Coeliac disease (CD) is often diagnosed only after a long period of sometimes quite severe symptoms. These symptoms may cause significant discomfort and anxiety, and interfere with everyday life. As part of a wider research project to explore living with CD in the UK, in collaboration with the charity Coeliac UK, we investigated whether delays to diagnosis and quality of life (QoL) pre- and post-diagnosis changed over the decade 2006-2015.

We designed a postal survey, with input from Coeliac UK, which included questions on age, gender, time to/since diagnosis, type/duration of symptoms and QoL pre- and post-diagnosis. The survey was sent to 4,000 Coeliac UK members in September 2015. The questionnaire responses were analysed using descriptive and regression methods, and these results were compared to those from a similar survey that we conducted in 2006.

The survey response rate was 40%. We found that 65% of respondents experienced at least four symptoms before diagnosis, an improvement on 78% in 2006. The most common symptoms were abdominal pain/bloating, diarrhoea, chronic fatigue, flatulence and anaemia. Mean QoL (measured using the EQ-5D-3L instrument) before diagnosis was 0.65 in 2015, better than the value of 0.56 we found in 2006. Mean QoL increased to 0.80 after diagnosis and adherence to a gluten-free diet in both surveys, comparable with the QoL of the general population. However, despite increasing availability of diagnostic tests and growing awareness of CD, we found little evidence that delay to diagnosis has shortened over time: 12.8 years in 2015, compared with 13.3 years in 2006. More active and better-informed screening strategies are needed to reduce these diagnostic delays and substantially improve QoL of people with CD.

For more information: [https://doi.org/10.1186/s12876-019-0980-6](https://doi.org/10.1186/s12876-019-0980-6)
What is the value of LDL cholesterol lowering in chronic kidney disease?

**Project team:** Iryna Schlackow, Seamus Kent, Alastair Gray, Boby Mihaylova

People with chronic kidney disease (CKD) are at increased cardiovascular disease (CVD) risk. In pre-dialysis CKD, statin-based treatments safely reduce LDL cholesterol and cardiovascular risk and are recommended for use. A number of such treatments are now available at low cost in the US and UK but their lifetime cost-effectiveness in people with CKD was largely unknown.

HERC researchers together with colleagues from the Clinical Trial Service Unit built upon their previous work and evaluated the lifetime cost-effectiveness of a range of statin and ezetimibe regimens in people with moderate-to-advanced CKD (stages 3B to 5). The patient-level data from the Study of Heart and Renal Protection (SHARP), the SHARP CKD-CVD lifetime policy model and the effects of statin-based therapies from the Cholesterol Treatment Trialists’ (CTT) patient-level meta-analyses were used to assess cost-effectiveness. Results were presented by patients’ severity of renal impairment, level of cardiovascular risk and age at initiation of treatment.

In this study, published in *Kidney International*, low-cost generic statins (e.g., atorvastatin 40mg daily) were found to be cost-effective (at thresholds of $100,000/QALY in the US and £20,000-30,000/QALY in the UK) in all categories of non-dialysis dependent patients with moderate-to-advanced CKD both in the US and UK, as was adding ezetimibe 10mg to statin treatment. The results were similar in sensitivity analyses with added potential statin adverse effects and simulated lower rates of adherence with treatments.

Low-cost statin/ezetimibe treatments are cost-effective for reducing cardiovascular risk in non-dialysis-dependent CKD, and the most cost-effective regimen is the one that maximises the statin dose without compromising safety.

For more information: [https://www.herc.ox.ac.uk/research/sharp](https://www.herc.ox.ac.uk/research/sharp)

---

Surgical time is money!

