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| **Institution:** University of York | | |
| **Unit of Assessment:** 16 - Economics and Econometrics | | |
| **Title of case study:** Characterising uncertainty and value of information in health care decisions | | |
| **Period when the underpinning research was undertaken:** 1999-2020 | | |
| **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:** |
| Karl Claxton | Professor | 1989-present |
| **Period when the claimed impact occurred:** 2014-2020 | | |
| **Is this case study continued from a case study submitted in 2014?** No | | |

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

Research at the University of York, on characterising uncertainty and value of information in health care decisions, has had impact in four domains. **First**, it has had a direct impact on how health technologies are evaluated when national guidance is issued to the NHS. Correspondingly, it has had a bearing on the technologies available in the NHS, the evidence available to support their use, and national immunisation programmes. **Second**, methods developed at York have influenced how publicly funded evaluative research is prioritised in the United Kingdom (UK) and the United States (US). **Third**, there has been an international impact, specifically upon national guidelines in Europe and Canada regarding how interventions are evaluated, that stresses the impact of uncertainty and the need for additional evidence on pharmaceutical prices. **Fourth**, the work has informed the methods endorsed by national agencies in health care systems in Asia, Africa, and South America, as well as recommendations by global bodies regarding how interventions for low and middle income countries (LMICs) should be evaluated with respect to the UN Sustainable Development Goals (SDGs).

**2. Underpinning research** (indicative maximum 500 words)

Research at York, undertaken by Karl Claxton (Department of Economics and Related Studies) and colleagues, has provided the methods used to assess whether a technology is expected to be a cost-effective use of NHS resources, how uncertain this assessment is likely to be, whether additional evidence is sufficiently valuable to recommend further research, or whether widespread use should be delayed until additional evidence is available. The key contribution **[A]** has changed the way uncertainties about the performance of health technologies (drugs, devices, diagnostics and public health interventions) are understood, quantified, and interpreted. Traditional statistical methods (whether based on frequentist hypothesis testing or Bayesian error probabilities and credible intervals) are rejected in favour of a more general framework, based on the principles of Bayesian decision theory. This identifies when: **(i)** a health technology should be approved based on existing evidence; **(ii)** whether the value of additional evidence would justify further research to inform these decisions in the future; and **(iii)** what type of research is needed and how it should be designed. Subsequent development of this framework identified when, upon the approval of a technology, it would be expected to be cost-effective based on current evidence or should be withheld until research findings or other sources of uncertainty are resolved **[D]**. An example would be when widespread use significantly reduces the prospects of conducting the type of research that would be valuable, and/or further research commits (opportunity) costs that cannot be recovered, should approval be withdrawn once research reports or other sources of uncertainty resolve over time. Work at York has also established the implications of these considerations, in general for research design and, importantly, for the price of new technologies **[F]**.

Taken together, this research demonstrates how this framework for decision making can be implemented using probabilistic decision analytic models (using simulation methods) and value of information analysis. It has fundamentally changed the way uncertainties about the cost-effectiveness of health technologies are characterised, represented **[B],** and used to inform health care decisions. York researchers have published widely in these areas. Furthermore, researchers at York have demonstrated how decisions can be informed during the appraisal of health care technologies, including when access to a technology should be restricted until further research is completed **[D][E]**. This body of underpinning research provides a means to

identify research priorities and the efficient design of subsequent research **[C]**, providing the methodological foundations for a range of diverse applications and further development of methods, much of which has been undertaken at York.

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

This programme of methodological research has been funded from a number of sources, including the MRC and NIHR methodology programme, demonstrating its originality and rigour. Funding from the National Institute for Health and Care Excellence (NICE) and the NHS HTA (Health Technology Assessment) programme, further demonstrates its significance and relevance. This has multidisciplinary recognition with York research contributing to methods within the related fields of clinical epidemiology, medicine and biostatistics. International reach is evidenced by the development of methods and applications relevant to global health and external funding from Global Challenges Research Fund (GCRF), Bill and Melinda Gates Foundation (BMGF) and other bodies in Norway and the USA.

