



In this issue: • Economic assessment of antibiotic resistance • Improving quality of life in diabetes • Effectiveness of total diet replacements • Statin usage in over 75s • Cost-effectiveness in a placebo surgery trial • Spotlight on Claire Simons • Latest staff news, recently funded projects, seminars, presentations and publications



Assessing the challenge of antibiotic resistance through an economic lens

Project team: Laurence Roope, Koen Pouwels, James Buchanan, Sarah Wordsworth

Driven by widespread antibiotic use, bacteria are becoming increasingly resistant to treatment, and the pipeline for new antibiotics is dry. Recent reports estimate that antimicrobial resistance will cause up to 10 million annual deaths globally by 2050 if no action is taken.

As pressure mounts to secure international commitments to tackle the problem, it is useful to consider what we can learn from another major global challenge – climate change. HERC researchers – in collaboration with colleagues in Oxford, Exeter, London, the Netherlands, Germany and Sweden – considered this topic in a recently published paper in *Science*.

In theory, carbon and antibiotic consumption could be reduced to 'optimum' levels, reflecting their social costs, via taxes or quotas. However, estimating these optimum levels is extremely complex. Rather than waiting for optimum policies to curb resistance, we should agree ambitious but pragmatic targets for reducing antibiotic use without delay.

A system in which GP practices are taxed on each antibiotic they prescribe, or a tax is applied at a local or national level, might provide an

effective incentive for reducing prescriptions. The revenue raised could then be invested in antibiotic development. An alternative may be to establish a regulatory body that gives prescribers permits or quotas for prescribing, then lets the market determine the price. Taxes and quotas could also be used to discourage unnecessary use of antibiotics in animals and reinvest in research and development. However, if the cost of antibiotics increases, it will be vital to develop mechanisms to reduce the risk that they will only be used by those who can afford them.

A key obstacle to developing new antibiotics is that the end product will be held back for as long as possible. This gives little incentive to developers, whose rewards depend on sales volumes. New ways are needed to make antibiotic development profitable, decoupling the rewards for developing new antibiotics from the volumes that will be sold.

There is a great opportunity for economists, across many different fields, to engage with this pressing global problem; we hope that they rise to this challenge.

For more information:

HERC



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Improving quality of life in people with diabetes

Project lead: Alastair Gray

Improving health-related quality of life (HRQoL) is a key goal when managing chronic diseases such as diabetes. As a result, patient-reported outcome measures are increasingly being collected during clinical trials. However, few of the diabetes outcomes trials reported in recent years have so far published quality of life information. In the Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial, 9,340 patients with type 2 diabetes at high risk of cardiovascular disease were randomised and followed up for a median of 3.8 years. The EQ-5D-3L survey instrument was administered at baseline and every 12 months in a subset of 3014 patients from Canada, Denmark, Germany, Ireland, Italy, Netherlands, Spain, Sweden, the UK and the USA.

We compared changes in utility index scores and visual analogue scale (VAS) scores from baseline to 36 months in participants randomised to liraglutide or placebo, and assessed which complications had the greatest impact on HRQoL.

At 36 months, we found that the EQ-5D utility index had deteriorated less in the liraglutide



group (-0.058) than in the placebo group (-0.082), a modest but significant difference. A significant difference was also observed in the VAS score. These differences appeared to be driven mainly by shifts in the domains of mobility and self-care.

The main events contributing to poorer HRQoL were stroke, heart failure, malignant neoplasm and confirmed hypoglycaemia. But even after taking all key factors and events into account a small estimated treatment difference was still observable in the EQ-5D index score.

LEADER is the first trial that we are aware of in a patient population of this type to report a modest but significant benefit in patient-reported health status using the EQ-5D with an antihyperglycaemic agent (liraglutide) compared with placebo. This benefit may be of clinical relevance and requires further study. It also demonstrates the value of including measures such as EQ-5D at more than one time point in such studies.

