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| **Institution:** University of Bristol | | |
| **Unit of Assessment:** 2) Public Health, Health Services and Primary Care | | |
| **Title of case study:** Evidence synthesis methods yield benefits to patients, organisations issuing healthcare policy and guidance, and commercial companies | | |
| **Period when the underpinning research was undertaken:** 01/01/2010 – 31/12/16 | | |
| **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:** |
| Nicky Welton | Professor of Statistical and Health Economic Modelling | 07/2002 – present |
| Tony Ades | Professor of Public Health Science | 05/2000 – present |
| David Phillippo | Senior Research Associate in Evidence Synthesis | 09/2015 – present |
| Sofia Dias | Senior Research Fellow in Evidence Synthesis | 09/2007 – 09/2018 |
| Patricia Guyot | Research Associate | 01/2011 – 09/2015 |
| Jonathan Sterne | Professor of Medical Statistics and Epidemiology | 04/1999 – present |
| Jelena Savovic | Senior Lecturer in Evidence Synthesis | 10/2005 – present |
| Julian Higgins | Professor of Evidence Synthesis | 11/2012 – present |
| Barnaby Reeves | Professorial Research Fellow in Health Services | 03/2002 – present |
| Penny Whiting | Associate Professor in Clinical Epidemiology | 09/2004 – present |
| **Period when the claimed impact occurred:** 01/08/13 – 2020 | | |
| **Is this case study continued from a case study submitted in 2014?** N | | |

## 1. Summary of the impact

Patients around the world are more likely to receive the most effective healthcare, at affordable cost, thanks to methods developed by University of Bristol researchers for combining and critiquing evidence. These methods are routinely used by the National Institute for Health and Care Excellence (NICE) to develop recommendations for healthcare in England and Wales and inform guidance on whether new and existing medicines/treatments are made available within the NHS. They are also used by pharmaceutical companies and consultancy firms in submissions to NICE, by academic groups critiquing those submissions, and by similar bodies responsible for healthcare policy in other countries.

## 2. Underpinning research

Healthcare policy and guidelines are developed by expert committees based on appraisals of the evidence for clinical and cost-effectiveness of treatment options. Randomised controlled trials (RCTs) are the best way to compare the effects of different treatments. When multiple RCTs have been conducted, evidence synthesis methods are used to combine their findings, and these pooled estimates are used to assess which treatments deliver the greatest health benefits and represent best value for money. The robustness of the resulting recommendations relies on the use of appropriate methods for evidence synthesis and thorough critiques of model assumptions, the available RCT evidence and, where no RCT evidence is available, relevant non-randomised evidence. University of Bristol (UoB) researchers have developed a suite of methods for evidence synthesis and critical appraisal of the evidence to support robust healthcare decision-making. Of the research described below, only reference **[1]** was included in a REF2014 impact case study.

### Network meta-analysis (NMA) methods

Network meta-analysis (NMA) **[1]** combines RCT results to compare multiple (more than two) treatment options, based on a connected network of treatments directly compared in various combinations within individual RCTs. NMA is particularly relevant for decisions between multiple treatment options, because a single RCT comparing all options is not typically available, or even feasible, and some treatment pairs may not have been directly compared in any RCT. NMA respects the randomisation in individual RCTs, allows ranking of treatments according to clinical and cost-effectiveness, and gives more precise estimates than standard meta-analyses that compare just two treatments that have been directly compared in 'head-to-head' RCTs. However, NMA assumes the included RCTs do not differ in factors that modify the treatment

effect, so that direct estimates from RCTs comparing a pair of treatments are similar to indirect estimates from the remaining evidence (the consistency assumption).

