnership [Publications List](#)
- E7. ONS '[The Impact of Updating Cancer Survival Methodologies for National Estimates, 2019](#)'
- E8. International Agency for Research on Cancer/WHO '[Estimating the Global Cancer Incidence and Mortality in 2018: GLOBOCAN Sources and Methods](#)'
- E9. Public Health England (2020) *Conditional crude probabilities of death, split by cancer and non-cancer causes, for adult cancer patients in England followed up to 2019* (Official Statistics). <https://www.gov.uk/government/publications/conditional-crude-probabilities-of-deaths-in-england-followed-up-to-2019/conditional-crude-probabilities-of-death-split-by-cancer-and-non-cancer-causes-for-adult-cancer-patients-in-england-followed-up-to-2019>
- E10. SurvMark-2 provided as the [Cancer Survival Modelling Tool](#)
- E11. National Cancer Registry Ireland '[Measuring Cancer Cure in Ireland: Latest Report from the National Cancer Registry](#)', 2019
- E12. NICE Guideline '[Total Hip Replacement and Resurfacing Arthroplasty for End-Stage Arthritis of the Hip](#)', 2014
- E13. NICE Technology Appraisal Guidance '[Ocrelizumab for Treating Relapsing-Remitting Multiple Sclerosis](#)', 2018
- E14. NICE Single Technology Appraisal Committee Papers '[Tofacitinib for Previously Treated Active Ulcerative Colitis](#)', 2018
- E15. COVID 19 MetaInsight APP <http://www.nihrcrsu.org/about/>