Research Agenda for Health Economic Evaluation

Expert Review Meeting

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2 Abbreviations

ACE	Angiotensin-Converting Enzyme
ARB	Angiotensin Receptor Blocker
AF	Atrial Fibrillation
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CMG	Continuous Monitoring of Glucose
COPD	Chronic Obstructive Pulmonary Disease
CV	Cardiovascular
DALY	Disability Adjusted Life Year
DM	Diabetes Mellitus
ESRD	End-Stage Renal Disease
EU	European Union
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IHD	Ischemic Heart Disease
NOAC	Novel Anti-Coagulants
QALY	Quality Adjusted Life Year
RAHEE	Research Agenda for Health Economic Evaluation
SGLT2	Sodium Glucose Transport Proteins
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
WTP	Willingness-to-pay

3 Executive Summary

Health systems are under pressure to address rising costs, making efficient resource allocation increasingly important. Health economic evidence can be used at various levels of the health system to improve cost-effectiveness of services, and to ensure that new technologies under consideration for reimbursement represent good value for money.

Scientific studies on the cost-effectiveness of health interventions (screening, prevention, diagnostics, treatments etc.) are increasingly being published, but it is unclear in which therapeutic areas there is still an unmet need for economic evidence. The Research Agenda for Health Economic Evaluation (RAHEE) project therefore aims to outline a list of priorities for health economic research for the EU by analyzing the available evidence for the 10 highest burden conditions in the region, and deriving research priorities from a panel of health economic and public health experts.

According to the Global Burden of Disease study, the most significant health conditions in the EU are:

1. Ischemic Heart Disease
2. Low Back Pain
3. Stroke
4. Major Depressive Disorder
5. Lung Cancer
6. Falls
7. Chronic Obstructive Pulmonary Disease
8. Diabetes
9. Other Musculoskeletal Disorders[1]
10. Neck Pain

Existing health economic evaluation studies for the prevention and management of these conditions were mapped against current clinical guidelines to identify evidence gaps. In addition, four case studies were developed on Belgium, England, Poland and Slovenia to highlight how economic evidence is used in practice. These findings were discussed by a panel of 20 health economic and public health experts, to identify specific economic evidence gaps for the prevention and management of each disease, methodological issues in health economics requiring further research, and how the use of economic evidence can be improved in practice.

The panel observed a number of constraints on the use of health economic evidence in practice, including isolated budgets (silos) between departments, limited capacity and lack of timely access to data (section 7.1). A series of recommendations were made based on evidence gaps in the health economic evidence for the 10 study

[1] A collection of 62 musculoskeletal disorders, including arthropathies, systemic connective tissue disorders, dorsopathies, soft tissue disorders, osteopathies and chondropathies, that together make up the 10th

conditions (section 7.2), reflecting the particular health interventions in each area. Finally, the panel proposed a range of methodological issues requiring further research, many of which were interlinked. The panel recommended a greater role for real-world evidence, which could improve understanding of the cost-effectiveness of health interventions outside clinical trial settings, and for more research on patient characteristics that are associated with improved effectiveness, allowing treatments to be targeted to patients who benefit the most. Such data would also facilitate reduction of unnecessary services that are both non-cost-effective and potentially associated with adverse outcomes for the patient. The panel highlighted the need for more research to understand the cost-effectiveness of current guideline recommended treatments and every-day practice, particularly when the same patient receives multiple treatments concurrently or consecutively. It was recognized that funding sources were a significant source of bias, and that risk of bias could be reduced by developing open-source, open-access and standardized economic models for high burden diseases. Finally, it was highlighted that cost-effectiveness thresholds, which are used as a cut-off for decision-making in some countries, are not based on scientific or transparent principles, and research is needed to determine what such thresholds should be (section 7.3).

4 Background

In recent years health economic evaluation has become more integrated in the planning of many European health systems, and since 2008 the financial crisis has given added incentive to ensure publicly provided services are cost-effective. In many contexts, health economic evidence is most explicitly taken into account in the development of clinical guidelines or in Health Technology Assessment (HTA), which reviews the cost-effectiveness of novel and potentially expensive health technologies and in some cases the cost-effectiveness of existing interventions as well. Importantly, ensuring that additional spending is cost-effective contributes only marginally to the overall cost-effectiveness of a health system, and focusing only on novel technologies is insufficient to ensure overall cost-effectiveness. Health economic evidence has the potential to impact decision making on many organizational levels, and prevention of high burden, high mortality conditions such as cancers and improved management of chronic conditions such as Chronic Obstructive Pulmonary Disease and back pain have the potential to generate substantial savings on health budgets in the longer term.