The UoB researchers developed methods and computer code (for freely available statistical software WinBUGS) to conduct NMA for a range of different outcomes (probabilities, rates, continuous, ordinal, survival) and to assess the consistency assumption **[1]**. Assessing consistency between direct and indirect estimates is important for decision-makers to assess robustness of NMA estimates. UoB researchers co-led in the development of an algorithm implemented in the GeMTC package (for freely available statistical software R) to automate this task and facilitate inconsistency checking **[2].** Population adjustment methods have been proposed when the consistency assumption does not hold and individual participant data are available for one study. UoB researchers reviewed these methods, clarified the underlying assumptions and statistical properties, and provided recommendations for their use in assessing effectiveness and cost-effectiveness of treatments **[3]**.

**Reconstruction of survival curve data**

The impact of treatments on life-expectancy is often a key consideration, especially in oncology, and cost-effectiveness can be very sensitive to models used for survival. Comparing different survival models requires access to individual participant data from each RCT. However, those making submissions to reimbursement agencies do not have access to individual participant data from their competitors' RCTs, only the published survival curves. UoB researchers developed an algorithm to reconstruct individual participant data from published survival curves and provide R-code to implement the algorithm **[4]**. This enables companies and evidence review groups to compare different survival models, so that committees can see how sensitive estimates of clinical and cost-effectiveness are to different survival models and, in turn, account for this in their decision-making.

**Assessing risk of bias in RCTs and non-randomised studies**

Studies conducted with lower methodological rigour can lead to exaggerated treatment effect estimates. Committees that appraise evidence therefore need to be aware of methodological flaws in both RCT and non-RCT evidence and account for this in their decision-making. UoB researchers co-led in the development of a tool to assess risk of bias in RCTs **[5]** and led on equivalent research for non-randomised studies (ROBINS-I) **[6]**. Both tools are adopted in the Cochrane Handbook for Systematic Reviews of Interventions and are widely used across the world.

## 3. References to the research

**[1]** NICE Decision Support Unit Technical Support Documents (TSDs) Evidence Synthesis series (TSD-ES) (2011): http://nicedsu.org.uk/technical-support-documents/evidence-synthesis-tsd-series/ and published in abridged form as a series of 7 papers: **Dias S**, **Welton NJ**, Sutton AJ, **Ades AE**. Evidence synthesis for decision making. Medical Decision Making 2013 33:597-691. (MDM1-7). www.wiley.com/en-gb/Evidence+Synthesis+for+Decision+Making+in+Healthcare-p-9781118305409

**[2]** van Valkenhoef G, **Dias S**, **Ades AE**, **Welton NJ**. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. Research Synthesis Methods 2016. 7:80-93. DOI: 10.1002/jrsm.1167.

**[3]** NICE Decision Support Unit Technical Support Document TSD18: on Population Adjusted Indirect Comparisons (2016): http://nicedsu.org.uk/technical-support-documents/population-adjusted-indirect-comparisons-maic-and-stc/ and published in abridged form: **Phillippo DM**, **Ades AE**, **Dias S**, Palmer S, Abrams K, **Welton NJ**. Methods for population-adjusted indirect comparisons in health technology appraisal. Medical Decision Making. 2018. 38:200-211. DOI: 10.1177/0272989X17725740.

**[4]** Guyot P, **Welton NJ**, Ouwens MJNM, **Ades AE**. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Medical Research Methodology 2012. 12:9 DOI: 10.1186/1471-2288-12-9.

**[5]** Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, **Savović J**, Schulz KF, Weeks L, **Sterne JAC**. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928. DOI: 10.1136/bmj.d5928.

**[6] Sterne JAC**, Hernán MA, **Reeves BC**, **Savović J**, … , **Whiting PF**, **Higgins JPT**. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions BMJ 2016; 355:i4919. DOI: 10.1136/bmj.i4919.

