



In this issue: SHARP project evaluates cost-effectiveness of statin-based regimens in chronic kidney disease • Impact of education on health in CKD • HERC goes to the Winter HESG meeting in Manchester • Rotator cuff solutions – open versus keyhole surgery • WGS use in TB diagnosis • The impact of social isolation on patient costs • Spotlight on Peter Eibich • Latest staff news, recently funded projects, courses, presentations and publications



Low cost generic statins preferred to simvastatin plus ezetimibe in chronic kidney disease: SHARP cost-effectiveness

Project team: Bobby Mihaylova, Iryna Schlackow, Seamus Kent and Alastair Gray on behalf of the SHARP Collaborators

In people at increased risk of cardiovascular disease, lowering cholesterol with statins safely reduces the risk of heart attacks, strokes and the need for surgery to unblock arteries. As cheap generic statins become more widely available, cost-effective statin interventions are increasingly being recommended for use in wider categories of people. The 9,270-large Study of Heart and Renal Protection (SHARP), the largest randomised controlled trial (RCT) in chronic kidney disease (CKD), showed that, compared to placebo, a combination of simvastatin 20mg plus ezetimibe 10mg taken daily reduces cardiovascular risk in patients with moderate-to-severe CKD, with relative risk reductions similar to those observed in patients with preserved kidney function receiving statins. However, is simvastatin plus ezetimibe a cost-effective option for cardiovascular prevention in CKD? HERC researchers collaborated with the SHARP trial team to answer this question.

The SHARP trial was used to evaluate the cost-effectiveness of simvastatin plus ezetimibe (£1.19 per day) as used during the five years in the study. Treatment was evaluated for SHARP participants at different five-year cardiovascular risks (low, <10%; medium, 10% to 20%; or high ≥20%) and at different stages of CKD (3, 4, 5, on dialysis). In addition, given that the effects of simvastatin plus ezetimibe treatment in this trial were consistent with those observed for other statin regimens in large trials, scenario analyses also evaluated the cost-effectiveness of alternative statin-alone regimens (£0.05 to £1.06 per day).

The cost-effectiveness results, recently published in the American Journal of Kidney Diseases, report that, compared to no cholesterol lowering, simvastatin plus ezetimibe appears to yield health improvements at additional cost (£13,000 to £43,300 per QALY in different categories of participant) not too far beyond the acceptable levels of cost-effectiveness in the UK (see **Figure**). However, cheaper generic statin-alone regimens would yield

(continued on page 2)

similar health benefits at substantially lower additional costs (£3,100 to £20,900 per QALY). Compared with these highly cost-effective alternatives, the substantially more expensive patented statin or statin plus ezetimibe regimens would not be cost-effective. The results were robust in all categories of CKD patients and, given the large differences in prices of generic and patented statin regimens are likely relevant internationally.

The implications of the SHARP cost-effectiveness study are both practical and methodological. Firstly, using the substantial body of randomised evidence for the efficacy and safety of different

statin regimens, together with detailed data from a single large RCT in CKD, the SHARP cost-effectiveness study demonstrated that generic statin-alone regimens are the most cost-effective interventions for reducing the elevated cardiovascular risk in CKD patients. Secondly, these RCT-data driven cost-effectiveness analyses illustrate the need to consider all relevant treatment options to usefully inform policy decisions, even when these options were not used in the RCT.

For more information:

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Figure: Cost effectiveness of 5-year LDL-lowering in chronic kidney disease (CKD)

		High-Intensity* generic Statin £0.05-0.10/day compared to No LDL-Lowering	Simvastatin plus Ezetimibe £1.19/day compared to High-Intensity generic Statin
CKD stage	3	£3,100 to 3,400/QALY	>£80,000/QALY
	4	£11,100 to 11,500/QALY	
	5	£17,900 to 18,800/QALY	
	On dialysis	£20,100 to 20,900	
By 5-year CVD risk	<10%	£17,300 to 18,100/QALY	>£130,000/QALY
	10-20%	£15,800 to 16,300/QALY	
	≥20%	£12,700 to 13,400/QALY	

*achieving ≥40% reduction in LDL cholesterol levels

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Does education affect health in people with established chronic kidney disease?