**Project team:** Matthew Little, Alastair Gray, Jacqueline Murphy

Coronary artery bypass grafting (CABG) is one of the most commonly performed operations globally and an established and effective treatment for symptomatic advanced coronary artery disease. Standard practice of using a single internal thoracic artery (SITA) graft is known to be safe and effective. Observational studies have suggested bilateral internal thoracic arteries (BITA) may offer improved long-term patient outcomes in comparison to SITA despite being a more complicated procedure. The Arterial Revascularisation Trial (ART) was designed to address these concerns, with a primary objective of comparing 10-year survival rates associated with BITA over SITA grafting. Five-year data from ART are now available, and we recently used this to assess the long-term cost implications of BITA grafting compared to SITA grafting from an English healthcare perspective.

We previously published a one-year cost comparison from ART showing BITA grafting to be associated with 9% higher costs, primarily due to longer time in theatre and in hospital, and higher costs related to the treatment of sternal wound infections during follow-up. This initial difference was maintained to five years of follow-up with total costs increasing by approximately £1,000 annually in each arm. There were no significant differences between the trial arms in the costs associated with healthcare contacts, medication use or serious adverse events. We found larger differences in certain patient subgroups, particularly for patients with diabetes compared with patients without diabetes, with differences driven by longer stays in hospital, higher outpatient costs and costs associated with sternal wound infections.

Our results were published in *Heart* in February 2019 and will be of value to clinicians and healthcare policymakers considering the potential cost implications of moving from SITA to BITA, and researchers looking to assess the long-term cost-effectiveness of BITA.

For more information: [http://dx.doi.org/10.1136/heartjnl-2018-313932](http://dx.doi.org/10.1136/heartjnl-2018-313932)

---

**Funding**

James Buchanan and Sarah Wordsworth have recently been awarded funding by Genome British Columbia’s (BC) Genesolve program and Illumina Inc. for the project “Quantifying the value of genomics driven health care for children with rare diseases: a multi-country economic analysis”. This project – which will also involve John Buckell at HERC – is a collaboration with Dean Regier at British Columbia Cancer, and colleagues at the University of British Columbia, BC Children’s Hospital and BC Women’s Hospital and Health Centre. The aim of this work is to generate evidence for the appropriate and sustainable adoption of exome and genome sequencing to diagnose and guide treatment for children with rare diseases.
Improving trial designs for estimating optimal antibiotic treatment durations

Project team: Koen Pouwels, Sarah Wordsworth

Antibiotic resistance is an important cause of morbidity, mortality and economic burden worldwide. A key driver of antibiotic resistance is antibiotic use. Doctors often prescribe antibiotic courses that are longer than guideline recommendations. One of the underlying reasons might be that for several infectious diseases the optimal antibiotic course length remains unclear. Courses should be long enough to treat infections effectively, yet short enough to reduce the incidence of side effects and the development and spread of antibiotic resistance.

Antibiotic durations for several infections are not guided by randomised controlled trial (RCT) evidence on optimal duration. Where treatment durations have been compared in RCTs, generally two rather arbitrarily chosen treatment durations were selected for comparison. An issue with such two-arm trials is that they are unlikely to identify optimal treatment durations, potentially leading to suboptimal clinical practice.

HERC researchers collaborated with colleagues from Oxford, London, the Netherlands, Singapore and Thailand to explore whether optimal antibiotic treatment durations could be better estimated using alternative trial designs that allow allocation of patients to multiple different treatment durations. Such multi-arm designs can be used to model duration-response curves (see figure). These curves provide information about outcomes associated with different durations, including those not considered in the trial, by ‘borrowing’ information from nearby durations. Different fixed and (response-)adaptive multi-arm duration designs that could be used to estimate optimal treatment durations were considered and compared on several relevant aspects, including the ability to model (subgroup-specific) duration-response curves, risk of allocation concealment bias and statistical efficiency.

This work was recently published in *BMC Medicine*.

Given the theoretical performance of the considered designs, we concluded that fixed duration designs or designs that can drop clearly inferior arms (drop-the-loser) have the most potential to identify optimal antibiotic treatment durations for different conditions and patient populations, compared to conventional two-arm RCTs. Strengthening the evidence on antibiotic treatment duration is critical in guiding antibiotic stewardship and reducing harm from antibiotic resistance and adverse drug effects.