It should be noted, however, that economic evidence and efficiency considerations are rarely (if ever) the only input to decision-making, and should therefore be considered in the context of other health system objectives. In particular, economic approaches that seek to maximize health across the population or make assertions based on the "average patient" do not necessarily take equity considerations into account. It may be relevant for society to consider which patient groups benefit from particular services from an equity perspective, eg. patients that are disproportionately affected by illness, that have limited or no treatment options, etc. Ethical issues also affect policy making, for example screening programs that identify certain risk factors inevitably provide information to individuals that changes their perception of their own health and potentially their prospects for self-realisation, such as screening for risk factors for sudden cardiac arrest in young athletes. Consequently there is not necessarily a direct link between favorable economic data and implementation. The present panel and authors recognize these constraints, but restrict the analysis to technical issues.

The Research Agenda for Health Economic Evaluation (RAHEE) project aims to outline a future research agenda for the EU on health economic evaluation, based on a mapping of existing economic evidence to identify gaps in the available evidence, and on case studies in selected countries to identify issues in applying health economic evidence in practice. The main objectives are 1) to prepare an overview of the state of health economic evidence for a selection of high burden conditions in the EU, based on a systematic assessment of published reviews and primary studies; 2) to identify difficulties in the translation of existing evidence on preventive public health interventions into practice based on case studies in selected countries; and 3) to derive research priorities for the European Union through an Expert Panel discussion of these materials.

The RAHEE project is implemented at and coordinated by the World Health Organization Representation to the EU (WEU) in collaboration with external partners, the World Health Organization Regional Office for Europe and the World Health Organization Headquarters.

In order to consolidate the health economic research priorities identified through the project's comprehensive analysis of existing evidence, an expert consultation was carried out. A panel of 20 international experts on health economics and public health and 10 WHO representatives discussed how key findings of the project could be translated into a research agenda to support more efficient use of resources in European health systems. This report presents the conclusions and recommendations from the consultation process, supported by the results of the systematic mapping of health economic evidence.

5 Objective of the meeting

The primary objective of the RAHEE expert meeting was to discuss the results of the RAHEE evidence mapping and case studies, and to establish research priorities based on this evidence. A secondary objective was to establish a dissemination plan for the resulting research priorities, including suggested channels of communication and key stakeholders to involve.

6 Methodology

The RAHEE Expert Meeting discussions were based on a range of materials developed prior to the meeting, specifically:

1. Four separate country case studies, detailing the economic considerations preceding the implementation of preventive interventions in Belgium (rotavirus vaccination), England (cardiovascular health checks), Poland (prevention of COPD exacerbations) and Slovenia (colorectal cancer screening)
2. A mapping of the published, peer-reviewed health economic evidence (cost-effectiveness, cost-benefit) on the 10 highest burden conditions by Disability Adjusted Life Years (DALY's) in the EU, based on a MEDLINE database search. The analysis was restricted to the 10 highest burden conditions due to project constraints.
3. A series of methodological papers addressing the following topics
    a. HTA of complex interventions
    b. Disinvestment
    c. Cross-country transferability of economic evidence
    d. Individualized medicine
    e. Pre-launch real-world evidence and potential impact on regulatory and HTA decision making
    f. Standardization of disease specific economic models

g. Generalized cost-effectiveness analysis
h. Economic evaluation of health effects in non-health policies
i. Methods of estimating indirect and productivity costs
j. Bias resulting from industry funded research

The methods of the meeting materials are described in detail elsewhere.[2]

The RAHEE Expert Meeting included a panel of 20 public health and health economic experts, along with 10 WHO representatives. The expert panel discussed the results from the evidence review and case studies and identified research gaps for each disease area and for the field of health economics generally.

7 Findings and recommendations for research

The key issues and recommendations identified through the evidence review and expert consultation fell into three broad categories:

- Barriers to the translation of health economic evidence into practice, as highlighted by case studies
- Condition-specific evidence gaps, where evidence on interventions is either insufficient or of insufficient quality
- Methodological challenges common to the field of health economics as a whole

The issues presented in this section, and the recommendations which have been suggested to address them, make up the proposed research agenda on health economic evaluation for the European Union.