Project team: Rachael Morton, Iryna Schlackow, Alastair Gray and Bobby Mihaylova on behalf of the SHARP Collaborators

The association between education and health is well established in the general population, with better health outcomes frequently reported across higher levels of educational attainment. Lifestyle factors, behaviours and access to healthcare are thought to be the main contributors to the education-health gradient. However, the relevance of education in people with established chronic kidney disease (CKD) is uncertain.

The Study of Heart and Renal Protection (SHARP), a 9,270-large RCT in moderate to advanced CKD, collected information on the educational attainment of participants in addition to a wide range of other patient characteristics at recruitment. This was supplemented by detailed data on health outcomes during five years of follow-up to support the investigation of the education-health gradient in CKD. Likely confounders of this association, such as age, gender and ethnicity, were controlled for, while characteristics that might mediate the effects of education on health, such as smoking, BMI and prior morbidities, were excluded from the main “total effects” models, but included in the “residual effects” models.

The study, recently published in the American Journal of Kidney Diseases, reports significant trends of increased cardiovascular risk and all-cause mortality in patients with lower levels of education, with modifiable lifestyle factors (e.g. cigarette smoking) and prior morbidities explaining most of the excess risks. However, no association was observed between educational attainment and chronic kidney

disease progression during the study. The study findings suggest that educational attainment should be taken into account when implementing interventions to reduce adverse health outcomes in CKD. This study of the education-health gradient in CKD was made possible by collecting information on participants' education in SHARP, the largest RCT in CKD, which illustrates the value of enriching interventional studies to address wider research questions.

For more information:

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HERC at the 2016 HESG meeting

Manchester, January 2016

HERC was well represented at the recent Health Economists' Study Group meeting, hosted by the Centre for Health Economics at the University of Manchester. Six members of HERC were present – James Buchanan, Alastair Gray, Seamus Kent, Filipa Landeiro, Jacqueline Murphy and Laurence Roope – along with HERC research associate Yaling Yang. Of the 65 papers discussed at the meeting, six had authors based at HERC (listed below) and HERC researchers acted as discussants or chairs for a further three papers. For more information about any of the HERC papers please contact the lead author via the link below.

James Buchanan, Sarah Wordsworth

Is genomic testing cost-effective? A case study in chronic lymphocytic leukaemia

Seamus Kent, Alastair Gray, Bobby Mihaylova

Hospital costs in relation to body mass index in over 1.1 million women in England: a prospective cohort study

Filipa Landeiro, Seamus Kent, Alastair Gray, José Leal

Delayed hospital discharges and social isolation among elderly hip fracture patients in England

Jacqueline Murphy, Alastair Gray

Using decision-analytic modelling to determine the optimal screening threshold prior to the introduction of FIT into the UK NHS Bowel Cancer Screening Programme

Laurence Roope, Sarah Wordsworth

The overuse of antibiotics: information, beliefs, and boomerang effects

Mara Violato, Richéal Burns

The impact of income-related inequality on the behavioural and emotional development of children: a decomposition analysis of the UK Millennium Cohort Study

For more information: **HERC**



Arthroscopic or open repair for rotator cuff tears: results from the UKUFF trial

Project team: Jacqueline Murphy, Alastair Gray

Shoulder problems account for 2.4% of GP consultations in the UK and are a significant socioeconomic burden, resulting in time out of employment and reduced physical ability at work or around the home. Tears in the rotator cuff (a group of muscles and tendons that control shoulder movement) may be repaired using either open surgery or arthroscopic (keyhole) surgery.

HERC researchers have recently been working in collaboration with researchers at the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, on the UK Rotator Cuff Surgery (UKUFF) randomised trial. Funded by the NIHR Health Technology Assessment (HTA) programme, the trial compared open and arthroscopic management in patients with degenerative full-thickness rotator cuff tears, aged 50 years and above in 47 hospitals in the UK.