For more information:

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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 March, **Dr Benjamin Craig**, Associate Professor, Department of Economics, University of South Florida, visited HERC to present his work on: *Health Preference Research: past, present and possible future*.

In May, **Dr Pdraig Dixon**, Research Fellow, Bristol Medical School, Population Health Sciences, was invited to HERC to present his work on: *The casual effect of adiposity on hospital costs: Mendelian Randomization analysis of over 300,000 individuals from the UK Biobank*.

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

Funding

Borislava Mihaylova, Alastair Gray and Iryna Schlackow were recently awarded NIHR HTA funding for a 3-year project entitled "Cost-effectiveness of statin therapies evaluated using individual participant data from large randomised clinical trials". In this project, jointly developed by the University of Oxford (HERC/CTS) and Queen Mary University of London, detailed assessment will be performed of the net effects and cost-effectiveness of statins in different categories of people using data from the Cholesterol Treatment Trialists' Collaboration (~28 large randomised trials), the UK Biobank and the Whitehall II study.

Total diet replacements for the routine treatment of obesity

Project team: Seamus Kent, Bobby Mihaylova

Despite widespread recognition of the impact of obesity on people's health and on healthcare services, there are few effective interventions for the routine treatment of obesity.

Two recent clinical trials – DiRECT and DROPLET – have demonstrated that low-energy total diet replacement (TDR) programmes, delivering 810-830 kcal/day, are safe and effective interventions to reduce weight. In DROPLET, the commercially provided TDR programme led to an extra 7.2kg weight loss at 12 months compared to nurse led behavioural support.

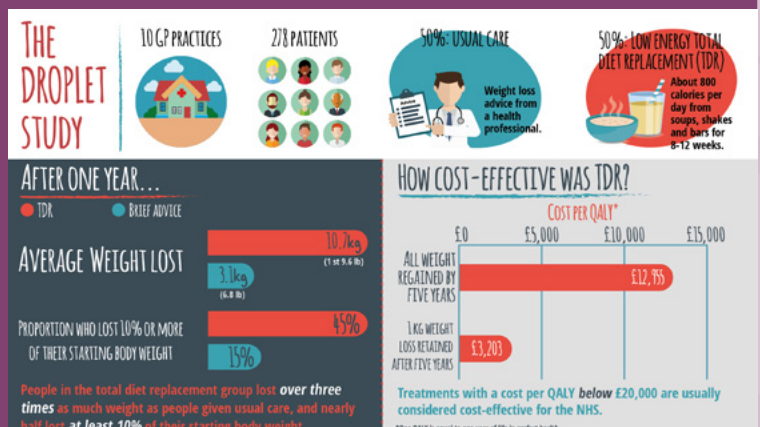
HERC researchers collaborated with colleagues at the Nuffield Department of Primary Care Health Sciences to estimate the long-term effectiveness and cost-effectiveness of the TDR programme studied in DROPLET. This was done by projecting the impact of the weight loss observed at 12 months in the study on obesity-related diseases and mortality over people's lifetime using the PRIMETIME-CE Obesity model (freely available at: <https://github.com/seamuskent/PRIMETIME-CE-Obesity>). An assumption was made that all weight loss was regained at five years following TDR.

The TDR programme was projected to reduce the incidence of obesity-related diseases, particularly type-2 diabetes, improve quality of life and increase length of life. The higher intervention cost (£762) was only partially offset by reductions

in subsequent healthcare costs (£100). The TDR programme was estimated to cost £13,000 for every additional year of life lived in full health, and is therefore likely to be cost-effective in the UK.

In light of the recent clinical and economic evidence, the use of, and funding for, such programmes for the routine treatment of obesity in the NHS should be considered.

For more information: **HERC**



Statins reduce cardiovascular morbidity and mortality in people over 75

Project team: Bobby Mihaylova



Despite overwhelming evidence that statins reduce the risk of heart attacks, strokes and cardiovascular deaths in a wide range of people, uncertainty about their benefits in older people has persisted. Cardiovascular risk increases markedly with age and virtually all people over 75 are at high risk; however, fewer than half of them are taking statins and many stop treatment with advancing age.