7.1 Translational issues: Case studies

The results of four country case studies were presented to highlight practical issues in the translation of health economic evidence into policy. The study countries (Belgium, England, Poland, Slovenia) were selected to represent a mix of income levels, cultural backgrounds and health system designs (multiple vs single payer, presence of institutionalized Health Technology Assessment, institutional processes for health economic evidence use). The following paragraphs recount the main points by country.

Belgium: Rotavirus vaccination

A Health Technology Assessment (HTA) report was the basis of the Belgian case study, describing an economic evaluation of changing the reimbursement status of the rotavirus vaccine from partially reimbursed to fully reimbursed universal coverage. The report concluded that fully reimbursed universal vaccination was more effective and less costly than the present situation of partial reimbursement,

[2] For more information see the RAHEE project website http://www.euro.who.int/en/RAHEEproject

but due to budgetary silos[3] and distribution of funding responsibilities between the federal and regional levels, universal coverage was not implemented.

This case study highlights that even when robust economic evaluations produce recommendations offering potential budgetary savings, the intricacies of individual healthcare systems and budgetary silos can influence the uptake of such recommendations.

England: NHS Health Check Program

In 2009, the Department of Health, which is responsible for health and social care services in England, implemented a preventative public health policy - the 'NHS Health Check Program'. This was aimed at identifying risk factors for vascular disease and preventing their development. Published economic evidence was reviewed and an economic model was built using parameters from the literature review and from experts. The Health Check policy was estimated to be very cost-effective (GBP 3,505/QALY) and the model was used to derive the optimal screening interval and age range.

The main challenges included a lack of evidence on similar programs elsewhere - one of the reasons why a simulation modeling approach was used. The existing cost-effectiveness evidence available for different interventions included in the intervention was also of varying quality.

Poland: Pomeranian Model of Integrated Care for Patients with Severe COPD (PMIC)

COPD mortality in Poland is among the highest in Europe. To address this, the Pomeranian Model of Integrated Care for Patients with severe COPD (PMIC) was started in 2009. The objective of the integrated care model was to limit exacerbations requiring hospitalization, since outpatient care is known to be less costly.

A review of existing economic literature was undertaken, but no formal economic evaluation was performed prior to implementation of the PMIC, although the program was anticipated to be more cost-effective than usual care due to lower rates of exacerbations. This case study emphasizes a number of barriers to performing economic evaluation: lack of institutional support for such evaluations, ie. public bodies with resources and expertise; limited cost data available for interventions; uncertainty around the clinical effectiveness of similar programs internationally; lack of epidemiological data on COPD. Institutional support and guidance on standard methodologies from a European level would be beneficial in encouraging the use of economic evaluation, which may otherwise not be performed for innovative programs in countries with less capacity for economic research.

Slovenia: Slovenian Colorectal Cancer Screening Program (SVIT)

[3] Budgetary silos refer to the strict separation of budgets between departments, organisations etc. where there is no incentive, for example, to invest in measures that generate positive returns in other budgets.

In 2006 the National Institute of Public Health (NIPH) of Slovenia proposed an initiative for colorectal cancer (CRC) screening at the national level. NIPH, together with an economic expert from the Health Insurance Institute of Slovenia and a range of other experts (specialists in Oncology and Gastroenterology), presented the economic benefits of organized, population-wide screening to the Slovenian government. The Slovenian CRC screening program (SVIT) was implemented as a pilot in 2008 and at a national level in 2009.

Comprehensive economic evaluation of health care programs is not considered a priority in Slovenia due to insufficient budget space in the national public health sector. Additionally, data from the Slovenian Cancer Registry are published with a four year delay (due to quality control, obtaining missing values etc.) making it difficult to obtain up-to-date effects of the program. Pre- and post-implementation economic evaluations (2006 and 2010) were produced with different methodologies, e.g. including different input costs, which limits the ability to compare their cost-effectiveness estimates. This example highlighted how lack of human and financial resources, data availability issues and non-standardized methodology can impede economic research.

7.2 Condition specific evidence gaps

The following sections describe both cases where there is limited evidence available, and where existing evidence is of insufficient quality or consistency to inform policy. Some gaps in the health economic evidence exist mainly due to a lack of clinical effectiveness evidence to inform the analysis. Results are presented by condition, and are organized in descending order according to burden of disease in the European Union.[4]

7.2.1 Ischemic Heart Disease

The cost-effectiveness of treatments for ischemic heart disease (IHD) is generally well studied, but less is known about which patient subgroups will benefit from which treatments, e.g. medical management versus stenting. Better stratification would lead to improved outcomes and more cost-effective care.