## 4. Details of the impact

The National Institute for Health and Clinical Excellence (NICE) issue technology appraisal guidance on whether new or existing treatments are effective, represent good value for money, and can be provided to NHS patients in England (with the guidance also adopted in Wales). The NHS is legally obliged to fund treatments recommended by NICE's technology appraisals, and so the appraisals directly impact the treatment options available to patients. NICE also issue clinical guidelines for healthcare professionals to help them decide on appropriate treatments and services for their patients. Whilst NICE clinical guidelines are not mandatory, their uptake is generally good (www.nice.org.uk/about/what-we-do/into-practice/measuring-the-uptake-of-nice-guidance/impact-of-guidance). NICE technology appraisals and clinical guidelines are based on both clinical and cost-effectiveness, therefore adoption of their recommendations secures more health-related quality of life per pound spent by the NHS and, hence, improves outcomes for patients.

The methods for evidence synthesis and critical appraisal tools developed by UoB researchers are used by pharmaceutical companies **[a]** and consultancy firms **[b]** preparing submissions to NICE technology appraisals, academic groups critiquing those submissions, and NICE guideline developers **[c]**. Here we demonstrate how the methods are routinely used in NICE technology appraisal guidance **[c][d]** and NICE clinical guidelines**[c][e]**, and so directly influence the resulting recommendations and treatment options available, improving health-related quality of life. Further, the methods have had global impact: they are also recommended and used in submissions to healthcare reimbursement agencies in several other countries **[a][b][f]**, in both insurance- and state-funded health systems, enabling better-informed decisions and supporting equitable and optimum resource allocation by health service purchasers around the world.

**Use of UoB methods in NICE Technology Appraisals (TAs) and Clinical Guidelines (CGs)**
Two reviews by UoB of the evidence synthesis methods used in all NICE Technology Appraisal (TA) guidance issued **[d]** and all NICE Clinical Guidelines (CGs) published **[e]** between 1 October 2017 and 30 September 2020, have determined the percentage that used UoB's methods **[1-6]**. The results, presented below, are based on the145 TAs **[d]** and 62 CGs **[e]** that were either new guidance or updated guidance containing new analyses during that period.

*Network meta-analysis (NMA) methods*
NMA was conducted in 51% of the TAs **[d]**. Across a variety of clinical areas, UoB's NMA methods **[1]** were cited in 36.6% and implemented in 35.9% of all TAs **[d]**, and cited and implemented in 33.9% of CGs **[e]**. We can expect the use of UoB's NMA methods to be similar for the earlier part of the current REF period (August 2013-September 2017), given that these recent results are in line with those from an earlier analysis (2009-2013), conducted for the research group's REF2014 Impact Case Study **[j]**. Among the 2017-2020 CGs, automated node-splitting method to assess inconsistency **[2]** was cited in 21% of CGs and implemented in 11.3% of CGs **[e]**. UoB's review, critique and recommendations for population adjustment indirect comparisons **[3]** was cited in 24.8% of TAs and implemented in 19.3% of TAs **[d]**.

*Reconstruction of survival curve data*
UoB's algorithm to reconstruct survival data from published Kaplan-Meier curves **[4]** has been widely used in submissions to NICE TAs, cited in 32.4% of TAs and implemented in 31% of TAs **[d]**. The algorithm was cited and implemented in 3.2% of CGs **[e]**.

*Risk of bias of RCTs and non-randomised evidence*
The risk of bias tool for RCTs **[5]** is cited in 22.8% of TAs and implemented in 20.0% of TAs **[d]**. It is cited in 50% of CGs and implemented in 83.9% of CGs **[e]**. The ROBINS-I risk of bias tool for non-randomised studies **[6]** is cited in 19.4% of TAs and implemented in 16.1% of TAs **[d]** and cited and implemented in 9.7% of CGs **[e]**.

