Institution: University of Leicester

Unit of Assessment: UoA2 - Public Health, Health Services and Primary Care

Title of case study: Development of methods to better inform healthcare decision making and innovation

1. Summary of the impact

The National Institute for health Care Excellence (NICE) in England and Wales makes timely and equitable decisions regarding the use of health technologies (medical devices and pharmaceuticals) within the NHS in order to improve patient care. Such decisions are reliant on Health Technology Assessment (HTA) – the processes of evidence generation and synthesis, and the methods that underpin these. Methods pioneered and developed at Leicester over the last 15 years are now used routinely in HTA both by NICE and the pharmaceutical industry and healthcare consultancy companies who make submissions to NICE. Internationally, these methods are also now being adopted in the US by Agency for Healthcare Research and Quality (AHRQ), as well as in rapidly developing countries such as Brazil and Colombia.

2. Underpinning research

The underpinning research that this case study is based upon has two inter-linked themes – *Evidence Synthesis and Decision Modelling Methodology* and *Survival Analysis Methodology*. The pioneering work that researchers in Biostatistics at Leicester have undertaken over the last 15 years is briefly summarised below.

Evidence Synthesis & Decision Modelling

In HTA the evidence on clinical effectiveness is often disparate and heterogeneous in both source and nature. As such the methods that have to used are by necessity flexible and often complex. Members of the Biostatistics Group at Leicester have been at the forefront of developing such methodology in the field of evidence synthesis over the last 15 years funded by MRC, NIHR, and the pharmaceutical industry. Such methodological developments have included: allowing for different types of evidence within a generalised evidence synthesis framework, publication bias, and network meta-analysis. Such syntheses are often undertaken in order to inform either a clinical net benefit model or an economic decision model, and it is important that the uncertainty (and correlation derived from the same source informing a numbers of inputs into such models) is appropriately accounted for. Many of these issues have been addressed using Bayesian methods which both allow for the heterogeneous nature of the evidence to be synthesised and the often complex structure, whilst enabling appropriate inputs into the decision models to be obtained.

Survival Analysis

The Cox proportional hazards model is one of the most widely cited methods in medical research and is used in wide variety of clinical setting in which time to an event is the main outcome, e.g. mortality, discharge, disease recurrence. However, the model makes a number of assumptions that often do not hold and that hinder the complexity of data that can be modelled, and hence 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 research in Biostatistics at Leicester – often using flexible parametric models. In HTA interest often focuses on differences in overall survival for decision making, but this can be problematic when patients switch from the treatment to which they have been randomised to in RCTs. Research at Leicester has focused on the evaluation of a variety of different methods that have been proposed for adjusting RCTs to account for treatment switching, and this work has been funded by ABPI, NICE and NIHR. In both HTA and other health-care policy contexts appropriate prediction of long term patient outcomes (including death) is important in either the evaluation of health technologies or the planning of patient services. The methods developed at Leicester using flexible parametric models are particularly suited to this aim of long term prediction.

The Biostatistics Group at Leicester comprises; Prof. Keith R Abrams, Dr Sylwia Bujkiewicz (L), Prof. Nicola J Cooper, Dr Clare L Gillies (L), Dr Laura Gray (L), Prof. David R Jones, Prof Paul C Lambert & Prof. Alex J Sutton.

3. References to the research [Underlined authors were members of staff/students at UoL at the time the research was undertaken]

Cooper NJ, Sutton AJ, Abrams KR, Turner D, Wailoo A. Comprehensive decision analytical modelling in economic evaluation: A Bayesian approach. *Health Economics*. 2004;13(3):203-226. [**MRC funded**]

Crowther MJ, Abrams KR, Lambert PC. Flexible parametric joint modelling of longitudinal and survival data. Stat Med. 2012 Dec 30;31(30):4456-71. doi: 10.1002/sim.5644. Epub 2012 Oct 4 [**NIHR funded**]

Gillies CL, Lambert PC, Abrams KR, Sutton AJ, Cooper NJ, Hsu RT, Davies MJ, Khunti K. Different strategies for screening and prevention of type 2 diabetes in adults: cost effectiveness analysis. *BMJ*. 2008;336:1180-5. [**ESRC-MRC funded**]

Morden JP, Lambert PC, Latimer N, Abrams KR, Wailoo AJ. Assessing statistical methods for dealing with treatment switching in randomised controlled trials: A simulation study. BMC Methodology 2011;11(4). [**NICE funded**]

Prevost TC, Abrams KR, Jones DR. Hierarchical models in generalized synthesis of evidence: an example based on studies of breast cancer screening. Stat Med. 2000 Dec 30;19(24):3359-76. [**NHS funded**]

Sutton AJ, Cooper NJ, Abrams KR, Lambert PC, Jones DR. A Bayesian approach to evaluating net clinical benefit allowed for parameter uncertainty. *Journal of Clinical Epidemiology*. 2005;58(1):26-40.