For more information: https://doi.org/10.1186/s12916-019-1348-z

How do economists help central government thinking?

Project team: Laurence Roope

Economic thinking is increasingly employed across most areas of government activity. The continuing rise of economics across central governments around the world has a potentially important role to play in how countries and international organisations think and operate. However, there is very little research on what professional economists in government actually do. As professional economists play an important role in government, better knowledge of what they do might help to identify training gaps, and may have implications for the content of economics degree courses.

In a recent HERC study, in collaboration with the Open University and Birkbeck College, we sought to improve our understanding of the role of economists in UK government. In the study, published in the *International Journal of Public Administration*, we surveyed over 500 members of the UK Government Economic Service, and used the results to shed light on the activities and thinking of practitioners.

The study found that government economists use a range of concepts and tools that have been developed throughout the subject’s history. Mainstream neo-classical ideas are still valuable to professional practitioners, but they are increasingly used alongside newer fields of economics, such as behavioural economics – particularly ‘nudge’ theory. While mainstream economics has the feeling of a single paradigm, professional practice draws on it in conjunction with other competing paradigms.

A key finding was that the portfolio of tasks that economists in government undertake is not necessarily well reflected in university curricula. For example, ‘synthesising evidence’ was reported as being the single most widely performed task in government. This gives rise to concerns that standard economic educational training, where quantitative skills are generally prioritised, may not provide government professionals with sufficient training for some of their most important economics-related job tasks.

Hopefully our paper will help to stimulate further scrutiny of ways in which economic thinking shapes the world, and how this process can be improved.

For more information: https://doi.org/10.1080/01900692.2019.1575668
Big biomedical data – big challenges for health economists?

Project team: Patrick Fahr, James Buchanan, Sarah Wordsworth

The growth in genomic data, linked with clinical information from electronic health records, has led to the production of biomedical big data (BBD). Such aggregated observational data can inform the use (or not) of “precision medicine”, which involves the tailoring of health interventions based on a patient’s individual characteristics. The latest technology used to provide genomics-based precision medicine is known as next-generation sequencing (NGS). NGS technologies can allow for the sequencing of the entire genome, enabling more precise diagnoses and contributing to the development of more tailored treatments.

Economic evaluations that make use of BBD could help to inform decisions on whether precision medicine approaches based on NGS are cost-effective. However, there are practical and methodological challenges associated with incorporating BBD into economic evaluations. We conducted a literature review to identify and summarise these challenges, which was recently published in Applied Health Economics and Health Policy.

We identified challenges related to data management, data quality and data analysis. The availability of large volumes of data from multiple sources and the need for data linkages within an environment of opaque data access and sharing procedures present practical challenges but these may be resolved if procedures for data access and sharing improve. However, the use of complex and aggregated heterogeneous BBD sources, of which observational data make up a significant proportion, results in challenges related to data quality, such as missing data or the presence of unobserved confounding. In addition, the need to accommodate the dynamic nature of genomics data (for example, periodically updated diagnostic yield) and the increase in information provided by BBD will likely require health economists to develop potentially more complex economic evaluation methods going forward.

Health economists face challenges when using BBD in economic evaluations but solutions to some of these challenges exist. Going forward, it will be important for health economists to document face similar challenges today and the degree to which we have been able to address these challenges. Second, if a Government was to commission a report to look at pharmaceutical expenditure today, what potential long-term recommendations could be made to address current challenges? For further information and registration: www.herc.ox.ac.uk/upcoming-events/60th-anniversary-of-the-hinchliffe-report

Pharmaceutical Policies in the Long Run: Reflections on the 60th Anniversary of the Hinchliffe Report

Symposium, 11th November 2019, Merton College, Oxford

HERC is organising a symposium to mark the 60th anniversary of the Hinchliffe Report, which was a government committee that was tasked with examining the rise in pharmaceutical expenditure following the introduction of the NHS. The symposium will first reflect on the report in order to understand the degree to which we face similar challenges today and the degree to which we have been able to address these challenges. Second, if a Government was to commission a report to look at pharmaceutical expenditure today, what potential long-term recommendations could be made to address current challenges? For further information and registration: www.herc.ox.ac.uk/upcoming-events/60th-anniversary-of-the-hinchliffe-report