**Illustrative examples of impact arising from NICE TAs and CGs using UoB methods**

*TA384 Nivolumab for advanced melanoma / TA417 Nivolumab for treated or metastatic renal cell carcinoma*

In TA384, Bristol Myers Squibb used the Guyot algorithm **[4]** to reconstruct survival data to inform the indirect comparison between two forms of treatment for renal cell carcinoma (a kidney cancer): nivolumab and BRAF inhibitors in BRAF mutant positive patients (p.178 of committee papers **[g]** reference 196). The Evidence Review Group (ERG) considered use of the method to be appropriate (pp. 445-6 in committee papers **[g]** ref 26), noting that it allows different survival curves to be fitted and compared. They further note that costs of the BRAF inhibitors were sensitive to this choice (costs differ by about GBP18,000, p 488 and p.500 committee papers **[g]**), but that nivolumab remained cost-effective (p.505 of committee papers **[g]** section 4.3.2). The company used the Cochrane risk of bias tool **[5]** to critically appraise the included studies (pp. 447-8 of committee papers **[g]**). The committee concluded that nivolumab is likely to cost less than an additional GBP30,000 per quality adjusted life year gained compared with existing treatment options and recommended it as a cost-effective option for the NHS. The NICE impact report for cancer **[g]** (Figure on p.10 of the report) showed there was a rapid increase in prescriptions of nivolumab after the TA384 guidance was issued in February 2016, from 100,000mg in early 2016 to over 300,000mg within just a few months. This indicates that patients are benefiting from the increased quality of life that nivolumab brings. A similar increase in prescriptions was seen for TA417 (Nivolumab for treated or metastatic renal cell carcinoma) issued in November 2016 **[g]** which also used the Guyot algorithm **[4]** (p.459 of committee papers).

*TA510 Daratumumab monotherapy for treating relapsed and refractory multiple myeloma*

For this TA, individual participant data were obtained for the comparator treatments for multiple myeloma (a bone marrow cancer): (POM+DEX) and (PANO+BORT+DEX) using the Guyot algorithm **[4]**; this enabled estimation of hazard ratios comparing daratumumab with existing treatment options, which would not otherwise be possible (p.213 committee papers **[h]**). The company performed a matched adjusted indirect comparison (MAIC), which the Evidence Review Group (ERG) critiqued using Phillippo *et al* **[3]**, highlighting the high level of uncertainty in the MAIC and the need to adjust for more factors and seek validation (pp. 688-9 or the committee papers **[h]**). The company adjusted for additional factors but was unable to validate the adjustment method (pp. 9-10 4.12 final appraisal determination document **[h]**). The committee recommended managed access through the Cancer Drugs Fund to collect data to resolve some of the uncertainties around clinical effectiveness, including the MAIC, as highlighted by the ERG using Phillippo *et al* **[3]** (pp. 20-23 final appraisal determination document **[h]**). It is predicted that 705 patients per annum will benefit from access to daratumumab while data are collected to determine if it is a clinically and cost-effective treatment for routine commissioning on the NHS (p.3 section 3.3 managed access agreement **[h]**).

*NG158 Venous thromboembolic diseases: diagnosis, management and thrombophilia testing*

Recommendations on pharmacological treatment in people with suspected or confirmed deep vein thrombosis and/or pulmonary embolism employed NMA to compare multiple interventions using methods and code from **[1]** (p.17 point 20 and Appendix O of Document D **[i]**). The automated node-splitting algorithm **[2]** was used to assess the consistency assumption (p.754 of Document D **[i]**). The Cochrane risk of bias tool **[5]** was used to assess the RCTs and quasi-RCTs, and the ROBINS-I tool **[6]** was used to assess the other studies (p.128 of Document D **[i]**). The resource impact report published in March 2020 **[i]** resulting from recommendations 1.3.8, 1.3.15, 1.3.17 (informed by Document D **[i]**), is estimated to save GBP0.4 million in 2020/21, rising to a saving of GBP2.1 million in 2024/25 (p.3 Resource Impact Report, Table 1 (total a+b) **[i]**).