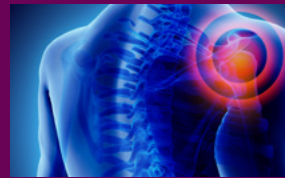
Bobby Mihaylova collaborated with colleagues from the Universities of Oxford and Sydney, as part of the Cholesterol Treatment Trialists' Collaboration (CTT), to review and synthesize the data from nearly 187,000 participants in 28 large randomised clinical trials of statin therapy. The study, published in the *Lancet*, showed that statin therapy produced similar proportional reductions in cardiovascular risk among people older than 75 years as among those younger than 75, and these benefits far outweighed any rare side-effects. Similar risk reductions were noted among older people with and without previous cardiovascular disease, though the evidence is more limited in older people without previous cardiovascular disease.

All statins are now generic and available for less than 10 pence per day. At these prices, current evidence suggests that statins are likely to be very cost-effective in all people considered for treatment. However, with a large and growing share of the population considered for treatment, further evidence is required to strengthen recommendations and uptake of statins. In a new HTA-funded project, co-led by Bobby Mihaylova and Colin Baigent (CTT and University of Oxford), detailed analyses of the net effects and cost-effectiveness of different statin regimens in different people, including older people with and without previous cardiovascular disease, are being developed using the individual participant data in statin trials and UK population cohorts.

For more information: **HERC**

Cost-effectiveness in a placebo surgery randomised controlled trial

Project team: Ines Rombach, Alastair Gray



HERC recently conducted the cost-effectiveness analysis of the Can Shoulder Arthroscopy Work (CSAW) placebo surgery trial. This study investigated the effectiveness of subacromial decompression in patients with subacromial shoulder pain (pain on raising the arm), a common condition linked to reduced quality of life and socioeconomic burden. The surgical procedure removes the bone spur thought to be the cause of this condition, and its use in the UK has increased sevenfold between 2000-2010, despite many patients responding to conservative treatment.

Consenting participants were randomised to subacromial decompression, placebo surgery (arthroscopy only without the removal of bone and soft tissue) and no treatment. The trial found a statistically significant but not clinically important difference in the outcomes between the surgical groups and the no treatment comparator. No difference was found between subacromial decompression and arthroscopy only, putting into question the value of this procedure for this patient population.

For the cost-effectiveness analysis, we carefully considered the potential interpretation of the results; arthroscopy only was offered in the trial to investigate any placebo surgery effects, but is not a valid treatment in this patient population. As such, even if arthroscopy was shown to be cost-effective, it could not be recommended for use in these patients. Given this, we focused our cost-effectiveness analysis on the comparisons with the subacromial decompression.

We found no evidence of subacromial decompression being cost-effective over no treatment over the 12 months of trial follow-up. Extrapolation to two years indicated that subacromial decompression could be cost-effective in the longer-term, but these results were very sensitive to the assumptions made about costs and quality adjusted life years beyond the follow-up of the trial.

For more information: **HERC**

The updated HERC Database of Mapping Studies is now available

This includes 38 new studies published before January 2019 describing 82 mapping algorithms, including new source instruments, such as the Glasgow Outcome Scale, Kessler Psychological Distress Scale and 22-item Sino-Nasal Outcome Test (SNOT-22). Version 7 includes a total of 182 studies reporting 386 mapping algorithms, including 42 mapping to EQ-5D-5L. The database can be filtered by disease area or source/target instruments to quickly identify mapping studies that may provide data inputs for economic evaluation and assess the novelty of new mapping studies. The database can be accessed at <https://www.herc.ox.ac.uk/downloads/herc-database-of-mapping-studies>.