Impact of achieving primary care targets in type 2 diabetes

Project team: Mi Jun Kang, Apostolos Tsachristas, José Leal, Alastair Gray, Borislava Mihaylova

Despite recent improvements in achieving NICE defined treatment targets for blood glucose, cholesterol and blood pressure among patients with type 2 diabetes, the percentage of patients achieving all three targets is relatively low in England and Wales. There is wide variation in target achievement rates across GP practices, ranging from 27% to 54% across deciles of GP practices.

In this study, we used data from the National Diabetes Audit and employed the UK Prospective Diabetes Study Outcomes Model to assess the impact of variation in treatment target achievement rates on lifetime risk of diabetes complications, (quality-adjusted) life expectancy and complication-related healthcare costs for patients with type 2 diabetes.

We found that achieving more treatment targets was associated with a lower risk of experiencing a range of diabetes-related complications, and patients would live on average six months longer for each additional treatment target achieved. Achieving all three treatment targets would reduce the costs of treating complications to the NHS by about £1,000 per patient. This could lead to substantial savings for the NHS, considering the high and increasing prevalence of type 2 diabetes in England and Wales (3 million patients as of 2018). Our results suggest that if the 10% lowest performing GP practices (27% patients achieving all targets) were to reach the target levels achieved by the top 10% performing GP practices (54% patients achieving all targets), they would realise an average gain of 30 years of life for every 100 patients. These benefits would double if these practices could get all their patients to achieve all three treatment targets.

The results of this study could help healthcare commissioners to evaluate the medium and long-term effects of strategies to improve diabetes care, and the comparative cost-effectiveness of these strategies. A simple template to explore these results for individual patients or GP practices is available at http://www.herc.ox.ac.uk/downloads/supportingmaterial.

For more information: https://doi.org/10.1111/dom.13821
Spotlight on Inna Thalmann

I joined HERC as a DPhil student in October 2017 to investigate the rates and determinants of medication use for the secondary prevention of cardiovascular disease (CVD) in the UK. Supervised by Boby Mihaylova, Iryna Schlackow, Alastair Gray and David Preiss, my research aims to explore determinants of cardiovascular medication use at different treatment stages and to assess the effect of medication non-adherence and low-dose statin prescribing on subsequent cardiovascular events. In addition, I will evaluate the impact of the abolition of prescription charges in Scotland and explore the application of machine learning techniques to provide further insight on the current barriers to CVD prevention and risk factors of suboptimal drug use. My research at Oxford is funded by an MRC, BHF and NDPH scholarship, and uses routinely collected administrative NHS Scotland data (including hospitalisations, prescribing and mortality), as well as the UK Biobank.

Prior to my doctoral research, I worked as a Public Policy Consultant at LSE Health, where I was involved in the evaluation of efficiency for treatment amelioration and lifestyle management that are potentials in the Austrian social insurance and health system. Before that, I completed an MSc in Health Economics and International Health Policy at the London School of Economics.

My time at HERC has allowed me to meet inspiring researchers and to work on innovative research that will support novel effective policies for treatment amelioration and lifestyle management that are urgently needed, given the high burden and costs of CVD.

HERC Seminars

Convenor: Stephen Rocks

HERC runs a series of seminars with invited speakers from the health economics community who talk on a wide range of applied and methodological topics.

In June, Dr Hong Il Yoo, Associate Professor in Economics, Durham University Business School, Durham University, visited HERC to present his work on: Dynamic Consistency, Sample Selection and Attrition: A Panel Experiment on Individual Discount Rates.

In June, Michelle Tew, PhD Candidate at the Centre for Health Policy, Melbourne School of Population and Global Health, The University of Melbourne visited HERC to present her work on: Quality of Life Trajectories in Total Knee Replacement Patients: What can they tell us?