4. Details of the impact

The impact emanating from the research has been to:

- Enable NICE to employ a rigorous, fair and standardised methodology with which medical devices and pharmaceuticals can be assessed, and thus;
- Support the selection of the most cost- and health-effective medical devices and pharmaceuticals to be approved for public use;
- Help pharmaceutical and device manufacturers seeking NICE approval to implement processes and practices which are more efficient and effective.

Healthcare Decision Making in NHS for England & Wales

The National Institute for health Care Excellence (NICE) was created in 1999 in order to make timely and equitable decisions regarding the appropriate use of health technologies (medical devices and pharmaceuticals) within the NHS for England and Wales thus improving patient care. Since its inception NICE has radically changed the way in which health technologies are assessed and appraised – using evidence on both clinical and cost-effectiveness[1,2]. Evidence regarding health technologies on both clinical and cost-effectiveness is identified, collated and synthesised by both commissioned academic groups and the pharmaceutical industry/device manufacturers (often subcontracted to specialist healthcare consultancy companies), and which is then appraised by an independent technology appraisal committee at NICE. This comprises NHS healthcare professionals, academics (including **Abrams** since 2006), industry representatives and lay members. The ensuing guidance issued regarding the use of such health technologies is mandatory within the NHS in England and Wales. In addition to the academic and pharmaceutical/device company submissions NICE may also call upon its own Decision Support Unit (DSU), in which Leicester (**Abrams, Cooper & Sutton**) is a key member, to undertake *ad hoc* analyses and bespoke methodological work,. For example, **Abrams**[3] led the NICE response to

the judicial review of the NICE appraisal of alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary (TA 160) and secondary (TA 161) prevention of osteoporotic fragility fractures in post-menopausal women. In addition to appraising health technologies, NICE also has a remit to undertaken the assessment of public health interventions under the auspices of its Public Health Guidance Committee (of which **Jones** is a member).

Methods Employed by NICE & Pharmaceutical/Device Industry for Technology Appraisal & Public Health Guidance

The methods to be employed by academic groups, DSU and industry in undertaking submissions for NICE are set out in the NICE *Methods Guide*, to which **Abrams** & **Sutton** have contributed extensively as members of *Methods Task Forces* ,and are specialist advisers on evidence synthesis methodology[1,2]. In particular, **Abrams**, **Cooper** and **Sutton** have pioneered at NICE, (through membership of the Appraisal Committee, DSU and contributors to the *Methods Guide}*, the use of indirect comparisons or network meta-analysis in technology appraisals and this has led to an increase in its use, for example all 10 of the 212 technology appraisals published to 2011 which used indirect comparisons or network meta-analysis appeared *after* publication of 2004 *Methods Guide* which approved its use[4]. **Abrams & Sutton** has further contributed extensively to a series of NICE DSU *Technical Support Documents* which have further articulated the rationale and use of network meta-analysis[5]. In addition **Abrams**, **Cooper** & **Sutton** have run tailored bespoke courses for the pharmaceutical industry on network meta-analysis, including courses for Novartis, Pfizer & Roche (approx. 150 participants), as well as for NICE (approx. 50 participants) and general courses (approx. 600 participants from consultancy companies, industry and academia). Further, **Abrams** has provided methodological consultancy services to both major pharmaceutical companies (Bristol-Meyers-Squibb, GSK, Janssen, Novartis, & Roche) and healthcare consultancy companies (Amaris, OptumInsight, & PRMA) on network meta-analysis. **Abrams**, **Bujkiewicz**, **Cooper** & **Sutton** undertook implementation of comprehensive decision model in user-friendly real-time software and piloted it in a NICE Technology Appraisal Committee meeting in order to aid more timely decision making on tumour necrosis factor-alpha inhibitors in psoriatic arthritis[6].