Alongside the clinical measures, resource use and quality of life (EQ-5D) were obtained from questionnaires sent to patients at various follow-up points after surgery. Resource use items included surgical equipment (bone anchors, consumables), theatre time, hospital stays, revision procedures, healthcare appointments, and prescribed medications.

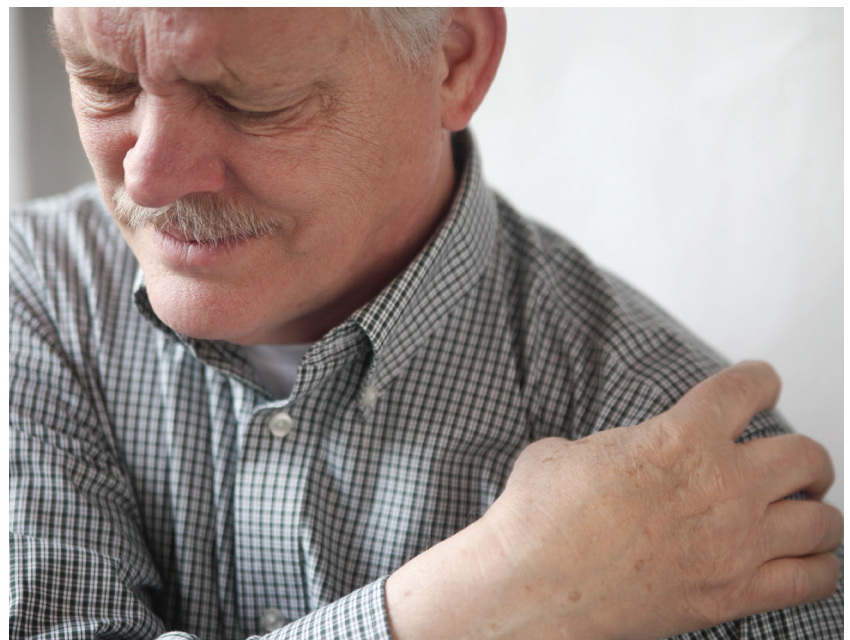
Results were analysed on an intention-to-treat basis, meaning that the comparison was based on the procedure the patient had been randomised to. A significant proportion of patients in the trial did not receive their randomised intervention once they had entered surgery due to the nature of the procedure (some tears cannot be repaired, and surgeons were free to select the best management strategy, even if this differed to the randomised procedure).

The trial showed no difference in clinical effectiveness between open and arthroscopic management on an intention-to-treat basis. This was also reflected in the economic analysis, where there was no significant difference in cost between the two arms for any category of resource use, nor in quality-adjusted life years up to 24 months.

The findings suggest that current trends toward arthroscopic repair may be unjustified, and that further trials to compare techniques on a randomised basis are warranted in other surgical areas.

For more information:

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The trial showed no difference in clinical effectiveness between open and arthroscopic management

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First health economics workshop takes place as part of 100,000 Genomes Project

Project team: Sarah Wordsworth, James Buchanan, José Leal

On 20th January 2016, HERC – in collaboration with health economists at the University of Manchester (Katherine Payne) and the PHG Foundation in Cambridge (Gurdeep Sagoo) – organised a one day health economics workshop at the Wellcome Collection in London as part of the Genomics England 100,000 Genomes Project.

This was the first event organised by the newly formed Health Economics Clinical Interpretation Partnership (HE GeCIP) and was funded by the National Institute for Health Research. The aim of the event was to provide an overview of the work planned by the HE GeCIP group, introduce non-economists to the methods that will be used within this programme of work, and to provide an opportunity for these researchers to initiate collaborations with health economists within the HE GeCIP.