**[A]** (2000) **Claxton K.**, Walker S. and Lacey L. 'Selecting treatments: a decision theoretic approach' *Journal of the Royal Statistical Society Series A (Statistics in Society)* 163(2): 211-225 https://www.jstor.org/stable/2680498

**[B]** (2001) Fenwick E., **Claxton K.** and Sculpher, MJ. 'Representing uncertainty: the role of cost-effectiveness acceptability curves' *Health Economics* 10(8): 779-89 https://doi.org/10.1002/hec.635

**[C]** (2006) **Claxton K.** & Sculpher M. 'Using Value of Information Analysis to Prioritise Health Research: Some Lessons from Recent UK Experience' *Pharmacoeconomics* 24(11):1055-1068 https://doi.org/10.2165/00019053-200624110-00003

**[D]** (2011) Griffin S., **Claxton K.**, Palmer S. & Sculpher M. 'Dangerous omissions: the consequences of ignoring decision uncertainty' *Health Economics* 20(2): 212-224 https://doi.org/10.1002/hec.1586

**[E]** (2012) **Claxton K.P.**, Palmer S.J., Longworth L., Bojke L., Griffin S., McKenna C. *et al*. 'Informing a decision framework for when NICE should recommend the use of health technologies only in the context of an appropriately designed programme of evidence development' *Health technology assessment* 16(46): 1-323 https://doi.org/10.3310/hta16460

**[F]** (2017) Rothery C., **Claxton K.**, Palmer S., Epstein D., Tarricone R. & Sculpher M. 'Characterising Uncertainty in the Assessment of Medical Devices and Determining Future Research Needs' *Health Economics* 26(Suppl 1):109-123. https://doi.org/10.1002/hec.3467

**[A]-[F]** Peer reviewed; **[D][E][F]** Funded by MRC, EU; **[D]** International Society for Pharmacoeconomics and Outcomes (ISPOR) Excellence Award for Methodological Excellence, 2012. **[F]** Returned to REF2021 (UoA16); **[D][E]** Returned to REF2014 (UoA18, UoA2).

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

Research at York has shaped the analysis NICE requires during the appraisal of new pharmaceuticals, diagnostic technologies, medical devices and public health interventions, as well during the development of clinical guidelines. Since 2014 NICE has issued over 600 pieces of guidance relevant to clinical practice in conditions that are major causes of mortality and morbidity, and which place significant demands on NHS resources. For example, over half of NICE guidance has been in the areas of cancer, cardiovascular and respiratory health. In 2014 alone, these conditions were responsible for over 320,000 deaths associated with 2,700,000 years of life lost, and accounted for more than GBP17.6 billion of NHS spending.

The **NICE Guide to the Methods of Technology Appraisal** specifies the type of analysis required in submissions made by pharmaceutical manufacturers and independent assessments by academic units. It also specifies how such analysis will be used by the Appraisal Committees in developing guidance about the use of health technologies in the NHS. The current NICE 'Guide to the Methods of Technology Appraisal', which has informed all subsequent NICE appraisals to the present day, was published in April 2013. It maintained the requirement to use probabilistic analysis to characterise decision uncertainty and continued to recommend the use of value of information to understand its consequences. These earlier requirements – first introduced in the 2008 guide, and maintained in the current guide – were based on briefing papers for the Methods Review Workshops and the Methods Review Working Party which drew heavily on the underpinning research. In 2011, York research also formed the basis of the Briefing paper for the update to the Methods Guide on uncertainty and 'only in research'

recommendations **[2a]**. The current guidance on when approval should be withheld until further research is conducted (an 'only in research' recommendation), or when additional research is required as a condition of approval, was further strengthened in 2013, reflecting the principles, considerations and type of assessments set out in York research **[E]**. The research was funded by the MRC at the request of NICE, with findings presented and evaluated at two stakeholder workshops hosted by NICE who subsequently noted that the York contribution was *"fundamental to our understanding of the issues that need consideration"* within the latest (2013) version of the guide **[1]**. Since 2014, York research has also informed a number of technical support documents and policy advice requested by NICE from the Decision Support Unit **[2b]**.