There is limited health economic evidence concerning strategies of screening and primary prevention of coronary heart disease and stroke. Implementing general screening for heart disease risk would medicalise a wide segment of the general population. Programs that screen the whole population by fixed cut-off will identify predominantly elderly people, who may not be those most likely to develop heart disease or benefit from treatment. In this sense, there is also limited evidence about the evaluation of sequential screening, with the aim of targeting scarce resources where they are most likely to benefit. More attention could be given to the potential benefits and cost of non-pharmacological interventions for prevention of cardiovascular disease in people with no history of prior cardiovascular disease.

[4] Neck pain has been paired with low back pain and therefore appears second in the order, despite having the tenth highest burden of disease.

7.2.2 Low Back and Neck Pain

There is a need for further high quality cost-effectiveness analyses in guideline recommended and commonly used diagnostics and treatments for low back and neck pain in general, such as exercise, different classes of pharmaceuticals, physiotherapy, spinal manipulation and mobilization, and heat therapy.

There is a scarcity of evidence examining the use of surgery vs. conservative care in low back pain, and/or in which subgroups each intervention may be most cost-effective. In addition, there are no cost-effectiveness analyses of competing treatment options for chronic low back pain, only for interventions versus usual care.

The stratification of non-specific low back pain patients according to risk profiles has recently been addressed and shown promising results for cost-effectiveness (1,2), this approach should be further explored.

Understanding uncertainty around cost-effectiveness estimates is central to decision-making, but is often neglected or poorly carried out in the low back pain literature. This can be improved by including appropriate sensitivity analysis, constructing cost-effectiveness planes to graphically illustrate uncertainty around the Incremental Cost-Effectiveness Ratio (ICER), and providing a summary measure of the joint uncertainty of costs and effects through the construction of cost-effectiveness acceptability curves.

Finally, the impact that unnecessary tests (e.g. imaging for acute non-specific low back pain) or ineffective treatments (e.g. prolotherapy) have on cost-effectiveness in real life settings should be examined.

7.2.3 Stroke

There is a paucity of knowledge regarding the optimal configuration of Early Supported Discharge services in terms of staffing levels, grades and multidisciplinary mix, and cost-effectiveness of these services according to patient sub-groups is not well described. Following treatment, there is a lack of long-term follow-up data for stroke patients, which is an important shortcoming as economic evaluation models for stroke are sensitive to quality of life following treatment and rehabilitation.

The cost-effectiveness of early access to highly specialized stroke treatment services is relevant only to urban settings where such services exist, and consequently there is a knowledge gap regarding patients from rural settings. Some services can be delivered remotely, and there is a rapidly growing body of evidence relating to the use of telemedicine and tele-rehabilitation, including some evidence relating to the costs of different modes of service delivery. For example, a virtual reality tele-rehabilitation program for balance recovery has been found to be as effective as clinical care and less costly (3), but the acquisition cost of equipment and how this is factored into the analysis, incl. time horizon choice, may have a bearing on the cost-effectiveness.

Often small, functional improvements are perceived as very important to patients undergoing stroke rehabilitation, but are difficult to objectively measure and account for in cost-effectiveness analyses with current methods. Additionally, given the volume of clinical evidence available the cost-effectiveness of stroke rehabilitation is significantly under-studied. Interest in physical fitness following

stroke is growing, but it is not known whether such interventions are cost-effective, or how to deliver such services most efficiently.

Screening for Atrial Fibrillation (AF) has been shown to be cost-effective in clinical trials of patients aged 65 and above. The following stroke-related questions remain unanswered: Would systematic screening for AF in high-risk groups enhance opportunities for primary prevention of stroke? Would close monitoring of high-risk patients be cost-effective in detecting AF? Which interventions may improve the use of warfarin as opposed to novel anticoagulants (NOACs)?

There are numerous gaps in the cost-effectiveness literature addressing stroke prevention, especially considering multiple risk factors and people at the greatest absolute risk of stroke.

To date, there has not been a systematic appraisal of the costs and benefits of stroke prevention opportunities in different countries using economic analyses that include a broad societal perspective (health sector, labour force and household productivity) and updated risk factor estimates. Most of the focus on stroke prevention examines the strongest modifiable risk factors - hypertension and smoking. While the relevance of these factors is clear, it is unclear whether management of other risk factors may be of equal or better value as investment choices for health policy.