Around 50 delegates attended the workshop, including health economists working in genomics, scientists and clinicians from disease-focused GeCIP domains and Genomic Medicine Centres, funders, and representatives from NICE and Genomics England. The day began with presentations on the outcomes, costs and preferences subdomains of the GeCIP. These presentations considered the challenges and opportunities for the generation of health economic evidence within the 100,000 Genomes Project and were followed by a lively discussion session which covered a variety of topics, including the relative importance of non-health outcomes in this context.

The afternoon session was opened by Tom Fowler, Director of Public Health at Genomics England, who explained why health economics is important for the 100,000 Genomes Project. This was followed

by presentations which considered issues surrounding capacity and implementation, health economics education and training, and how to deal with incidental findings in health economic analyses. The day ended with a broader discussion in which delegates explored opportunities for collaboration going forwards.

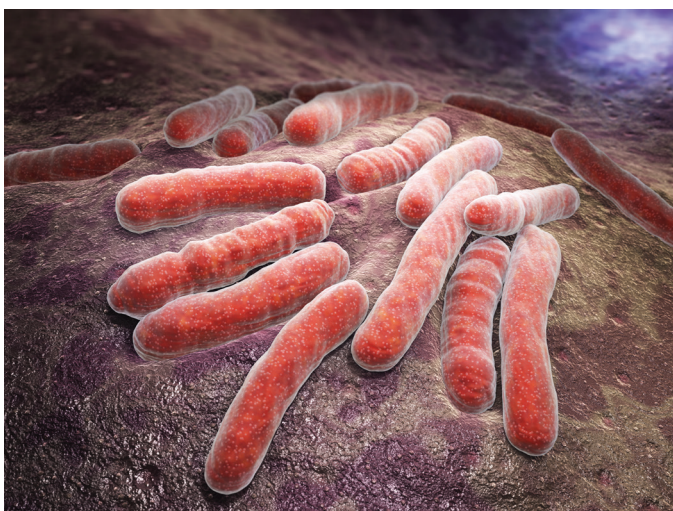
All delegates were enthusiastic about the need to effectively integrate health economics into the 100,000 Genomes Project and the HE GeCIP team left the workshop with plenty of food for thought. Keep an eye on the HERC website for further details of our work in this area later in 2016.

For more information: **HERC**



Whole genome sequencing is a cost-effective option for diagnosing tuberculosis

Project team: Sarah Wordsworth and Jilles Fermont



The World Health Organisation has estimated that *Mycobacterium tuberculosis* complex (MTBC) causes nine million new infections and 1.5 million deaths around the world each year. To identify MTBC, infectious disease laboratories use several methods sequentially to detect every bacterium causing a patient's infection and to determine if these bacterium are resistant to a range of drugs (antibiotics). This is a slow, labour-intensive process which can delay treatment and cause poor patient outcomes. Whole-genome sequencing (WGS) is a potential solution

to these problems because it sequences the entire microbial genome simultaneously, but it is considered very expensive.

HERC researchers have recently completed a prospective study to compare WGS with routine MTBC diagnostic processes in terms of effectiveness (diagnostic accuracy) and cost-effectiveness. The project involved eight laboratories in Europe and North America and was led by Professor Derrick Crook (University of Oxford). The results of this work were published in *Lancet Respiratory Medicine* in December 2015.

The results of the study indicated that WGS was more accurate than routine diagnostics in both identifying the bacterium and determining drug susceptibility. WGS diagnostics were also generated a median of 21 days faster than current routine diagnostic approaches (9 versus 31 days). Furthermore, WGS cost £481 per culture-positive specimen, whereas routine diagnosis cost £518. This equates to a WGS-based diagnosis being 7% less expensive per year than current diagnostic methods in infectious disease laboratories.

The study concluded that the use of WGS to diagnose MTBC has clear benefits compared with traditional diagnostics, including rapid identification and control of infection outbreaks, faster and more appropriate treatment selection, all at an affordable cost. These study results represent a potential paradigm shift in infectious disease diagnostics. The study team are now exploring WGS in the context of other infectious diseases including *C. difficile*.