Since 2014, In addition to the 71 pieces of guidance on the use of diagnostic technologies and medical devices, the current Guide has informed 330 Technology Appraisals and the (mandatory) guidance that NICE issues to the NHS about the use of new pharmaceuticals. During this period the underpinning research has also informed the development of 165 clinical guidelines **[2c]** and 40 public health guidelines.

The UK **Joint Committee on Vaccination and Immunisation** (JCVI) advises ministers on the commissioning of new vaccines, and changes to existing immunisation programmes. The JVCI (published June 2013) adopted the NICE methodological guidance **[3]**, and since 2014 has issued 18 pieces of guidance on national immunisation programmes in the UK. During this period it has also used explicit decision criteria using a quantitative assessment of decision uncertainty based on probabilistic decision analytic methods from the underpinning research, as well as recommending the use of value of information analysis. In 2016 the use of this type of explicit criteria, proposed by the Cost-effectiveness Methodology for Immunisation Programmes and Procurement (CEMIPP) group, based on these methods, was reaffirmed and strengthened **[4]**.

The research has had an impact on how publicly funded evaluative research is prioritised and commissioned. In the US the Affordable Care Act (Obamacare) created the **Patient Centred Outcomes Research Institute** (PCORI), which has used the principles of value of information analysis to inform the prioritisation of funding allocated by the US Congress for 'comparative effectiveness research'. Since 2014 PCORI has used the principles of value of information analysis, outlined in York research, to inform the prioritisation of USD2.6 billion of research funding. As the Chair of the PCORI Methodology committee attests, York research *"has made fundamental contributions to developing and promulgating the application of rational approaches to inform priorities for medical research… it was not until Karl and his colleagues at York began developing the use of these models in the UK that the value of the approach began to be appreciated and progressively refined and applied… The York VOI group's work with NICE has been an international example in how to use VOI to inform health policy decisions. The VOI methods Karl and his colleagues pioneered have played important roles in work in the US at the National Institutes of Health, the Agency for Healthcare Quality and Research, and the Institute of Medicine."* **[5a]**. Claxton was an expert advisor to the Methodology Committee that commissioned York researchers to establish how these methods could be used by PCORI, demonstrating their application through a number of case studies **[5b]**. This original work for PCORI, and allied underpinning research, is also informing the prioritisation of cancer research in the US by the National Academy of Medicine, National Cancer Institute **[6a]** and the Southwest Oncology Group (SWOG), **[6b]** one of the nation's largest cancer clinical trials networks.

The **NIHR Evaluation, Trials and Studies Coordinating Centre** (NETSCC) asked York to apply methods of value of information analysis to the research proposals they receive. This followed invitations to present to the Health Technology Assessment Commissioning Board (June 2013) and NETSCC Prioritisation Group (January 2014) on how the principles of value of information analysis could be applied to the results of standard meta-analysis. From 2015 NETSCC funded research at York to demonstrate how methods could be applied and used to prioritise proposed research topics. Following the analysis of a sample of research proposals presented to the HTA Commissioning Board (November 2015) and the HTA Funding Director

and Board Chairs (May 2017), funding was extended to develop tools (accessible software and documentation) which could be used by those developing and submitting research proposals. According to the former Director of the NIHR HTA Programme, this work has offered a *"significant step forward in making value of information more accessible and understandable for research funders"* **[7]**. In 2020 the NIHR HTA programme funded a prospective pilot study of the use of these tools within their existing processes and funding round, the results of which were presented to the Clinical Evaluation and Trials Committee in November 2020.