An important challenge in stroke is compliance and adherence to treatments. As the risk of stroke increases sharply with age, lack of adherence in particular can leave patients untreated when they are at greatest risk of events. The long time horizons in stroke prevention also create challenges in terms of drug pricing, in particular future availability of generic equivalents should be factored in to economic evaluations. Finally, the effect of combinations of prevention approaches and treatments is a critical evidence gap. Evaluating the approaches individually poses a risk of substantially overestimating their potential benefits.

7.2.4 Major Depressive Disorder

A relatively large number of economic evaluations have been conducted in the area of depression. These have covered drug treatments as well as psychological therapies, with some studies comparing both. A small number of studies have evaluated electroconvulsive therapy and transcranial magnetic stimulation. The evidence is very mixed, with all four treatment options proving cost-effective in at least one study. Some treatments (e.g. electroconvulsive therapy in severe depression, transcranial magnetic stimulation in refractory depression) were reported to be cost-effective in some studies and non-cost-effective in others. Further primary studies examining Selective Serotonin Reuptake Inhibitors or Cognitive Behavioral Therapy appear unnecessary.

There are gaps in knowledge regarding which medication is likely to be most cost-effective and for which patient groups; which psychological therapy is to be preferred; the cost-effectiveness of exercise for mild or pre-depressive symptoms; and the long-term impact of treatments.

Research priorities also include: long-term head-to-head comparisons of treatments for which there already exists good evidence against usual care using routinely available real-world data; and analysis of the course of depression to enable

prediction, thereby ensuring treatments are targeted at those unlikely to recover naturally.

Further studies on the cost-effectiveness of genetic testing for treatment response are required, and when considering interventions that are supported by extensive evidence and are known to work in treating depression, the next step should be to target patients most likely to respond in order to influence real clinical practice.

7.2.5 Lung Cancer

Most health economic literature addressing pharmacological interventions in lung cancer are funded by pharmaceutical companies, and may be susceptible to bias. In addition, early stage interventions for lung cancer (e.g. surgery, radiotherapy) are under-represented in the economic literature, as is end-of-life care. Studies examining the cost-effectiveness of lung cancer screening should be a priority to assess potential reduced mortality against both high costs of screening (e.g. computerized tomography) and health risks associated with radiation dose. A pilot study is under way in the UK (4).

Areas requiring greater health economic scrutiny include stereotactic radiation treatment, companion (in vitro) diagnostic tests, new robotic surgical techniques and end of life care.

There are gaps in knowledge pertaining to the cost-effectiveness of electronic cigarettes as part of a smoking cessation program, including harms and benefits arising from their use, and smoking cessation interventions targeted at younger people and through brief GP interventions.

Methodological factors requiring attention include the need for robust independent and publicly available cost-effectiveness models for early stages of disease.

7.2.6 Falls

Currently, illnesses that increase the risk of falls have not been comprehensively studied or identified. Falls are often overlooked as an endpoint in studies relevant to elderly populations, and as such there are missed opportunities for gathering evidence. Follow-up periods of studies looking at falls are often too short to capture relevant long-term outcomes which may impact cost-effectiveness, and studies that combine and/or compare interventions rather than studying single interventions are needed.

Economic evaluations should address fall events by underlying cause, thus there is a need to consider falls from a multi-causal perspective. Finally, despite availability of a common definition of falls and guidelines for economic evaluation(5) the definition of ‘falls’ is not used uniformly in all studies, and it is not known how well published studies conform to the guidelines on economic evaluation. Finally, little attention has been given to falls and fall risks over the life course, with the majority of work focusing on the elderly. Some studies have considered falls in children under 5 years(6,7), but economic evidence is lacking.

7.2.7 Chronic Obstructive Pulmonary Disease

Analysis of existing evidence for Chronic Obstructive Pulmonary Disease (COPD) highlighted that there are few health economic studies addressing life style factors for COPD patients, such as behavioural interventions to improve physical activity, and on prevention of COPD over the life course, such as early (adolescent) smoking cessation interventions and brief smoking cessation interventions by GPs.

In clinical management, there is a lack of health economic evidence regarding nutritional supplements for less severe COPD patients. For more severe patients, evidence on overlapping conditions such as Asthma and COPD Overlap Syndrome (ACOS); off-label therapies used in clinical practice for COPD and ACOS (triple-quadruple combination therapies) and oxygen therapy is lacking. There is a paucity of economic evidence on quality of life improvements for existing treatments and on end of life care.