For more information: **HERC**

Social isolation and delayed discharges: the costs to the Portuguese National Health Service

Project lead: Filipa Landeiro, José Leal and Alastair Gray

While acute hospital services are the most costly component of healthcare budgets, many acute hospital beds are still inappropriately occupied by older patients who are medically fit for discharge but cannot be transferred back to the community. These delayed discharges can block emergency admissions, lead to the cancellation of elective surgeries, expose patients to complications and adverse events and worsen their social isolation.

HERC researchers have recently undertaken a prospective cohort study at the Hospital de Santa Maria in Lisbon to further explore the consequences of delayed discharges. This study evaluated 278 patients that were admitted to the Orthopaedics Unit via the Emergency Room with a diagnosis of hip fracture over the course of a year in order to determine the incidence, drivers and costs of delayed discharges. Social isolation was measured using the Lubben Social Network Scale.

The study results show that 31% of these patients were either at high risk for social isolation or were already socially isolated prior to admission. Patients with delayed discharges spent, on average, 7 excess days in hospital, and patients who were at higher risk of social isolation spent more unnecessary days in hospital than lower risk patients. Patients who were admitted from a care home had fewer days of delay than patients admitted from their own homes, whereas patients referred to publicly-funded rehabilitation units experienced longer periods of delay than non-referred patients.

The average hospital cost of a patient with a delayed discharge was 78% higher than that of a patient without a delay and total costs of delayed discharges varied between 11%-31% of total costs (between €2,352 and €3,317 per patient with a delayed discharge), depending on whether waiting costs for placement in publicly-funded rehabilitation units were included.

The study concludes that an increase in the number of publicly funded rehabilitation beds would reduce the number of days of delayed discharge for these patients, allowing them to return to the community and thus preventing further social isolation.

For more information: **HERC**



“ The average hospital cost of a patient with a delayed discharge was 78% higher than that of a patient without a delay ”

Spotlight on **PETER EIBICH**



I joined HERC in January 2015 as a Researcher. In my current work at HERC I am investigating the cost-effectiveness of hip and knee replacement. The project focuses in particular on how the cost-effectiveness of these procedures differs by patient characteristics, with the ultimate aim of establishing a tool and a threshold that can be used as a decision aid for GPs in the referral process for joint replacement surgery. I am also involved in the Mastermind project, in which we are investigating the scope for cost-effective stratification of treatment for type 2 diabetes. Finally, I am developing a research programme that analyses economic determinants of the uptake of cancer prevention in middle-aged and older people.

Before joining HERC, I worked as a research associate at the German Institute for Economic Research (DIW) in Berlin. There, I was responsible for the socio-economic

module of the Berlin Aging Study II, a multidisciplinary study on the determinants of successful ageing. At the same time I conducted my doctoral studies at the University of Hamburg, Germany, where I investigated the economics of ageing and retirement.

My first year at HERC has been very rewarding. My work on the health effects of retirement was published in the Journal of Health Economics and widely covered in the national and international media. Moreover, my work on regional differences in health in Germany (published in 2014 in Regional Science and Urban Economics) was awarded the scientific prize of the Central Research Institute of Ambulatory Health Care in Germany (ZI Berlin). I have been able to develop new skills in economic evaluation and benefitted greatly from the support of talented researchers and administrators at HERC.

Staff News – Welcome to:



Tae Lee

Tae, an NHS junior doctor on a four-month rotation with HERC, is currently working with José Leal and Filipa Landeiro on the REFRESH and Fracture Free studies looking into differences in HES and CPRD datasets as well as cost-legacy effects post-treatment for hip fractures.



Ahmad Saif

Ahmad is a junior doctor, training in the Oxford University Hospitals NHS Foundation Trust. He is currently on his public health rotation, working with HERC for four months, where he is developing his research skills and undertaking a cost-effectiveness

analysis of parent guided cognitive behavioural therapy on childhood anxiety disorder with Mara Violato. He has also been contributing to the Fracture Free study alongside Filipa Landeiro.