The underpinning research has also shown how uncertainty and the value of additional evidence should influence **pricing decisions**. This has had an impact on how much the NHS pays for new immunisation programmes **[4]** and researchers at York (via the Department of Health and Social Care (DHSC) funded EEPRU (Economic Evaluation Policy Research Unit)) are advising NHS England on how new antimicrobials should be priced based on these methods. The impact of York research on the 2013 NICE Guide **[2a][2b]** has also contributed to the increase in discounts (Patient Access Schemes) offered by pharmaceutical manufacturers during Technology Appraisal (214 Patient Access Schemes since 2014 compared to 30 between 2007 and 2014) **[8a]**. In 2018 researchers at York advised the Canadian Patented Medicines Price Review Board (PMPRB) in their reform of pharmaceutical pricing. The recommendations of the Technical Working Group, which informed the 'Modernization of Price Review Process Guidelines', proposed that rebates to list prices should be founded upon an analysis of uncertainty using guidelines which draw on the underpinning research **[8b]**. Researchers at York were invited to present the implications of this work for pharmaceutical pricing by the Norwegian Pharma Industry Association and the Norwegian Medicines Agency (Oslo, Nov 2017) and are collaborating with members of the Norwegian Medicines Agency in research funded by the Nordic research councils (NordForsk) to apply these methods in the Norwegian context.

Research at York has had a sustained **international impact** on how uncertainty should be characterised and the adequacy of evidence judged. The continued international reach of this research since 2014 is evidenced by recent international good practice guides to methods of evaluation **[9a][9b]** and the guidance adopted by national agencies around the world, including federal agencies in North America (e.g. USA **[9c]**, Canada **[9d]**), national agencies in South America (e.g. Columbia **[9e]**), and in India where researchers from York were invited by the Department of Health Research (Chandigarh, February 2017) to provide training for those conducting analysis to inform the Medical Technology Assessment Board (MTAB) **[9f]**. A number of national agencies in Europe have also utilised York research, (e.g. Sweden **[9g]**, Spain **[9h],** Norway **[9i]** and Belgium **[9j]**).

The research continues to have an impact on how the cost-effectiveness of interventions in low and middle income countries are assessed by global bodies (e.g. the World Health Organization **[9k]**). The Bill & Melinda Gates Foundation (BMGF) commissioned a guide for the methods used to conduct and report their funded research. Researchers at York played a key role in developing this guide, including how uncertainty and the need for evidence should be assessed. As the former Deputy Director of Data and Analytics testifies: *"Professor Claxton's work… and other York research on how uncertainty and the need for evidence should be assessed… influenced hundreds of applied economic evaluations, as well as numerous national HTA guidelines, e.g. Indonesia and Malawi"* **[10]**. Moreover, as well as having a direct impact how analysis is conducted to inform specific decisions in a number of LMICs, work at York has also influenced broader policies, beyond health, including how the Sustainable Development Goals, adopted by the United Nations in 2015, are being evaluated and might be achieved **[9l]**.

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

**[1] NICE Testimonials**: **(a)** Director of the Centre for Health Technology Evaluation, Chair of the Appraisal Committee and Chair of the Methods Working Party, and Programme Director, Technology Appraisals Centre for Health Technology Evaluation, 27 August 2013; **(b)** Director of the Centre for Health Technology Evaluation, 1 February 2021