**Use of UoB methods by reimbursement agencies globally**

UoB have further reviewed methods guidance for evidence synthesis in submissions to reimbursement agencies (similar to NICE for England and Wales), issued between 2014 and 2020, in Australia (Pharmaceutical Benefits Advisory Committee), Canada (Canadian Agency for Drugs and Technologies in Health), France (Haute Autorité de Santé), Germany (Institut für Qualität und Wirtschaftlichkeit im Gesunheitwesen), Ireland (Health Information and Quality

Authority), the Netherlands (Zorginstituut Nederland), the USA (Agency for Healthcare Research and Quality), and the World Health Organisation (WHO) **[f]**. The Technical Support Document Evidence Synthesis (TSD-ES) series and corresponding Medical Decision Making papers **[1]** are cited in the methods guidance in Canada, England and Wales, France, Germany, Ireland, the Netherlands, and the USA **[f]**. The automated method for node-splitting to assess inconsistency **[2]** is cited in the methods guidance in Ireland, the Netherlands, and the USA **[f]**. TSD18 **[3]** and the corresponding paper on population adjusted indirect comparisons is cited in the methods guidance in England and Wales, France, and Ireland **[f]**. The algorithm to reconstruct survival data from published survival curves **[4]** is cited in the methods guidance in Canada **[f]**. The risk of bias tool for RCTs **[5]** is cited in the methods guidance in Australia, Ireland, the USA and the WHO, and the updated version 2 tool (published in 2019) is cited in the methods guidance in England and Wales **[f]**. The ROBINS-I tool **[6]** is cited in the methods guidance in Australia, England and Wales, the USA, and the WHO **[f]**. The use of UoB methods in international submissions in France, Sweden, Canada, Australia, South Korea and the USA is confirmed in letters from pharmaceutical firms AstraZeneca and Eli Lilly **[a],** and the consultancy firms Precision Health Economics and Outcomes Research and Clifton Insight **[b]**.

**Commercial impact**

The use of methods developed by UoB researchers by pharmaceutical firms in about 36% of all submissions to NICE TAs **[d]** represents a substantial impact in supporting commercial activity, confirmed in the letters from pharmaceutical companies **[a]** and consultancy companies **[b].** These methods are used in submissions to other reimbursement organisations worldwide **[a][b][f]**.

## 5. Sources to corroborate the impact


**[a]** AstraZeneca (2021) Supporting letter – Statistical Innovation Group, Oncology Data Science & Analytics
Eli Lilly (2021) Supporting letter – Principal Research Scientist

**[b]** Precision Health Economics and Outcomes Research (2021) Supporting letter – Chief Scientist
Clifton Insight (2021) Supporting letter - Director

**[c]** NICE Centre for Guidelines (2020) Supporting letter - Senior Technical Adviser (Health Economics)
NICE Centre for Health Technology Evaluation (CHTE) (2021) Supporting letter – Deputy CEO and Director of CHTE

**[d]** Review of evidence synthesis methods used in all NICE Technology Appraisal (TA) guidance issued 1/10/17 – 30/9/20

**[e]** Review of evidence synthesis methods used in all NICE Clinical Guidelines (CGs) published 1/10/17 – 30/9/20

**[f]** Review of Guidance on Methods for Evidence Synthesis for International Reimbursement Agencies

**[g]** Nivolumab for advanced melanoma (TA384) and renal cell carcinoma (TA417) evidence:
NICE (2015) TA384 committee papers
NICE (2018) Impact Report for Cancer
NICE (2016) TA417 committee papers

**[h]** Daratumumab for relapsed and refractory multiple myeloma (TA510) evidence:
NICE (2017) TA510 Committee papers
NICE (2017) Final appraisal determination document
NICE (2019) Managed access agreement

**[i]** Pharmacological treatments for venous thromboembolic diseases (NG158) evidence:
NICE (2020) Document D: Pharmacological Treatment
NICE (2020) Resource impact report

**[j]** REF2014 (2014) Patients, organisations providing clinical guidelines, and commercial companies benefit from new approach to comparing multiple healthcare options