Spotlight on CLAIRE SIMONS



I returned to HERC in January 2018 to work on, in the first instance, a monitoring project alongside Bobby Mihaylova and Iryna Schlackow. This work

aims to identify the optimal monitoring strategy for people with reduced renal function in primary care making use of large, UK based, routine healthcare sources of individual patient datasets to help develop the models. These models project the long-term cardiovascular events, quality of life, survival and healthcare costs of people with reduced renal function and can be used to evaluate the cost-effectiveness of CVD preventive interventions in this population.

Going forward, I will be working alongside Bobby and Iryna on a project estimating the cost-effectiveness of statin therapies in different populations using individual participant data from large randomised clinical trials.

Prior to January 2018, I was a PhD student at the MRC Biostatistics Unit, University of Cambridge. My thesis developed statistical methods to quantify uncertainty and target where reducing this uncertainty would be most beneficial in a CEA. This would enable policy decisions, based on the CEA models, to be better informed. I focused in particular on two under-explored areas of uncertainty –

adherence to interventions and stratification of the optimal treatment decision by continuous disease measures. I hold a MMATH in Maths and Statistics (University of Oxford) and an MSc in Health Economics (University of York) and was also an NIHR Research Methods Fellow in Health Economics in HERC between 2012 and 2014.

Since returning to HERC all members of staff and students have made me feel welcome. I am looking forward to further developing my skills as a researcher through my current and future projects.

staff • visitors • funding • publications • presentations • seminars

Staff News – Welcome to:



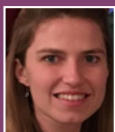
Rositsa Koleva-Kolarova, who joined HERC as a Senior Researcher in May 2019 from King's College, London. Rositsa will be working with Sarah Wordsworth and Apostolos Tsiachristas on the EU-funded HEcoPerMED project to develop state-of-the-art economic models and explore financial incentives for the development and uptake of personalised medicine.



John Buckell, who joined HERC in May 2019 as a Senior Researcher from the Yale School of Public Health. He will be working with Sarah Wordsworth and James Buchanan on genomics, and with Philip Clarke on obesity. John's interests include experimental approaches to understanding health behaviours and econometric modelling.



Teresa Day, who has joined the HERC admin team as PA, to Alastair Gray and Philip Clarke and will also be administering the 3 day Applied Methods of Cost-Effectiveness Analysis course.



Nicky Beddows, who is a foundation doctor on a 4-month rotation in HERC working with Alastair Gray and Filipa Landeiro on a systematic review on resources used and costs incurred by people with predementia or dementia as part of the ROADMAP project. Nicky is also helping Ramón Luengo-Fernández with the Oxford Vascular Study, by collecting resource use data to evaluate the costs of intracerebral haemorrhages and cryptogenic stroke.



Lisanne Schoutens, who is a foundation doctor on a 4-month rotation in HERC working with Alastair Gray and Filipa Landeiro on a systematic review of the literature on economic models for Alzheimer's disease as part of the ROADMAP project.

Farewell to:



Darren Barber who for the last two years, held the position of Administrator and Assistant to Professors Alastair Gray and Philip Clarke. As well as contributing greatly to the production of ten editions of the newsletter, Darren was involved in a wide range of Unit activities from providing PA support, to administering HERC's three day Applied Methods teaching course to organising a hiking party of HERC researchers to climb Snowdon. He was a valued member of HERC who will be greatly missed by all. Darren has joined the Metropolitan Police force as an Information Analyst. We wish Darren much happiness and success in the future.



Liam Mc Morrow, who joined HERC in April 2017 after completing his PhD in health economics at the University of Aberdeen. Liam worked on the ACE trial, a large multicentre randomised control trial in China evaluating the effect of acarbose on patients with prediabetes and a history of cardiovascular disease. He also worked on RHAPSODY, a EU public private consortium funded by the Innovative Medicines Initiative, evaluating novel biomarkers to manage populations with prediabetes and diabetes. In all his work Liam has been able to demonstrate his strong health economics skills. Liam has been awarded funding from EIT Health Headstart to develop an innovative medical device that helps people with diabetes to manage their condition by automatically tracking insulin doses. We are very sorry to see him leave, but are delighted at the recognition of his talents and wish him every success for the future.