In addition to short courses and consultancy activities on evidence synthesis, including network meta-analysis, **Abrams** & **Lambert** have delivered courses, provided consultancy and undertaken contract research projects on methods for dealing with treatment switching in oncology clinical trials to inform HTA for ABPI, Amaris, GSK, OptumInsight, and Roche. For example, in the area of locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma **Abrams** provided expert advice on most appropriate methods for adjusting for treatment switching which led to an eventual positive decision by NICE (subject to a patient access scheme) for Vemurafenib [Roche] which represents an innovative therapy in this poor prognosis condition in which 80% die within 2 years of diagnosis[7]. **Lambert** has also provided methodological advice as a member of the Academic Reference Group to the International Cancer Benchmarking Partnership.

As a measure of contribution to UK economy, since 2010 the ability to **Abrams** to provide expert methodological advice on methods for evidence synthesis and treatment switching to Amaris (a health-care consultancy company) has resulted in them being awarded projects with a combined revenue of [text removed for publication], including them being awarded 'preferred vendor status' by Roche in 2013.

In terms of Public Health decision making, **Cooper** & **Sutton** undertook a network meta-analysis to evaluate the effectiveness of interventions to increase the uptake of smoke alarms as part of a NIHR Programme Grant and which has been included in an update to NICE Public Health Guidance 29: *Strategies to prevent unintentional injuries among children and young people aged under15*[8]. Using comprehensive decision modelling techniques pioneered at Leicester, **Abrams** & **Gillies** undertook further modelling for the Department of Health to inform the UK Vascular Screening Programme[9].

International Impact

As well as disseminating and promoting methodological developments in the UK, **Abrams**, **Cooper** & **Sutton** have delivered short courses of evidence synthesis in the US to the Agency for Healthcare Research and Quality (AHRQ) which have adopted some of these innovative methods[10]. In addition **Abrams** has acted as an advisor to both the Brazilian and Colombian Ministries of Health as regards methods for HTA, whilst **Lambert** has delivered short courses on advanced survival methodology, developed at Leicester, to the International Association of Cancer Registries (approx. 60 individuals) and North American Association of Central Cancer Registries (approx. 30 individuals).

This significant body of translational activity – delivered through committee membership, contract research, consultancy and training delivered by key academics – is fundamentally underpinned by research in *Evidence Synthesis and Decision Modelling Methodology* and *Survival Analysis Methodology* pioneered at Leicester.

5. Sources to corroborate the impact

Contactable individuals to corroborate impact:
1. Director, Centre for Health Technology Evaluation, NICE (to corroborate impact on NICE methodology)
2. Director, Health Economics and Outcomes Research, Amaris, UK (to corroborate impact on healthcare consultancy companies)
3. Group Health Economics Manager, Roche Products Limited, UK (to corroborate impact on pharmaceutical companies)
4. Executive Director, Instituto de Evaluación de Tecnologías en Salud (IETS)
Bogota, Colombia (to corroborate international impact).

Documents to corroborate impact

1. http://www.nice.org.uk/niceMedia/pdf/TAP_Methods.pdf
2. http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
3. http://www.nicedsu.org.uk/PDFs%20of%20reports/Final%20submitted%20to%20NICE%2025%2009%2010.pdf
4. Tan SH, Bujkiewicz S, Sutton A, Dequen P, Cooper N. Presentational approaches used in the UK for reporting evidence synthesis using indirect and mixed treatment comparisons. J Health Serv Res Policy Online First, published on August 14, 2013 as doi:10.1177/1355819613498379.
5. http://www.nicedsu.org.uk/Technical-Support-Documents(1985314).htm
6. Bujkiewicz S, Jones HE, Lai MC, Cooper NJ, Hawkins N, Squires H, Abrams KR, Spiegelhalter DJ, Sutton AJ. Development of a transparent interactive decision interrogator to facilitate the decision-making process in health care. Value Health. 2011 Jul-Aug;14(5):768-76.
7. Vemurafenib [Roche] for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma [TA269] http://publications.nice.org.uk/vemurafenib-for-treating-locally-advanced-or-metastatic-braf-v600-mutation-positive-malignant-ta269
8. NICE public health guidance 29 'Strategies to prevent unintentional injuries among children and young people aged under 15' (2010) – Updated Feb 2013. http://arms.evidence.nhs.uk/resources/hub/930820/attachment
9. http://www.screening.nhs.uk/vascularrisk
10. Agency for Healthcare Research and Quality (AHRQ) – Methods Guide
http://effectivehealthcare.ahrq.gov/tasks/sites/ehc/assets/File/MethodsGuide_ConductingQuantitativeSynthesis.pdf