Details of forthcoming talks can be found on the HERC website: http://www.herc.ox.ac.uk. To be added to our mailing list for future seminars, email us at herc@ndph.ox.ac.uk

Oxford Health Economics Workshop 2019

On 23rd May HERC hosted the 2019 Oxford Health Economics Workshop. The morning session acted as an opportunity for HERC staff and DPhil students to “show and tell” our work to the rest of the group. In the afternoon we had the pleasure of welcoming health economists based in other groups across the University. We enjoyed learning more about health economics work around the University, and we discussed topical health-economic issues and potential collaborations.

Apostolos Tsiaochristas: Budget allocation at the commissioning level: does child mental health lose out?

Francesco Salustri: Breaking away from central tendencies to derive more individualised estimates on costs and effects.


Ines Rombach: Obtaining EQ-5D-5L utilities from the disease specific Quality of Life Alzheimer’s Disease Scale: development and results of a mapping study.

James Buchanan: Cost-effectiveness modeling of testing strategies: methods to appropriately capture uncertainty. [Discussant!]


James Buchanan: Is there an appetite in the United Kingdom for online antibiotic prescribing? Evidence from a discrete choice experiment.

John Buckell: Capturing the role of addiction in smokers’ choices: an addiction-conditioned, hybrid choice model approach applied to smokers in the US.

Koen Pouwels: Modelling the long-term consequences of antibiotic use.

Laurence Roopen: Reducing expectations for antibiotics in primary care: a randomised experiment to test the provision of different types of information.


Philip Clarke: Should we consider baseline health utility scores when developing decision models for economic evaluations? A case study of joint replacement.

Philip Clarke: Defining and measuring health poverty.

Sarah Worsworth: How much economic evidence is really needed to change a healthcare system? An insight from the UK 100,000 Genomes Project.

Winnie Mei: Predicting utility that is missing by design using directed acyclic graphs.
Recent Publications


7. Kong AH, Mistry P, et al. [Includes Jones D, Gray A]. Analysis of hydration and anticoagulants policies in preventing clopidogrel-related gastrointestinal and renal toxicities in low-risk and high-risk patients with Laurence Roope, Mara Violato and Philip Clarke on a project analysing ambient air pollutant levels across the world, and how they vary within and between countries.


25. Kong AH, Mistry P, et al. [Includes Jones D, Gray A]. Analysis of hydration and anticoagulants policies in preventing clopidogrel-related gastrointestinal and renal toxicities in low-risk and high-risk patients with Laurence Roope, Mara Violato and Philip Clarke on a project analysing ambient air pollutant levels across the world, and how they vary within and between countries.


Kusal Lokugamage, who joined HERC in October 2014 to pursue his DPhil. In early 2018, Kusal completed his thesis, titled "What are the optimal treatment strategies in people of increased stroke risk due to cardiac stenosis: using clinical trial and external data to evaluate the long-term benefits and cost-effectiveness of medical therapy alone more cost-effective in older people. The outputs from Kusal's work are already emerging and will inform treatment guidelines. During his time at HERC Kusal contributed to a wide range of activities from research to social gatherings for which we are grateful. We wish him lots of happiness and success for the future.

Congratulations to:

Seun Esan, who successfully defended her DPhil in May 2019, titled: "Sequelea of selected gastrointestinal infections: incidence, risk factors and economic impact on the National Health Service in England". Seun was based in the Nuffield Department of Primary Care Health Sciences and was co-supervised by Mara Violato.

Sarah Briggs, who was successful in obtaining a place at The League of European Research Universities (LERU) Summer School 2019. Their annual doctoral summer school provides students with development opportunities beyond the usual scope of PhD training, and this year focuses on "Building Research Capacity and a Collaborative Global Community".


Winter Newsletter 2019: The most recent newsletter is available to read online. To receive this newsletter quarterly email updates, please complete the form on our website.