Congratulations to:



Ines Rombach, who was promoted to Senior Researcher in March 2019.



Kusal Lokuge on successfully defending his DPhil titled "What are the optimal treatment strategies in people of increased stroke risk due to carotid stenosis: using clinical trial and external data to evaluate long-term benefits and cost-effectiveness?" in April 2019.

Presentations by members of HERC

Queen Mary University of London Seminar
London, February 2019
Seamus Kent

Is a total diet replacement programme cost-effective for the routine treatment of obesity?

Manchester Centre for Health Economics

Manchester, March 2019
James Buchanan

Improving the health economics evidence base for genomic testing

NIHR Health Protection Research Unit in Gastrointestinal Infection Annual Scientific Conference
London, March 2019
Mara Violato

Family income and utilisation of primary and secondary healthcare for diarrhoeal and respiratory infection: evidence from the UK Millennium Cohort Study [Poster]

Fourteenth Workshop on Costs and Assessment in Psychiatry – The Value of Mental Health Services
Venice, Italy, March 2019
Stephen Rocks

Budget allocation at the commissioning level: Does child mental health lose out?

Centre for the Study of African Economies Conference: Economic Development in Africa
Oxford, March 2019
Laurence Roope

Gravitational allocation problems

Leeds University Business School
Leeds, April 2019
Laurence Roope

Identifying inequality benchmark incomes

Universidade de Coimbra
Coimbra, Portugal, May 2019
Filipa Landeiro

Social isolation and delayed hospital discharges

A number of HERC researchers presented at the Nuffield Department of Population Health Annual Symposium, University of Oxford, in March 2019

Plenary Talks

Philip Clarke

Price is what you pay, value is what you get. How drug prices impact on population health

Ramón Luengo-Fernandez

Healthcare costs associated with bleeding on long-term antiplatelet treatment in secondary prevention after vascular events - PPI: good idea after a vascular event

5-by-5 Talks (5 slides in 5 minutes)

Filipa Landeiro

Losing capacity: who should report quality of life?

Helen Dakin

Who should be referred for hip or knee replacement? Personalising medicine using PROMs, cost-effectiveness and big data

Iryna Schlackow

What is the value of LDL cholesterol lowering in chronic kidney disease?

Speed Geeking (10 minute small group presentations)

Ines Rombach

Costing what? Experiences from the cost-effectiveness analysis of a placebo surgery trial

James Buchanan

The doctor will text you now: do we care who prescribes our antibiotics?

Mi Jun Keng

Is the UKPDS Outcomes Model applicable for contemporary well-managed diabetes patients?

Apostolos Tsiachristas

Effective coverage and budget implications of skill-mix change to improve neonatal nursing care in Kenya: an exploratory simulation study

Koen Pouwels

More fuel for the 'Should you finish your antibiotic course?' debate: doctors are frequently prescribing longer courses than recommended

Seamus Kent

Is doctoral referral to a low-energy total diet replacement programme cost-effective for the treatment of obesity in routine care?

Recent Publications

1. Anand P, Roope L, Ross A. *How Economists Help Central Government Think: Survey Evidence from the UK Government Economic Service*. Int J Pub Admin. 2019. doi:10.1080/01900692.2019.1575668

2. Becchetti L, Salustri F. *The vote with the wallet. Responsible consumerism as a multiplayer prisoner's dilemma*. Sustainability. 2019. 11(4):1109. doi:10.3390/su11041109

3. Becchetti L, Salustri F, Scaramozzino P. *Making information on CSR scores salient: A randomised field experiment*. Oxf Bull Econ Stat. 2019. doi:10.1111/obes.12301

4. Brazzelli M, Javanbakht M, et al. [includes Becker F]. *Surgical treatments for women with stress urinary incontinence: the ESTER systematic review and economic evaluation*. Health Technol Assess. 2019. 23(14). doi:10.3310/hta23140