Congratulations to:



Peter Eibich

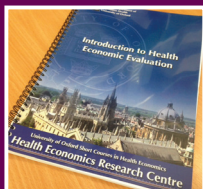
HERC researcher, Peter Eibich's paper titled *Examining the structure of spatial health effects in Germany using Hierarchical Bayes Models* was one of two papers that were awarded the "Regional Health Research" Scientific Prize by the Central Research Institute of Ambulatory

Health Care in Germany (Zi). The prize comes with €2,500. Peter presented the paper in Berlin on the 26th November 2015.

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HERC courses



Introduction to Health Economic Evaluation one day course

Spaces are still available for either the 21st or 22nd April 2016. Booking is also open for either the 13th or 14th October. All

courses will be held at St. Catherine's College, Oxford, UK. If you would like more information on course content or how to reserve a place, please go to:

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Recently Funded

The role of hospital organisation, surgical factors, and the enhanced recovery pathway, on patient outcomes and NHS costs following primary hip and knee replacement surgery: spatial and longitudinal analysis of routine data.

José Leal is the Health Economics lead for this recently funded research project by NIHR HS & DR. The study will start in April 2016 and run for two years.

Presentations by members of HERC

CLOSER Conference – The importance of early years, childhood and adolescence: Evidence from longitudinal studies
London, November 2015

Mara Violato

The impact of income-related inequality on the behavioural and emotional development of children: a decomposition analysis of the UK Millennium Cohort Study

Modernising Medical Microbiology Annual Conference
Oxford Maths Institute, December 2015

Laurence Roope

What behavioural traits are associated with overuse of antibiotics and how can we exploit them?

Health Economists' Study Group (HESG) Meeting
Manchester, January 2016

James Buchanan

Is genomic testing cost-effective? A case study in chronic lymphocytic leukaemia

Seamus Kent

Hospital costs in relation to body mass index in over 1.1 million women in England: a prospective cohort study

Filipa Landeiro

Delayed hospital charges and social isolation: a study of older hip fracture patients in England

Jacqueline Murphy

Using decision-analytic modelling to determine the optimal screening threshold prior to the introduction of FIT into the UK NHS Bowel Cancer Screening Programme

Laurence Roope

The overuse of antibiotics: information, beliefs, and boomerang effects

Nuffield Department of Population Health Symposium
Oxford, January 2016

Oral presentations

Peter Eibich

Costs and pathways of medication therapy for type 2 diabetes in the UK: the scope for stratification

Seamus Kent

Hospital costs in relation to body mass index in 1.1 million women in England

Jacqueline Murphy

FIT for colorectal cancer screening in England: will capacity constraints limit health benefits?

Laurence Roope

The overuse of antibiotics: information, beliefs, and boomerang effects

Iryna Schlackow

Life expectancy in chronic kidney disease: the SHARP CKD-CVD model

Poster Presentations

Seamus Kent

Hospital costs in relation to body mass index in 1.1 million women in England

Filipa Landeiro

The impact of social isolation on delayed hospital discharges of older hip fracture patients and associated costs

Kusal Lokuge

Procedural and long-term effects of treatment methods for carotid stenosis: a systematic review of randomised and observational evidence

Translating the variability in the performance of Clinical Commissioning Groups in diabetes care to lifetime health outcomes and health care costs.

This study began in January 2016 and will finish in July 2016 and Apostolos Tsiachristas is leading the economic analysis. The aim of the proposed research is to investigate the relation between the performance of GP practices in diabetes care and health outcomes and costs in order to raise awareness about suboptimal performance in diabetes care.