**[2] NICE Documents: (a)** (2011) **'**Briefing paper for methods review working party on uncertainty and only in research recommendations' (cites **[E]**); **(b)** (2014-16) NICE Decision Support Unit 'Technical Support Documents 15, 16 & 17 (plus 'Framework for analysing risk in

health technology assessments and its application to managed entry agreements)' (cites **[D] [E]** and other York work); **(c)** (2014) 'Developing NICE guidelines: the manual. Process and methods' (cites **[C]** and other York work)
**[3] JCVI** (2013) 'Report from the working group on uncertainty in vaccine evaluation and procurement. Annex 5 to JCVI Code of practice'
**[4] CEMIPP** (2016) **'**Review of Cost-Effectiveness Methodology for Immunisation Programmes & Procurements (CEMIPP Report to the Department of Health, see rec. 7.6)
**[5] PCORI: (a) Testimonial**, Chair, Methodology Committee, 28 August 2013; **(b)** PCORI 'Methodology Report' (2019) (cites **[C]**)
**[6] Cancer Research**: **(a)** (2018) Carlson JJ, Kim DD, Guzauskas GF, *et al*. 'Integrating value of research into NCI Clinical Trials Cooperative Group research review and prioritization: A pilot study' *Cancer Medicine* 7(9) (cites **[C]** and other York research); **(b)** (2016) Bennette CS, Veenstra DL, Basu A, *et al* 'Development and Evaluation of an Approach to Using Value of Information Analyses for Real-Time Prioritization Decisions Within SWOG, a Large Cancer Clinical Trials Cooperative Group' *Medical Decision Making* 36(5) (cites **[C]** and other York research)
**[7] Testimonial**: Director of the NIHR Health Technology Assessment Programme (October 2015 to September 2020), 15 January 2021
**[8] Pricing Decisions**: **(a)** Technologies recommended by NICE that include a commercial arrangement (spreadsheet); **(b)** (2019) Working Group to Inform the Patented Medicine Prices Review Board (PMPRB) Steering Committee on Modernization of Price Review Process Guidelines: Final Report (Recommendation 4.2. cites **[D]** and **[9d]**)
**[9] International Impact: (a)** (2020) ISPOR 'Good Practices for Outcomes Research Reports: Value of Information Analysis for Research Decisions—An Introduction and Value of Information Analytical Methods' (Report 2 cites **[B] [C] [E]** and other York research); **(b)** (2015) European Network for Health Technology Assessment 'Methods for health economic evaluations: A guideline based on current practices in Europe' (cites **[D]**); **(c)** (2016) Agency for Healthcare Research and Quality (ARHQ) 'Guidance for the Conduct and Reporting of Modelling and Simulation Studies in the Context of Health Technology Assessment.' (cites York Research); **(d)** (2017) CADTH 'Guidelines for the Economic Evaluation of Health Technologies: Canada' (4th Edition) (cites York research); **(e)** (2014) Instituto de Evaluación Tecnológica en Salud 'Guidelines for the economic evaluation of healthcare technologies in Colombia: technical support documents' (cites **[C] [E]** and other York research); **(f)** (2018) Department of Health Research Ministry of Health & Family Welfare 'Health Technology Assessment in India (cites York work); **(g)** (2017) SBU 'handbok Utvärdering av metoder i hälso- och sjukvården och insatser i socialtjänsten' (cites York research); **(h)** (2017) AHTA 'GUIDE for the preparation of recommendations and criteria for the adequate use of health technologies (cites **[E]**); **(i)** (2018) Norwegian Medicines Authority 'Guidelines for the submission of documentation for single technology assessment (STA) of pharmaceuticals' (cites York work); **(j)** (2017) Belgian Health Care Knowledge Centre (KCE) 'How to improve the Belgian process for Managed Entry Agreements? An analysis of the Belgian and international experience' (cites **[E]**); **(k)** (2019) WHO 'Guide for standardization of economic evaluations of immunization programmes, 2nd edition (cites **[B]**); **(l)** (2019) United Nations, Independent Group of Scientists 'The Future is Now: Science for Achieving Sustainable Development. Global Sustainable Development Report' (cites an article in *Nature* for which Claxton was co-author)
**[10] Testimonial:** Former Deputy Director of Data and Analytics (2016-19), Global Development, and Strategy Planning, BMGF, 30 November 2020