5. Copesey B, Buchanan J, et al. *Duration of Treatment Effect Should Be Considered in the Design and Interpretation of Clinical Trials: Results of a Discrete Choice Experiment*. Med Decis Making. 2019. doi:10.1177/0272989X19841877

6. Fahr P, Buchanan J, Wordsworth S. *A Review of the Challenges of Using Biomedical Big Data for Economic Evaluations of Precision Medicine*. Appl Health Econ Health Policy. 2019. doi:10.1007/s40258-019-00474-7

7. Gardner M, Shepperd S, et al. [includes Tsiachristas A]. *Comprehensive Geriatric Assessment in hospital and hospital-at-home settings: a mixed-methods study*. Health Serv Deliv Res. 2019. 7(10). doi:10.3310/hsdr07100

8. Ke C, Lau E, et al. [includes Clarke P]. *Excess burden of mental illness and hospitalization in young-onset type 2 diabetes: A population-based cohort study*. Ann Intern Med. 2019. 170(3):145-154. doi:10.7326/M18-1900

9. Kent S, Aveyard P, et al. [includes Mihaylova B]. *Is Doctor Referral to a Low-Energy Total Diet Replacement Program Cost-Effective for the Routine Treatment of Obesity?* Obesity. 2019. 27(3):391-398. doi:10.1002/oby.22407

10. Leal J, Mc Morrow L, Khurshid W, et al. *Decision models of prediabetes populations: a systematic review*. Diabetes Obes Metab. 2019. doi:10.1111/dom.13684

11. Little M, Gray A, et al. [includes Murphy J, Campbell H]. *Five-year costs from a randomised comparison of bilateral and single internal thoracic artery grafts*. Heart. 2019. doi:10.1136/heartjnl-2018-313932

12. Nauck MA, Buse JB, et al. [includes Gray A]. *Health-related quality of life in people with type 2 diabetes participating in the LEADER Trial*. Diabetes Obes Metab. 2019. 21(3):525-532. doi:10.1111/dom.13547

13. Png ME, Dritsaki M, et al. [includes Gray A]. *Economic evaluation plan of a randomised controlled trial of intranasal injection of anti-TNF and placebo among patients with early Dupuytren's disease: Repurposing Anti-TNF for Treating Dupuytren's Disease (RIDD)*. Wellcome Open Res. 2019. doi:10.12688/wellcomeopenres.14936.2

14. Pouwels K, Hopkins S, et al. *Duration of antibiotic treatment for common infections in English primary care: cross sectional analysis and comparison with guidelines*. BMJ. 2019. 364:i440. doi:10.1136/bmj.i440

15. Roope LSJ, Smith RD, et al. [includes Pouwels KB, Buchanan J, Eibich P, Wordsworth S]. *The challenge of antimicrobial resistance: What economics can contribute*. Science. 2019. 364(6435). doi:10.1126/science.aau4679

16. Rooshenas L, Scott LJ, et al. [includes Wordsworth S, Gray A, Rombach I]. *The QuinteT Recruitment Intervention supported five randomized trials to recruit to target: a mixed-methods evaluation*. J Clin Epidemiol. 2019. 106:108-120. doi:10.1016/j.jclinepi.2018.10.004

17. Schlackow I, Kent S, et al. [includes Gray A, Mihaylova B]. *Cost-effectiveness of lipid lowering with statins and ezetimibe in chronic kidney disease*. Kidney International. 2019. doi:10.1016/j.kint.2019.01.028

18. Taylor L, Waite W, et al. [includes Violato M]. *Protocol for a randomised controlled feasibility study examining the efficacy of brief cognitive therapy for the Treatment of Anxiety Disorders in Adolescents (TAD-A)*. Trials. 2019. 20:240.

19. Tran-Duy A, McDermott R, et al. [includes Clarke PM]. *Development and Use of Prediction Models for Classification of Cardiovascular Risk of Remote Indigenous Australians*. Heart Lung Circ. 2019. doi:10.1016/j.hlc.2019.02.005

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