Jacqueline Murphy

Using decision-analytic modelling to determine the optimal threshold for FIT in the NHS Bowel Cancer Screening Programme in England (awarded 'Highly Commended' by the NDPH Symposium poster judging panel)

Ines Rombach

The current practice of handling and reporting missing outcome data in 8 widely-used PROMs in RCT publications: A review of the current literature

Newcastle University, Health Economics Group
Newcastle, January 2016

James Buchanan

Identifying the most appropriate economic evaluation approach in genomics: a comparison of methods

NIHR Health Economics GeCIP Workshop
London, January 2016

James Buchanan

Capturing stakeholder preferences in the 100,000 Genomes Project
Sarah Wordsworth
Measuring costs in the 100,000 Genomes Project

Oriel College Talks, University of Oxford
Oxford, January 2016

Filipa Landeiro

Delayed Hospital Discharges

HERC Seminars Convenor: Laurence Roope

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 mid-January 2016 we welcomed **Markus Haacker**, from the Harvard School of Public Health, who gave a presentation on *Cost-effectiveness - Lessons from the Global Response to HIV/AIDS*.

During Hilary Term, **James O'Mahony**, from Trinity College Dublin, visited HERC to give a talk on *Beware of Kinked Frontiers: A Systematic Review of the Choice of Comparator Strategies in Cost-Effectiveness Analyses of Human Papillomavirus Testing in Cervical Screening*.

Details of forthcoming talks can be found on the HERC website:

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To be added to our mailing list for future seminars, email us at herc@dph.ox.ac.uk

Recent Publications

Wordsworth S, Buchanan J, Towse A. *Health Economic Perspectives of Genomics in Genomics and Society Ethical, Legal, Cultural and Socioeconomic Implications*. 2015 Oct. 5:83-117

Freeman D, Waite F, Startup H, Myers E, Lister R, McInerney J, Harvey AG, Geddes J, Zaiwalla Z, **Luengo-Fernandez R**, Foster R, Clifton L, Yu LM. *Efficacy of cognitive behavioural therapy for sleep improvement in patients with persistent delusions and hallucinations (BEST): a prospective, assessor-blind, randomised controlled pilot trial*. *Lancet Psychiatry*. 2015 Nov. 2(11):975-83. doi: 10.1016/S2215-0366(15)00314-4

Mihaylova B, Schlackow I, Herrington W, Lozano-Kühne J, **Kent S**, Emberson J, Reith C, Haynes R, Cass

A, Craig J, **Gray A**, Collins R, Landray MJ, Baigent C. *Cost-effectiveness of Simvastatin plus Ezetimibe for Cardiovascular Prevention in CKD: Results of the Study of Heart and Renal Protection (SHARP)* *American Journal of Kidney Diseases*. doi:10.1053/j.ajkd.2015.09.020. Epub Nov 2015

Carr AJ, Murphy R, Dakin SG, **Rombach I**, Wheway K, Watkins B, Franklin SL. *Platelet-Rich Plasma Injection With Arthroscopic Acromioplasty for Chronic Rotator Cuff Tendinopathy: A Randomized Controlled Trial*. *Am J Sports Med*. 2015 Dec. 43(12):2891-7. doi: 10.1177/0363546515608485

Tsiachristas A, Burgers L, Rutten-van Molken MP. *Cost-Effectiveness of Disease Management Programs*

for Cardiovascular Risk and COPD in The Netherlands. *Value Health*. 2015 Dec. 18(8):977-86. doi: 10.1016/j.jval.2015.07.007

Pankhurst LJ, del Ojo Elias C, Votintseva AA, Walker TM, Cole K, Davies J, **Fermont JM**, Gascoyne-Binzi DM, Kohl TA, Kong C, Lemaitre N, Niemann S, Paul J, Rogers TR, Roycroft E, Smith EG, Supply P, Tang P, Wilcox MH, **Wordsworth S**, Wyllie D, Xu L, Crook DW, for the COMPASS-TB Study Group *Rapid, comprehensive, and affordable mycobacterial diagnosis with whole-genome sequencing: a prospective study*. *The Lancet Respiratory Medicine*. 2016 Jan. 4(1):49-58. doi:10.1016/S2213-2600(15)00466-X

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