There is also a lack of economic evidence regarding effective integrated care interventions; in the setting of pulmonary rehabilitation programs (inpatient, outpatient home-based); on diagnosis at an early stage of disease where the benefits would be greater (e.g. case finding strategies); and on interventions that improve medication adherence. In addition, quality of life outcomes in the context of integrated care programs are not well studied but required for economic evaluations.

Early HTA engagement is necessary, especially in the realm of new biological drugs for COPD, to ensure novel therapies have the potential to be cost-effective.

There is currently no consensus on whether the additional cost of health gains in smoking cessation interventions, through increased service utilisation over the life course, should be included in cost-effectiveness studies.

Finally, improvements in respiratory outcomes are not well detected by generic quality of life questionnaires and utility measures because questions on (the impact of) respiratory symptoms (breathlessness, cough, sputum production, wheeze) are not included in these instruments.

7.2.8 Diabetes

Better studies of the costs and quality of life losses associated with hypoglycemia and weight gain would allow the side effects of diabetes management to be assessed alongside the impact of glycemic control. Recent studies have indicated that tight glycemic control may be less important and even harmful in older persons with longer durations of diabetes who are already taking more than one anti-hyperglycemic drug. Cost-effectiveness models have not always accounted for this and may not provide guidance on the optimal treatment for these patients.

Favourable cost-benefit for statin use in patients with diabetes mellitus (DM) with End-Stage Renal Disease (ESRD) treated with dialysis is highly unlikely and the cost-benefit of their use on non-dialysis chronic kidney disease in DM is highly uncertain. As such, further investigation should guide dis/investment decisions.

Regenerative medicines that aim to repair, replace and regenerate damaged organs, tissues and cells, often with the use of stem cell therapies, are increasingly being

developed. There is lack of knowledge of clinical effectiveness and economic implications of adipose-derived stem cells (ACS) and the mesenchymal stem cell (MSC) for the healing of venous leg and diabetic foot ulcers.

Following a 2010 systematic review of cost-effectiveness of diabetes treatments (8), several clinical areas were highlighted based on clinical guidelines for diabetes treatment where no health economic evidence was found, as detailed below (treatments referenced in the 2008 American Diabetes Association clinical guidelines for diabetes categorized by level of evidence – A,B,C,E):

- Continuous monitoring of glucose (CMG) in conjunction with intensive insulin regimen (A)
- CMG in children, teens, and younger adults (E)
- CMG as a supplemental tool to self-monitoring of blood glucose in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes (E)
- People with type 2 diabetes should be encouraged to perform resistance training three times a week (A)
- Treatment for hypoglycemia (E, B)
- Annually provide an influenza vaccine to all diabetic patients >=6 months of age
- Administer pneumococcal polysaccharide vaccine to all diabetic patients >=2 years of age (C)
- Multiple drug therapy is generally required to achieve blood pressure targets (B)
- Blood pressure goals of 110-129, 65-79 mmHg in pregnant patients with diabetes and chronic hypertension. ACEI and ARBs are contraindicated during pregnancy (E)
- In most adult patients, measure fasting lipid profile at least annually. For low-risk adults, lipid assessments may be repeated every 2 years (E)
- Lifestyle modification should be recommended to improve the lipid profile in patients with diabetes (A)
- Combination therapy with ASA (75-162 mg/day) and clopidogrel (75 mg/day) is reasonable for up to a year after an acute coronary syndrome (B)
- Coronary heart disease (CVD) screening: in asymptomatic patients, evaluate risk factors to stratify patients by 10-year risk, and treat risk factors accordingly (B)
- In patients with known CVD, angiotensin-converting enzyme inhibitor (C), aspirin (A), and statin therapy (A) (if not contraindicated) should be used to reduce the risk of cardiovascular events
- In patients with a prior myocardial infarction, add beta-blockers (if not contraindicated) to reduce mortality (A)

- In patients >40 years with another cardiovascular risk factor, aspirin and statin therapy (if not contraindicated) should be used to reduce the risk of CVD events (B)
- Metformin may be used in patients with stable congestive heart failure if renal function is normal. It should be avoided in unstable or hospitalized patients with CHF (C)
- Reduction of protein intake in individuals with diabetes and chronic kidney disease (B)
- Diabetes care in hospital settings (C, E)
- Diabetes care in school and day care setting (E)
- Diabetes care in correctional institutions (E)
- Diabetes care in emergency and disaster preparedness (E)

Although some evidence exists in the following areas, additional research is needed:

- Variable screening interval for retinopathy according baseline retinopathy status
- Comparative cost-effectiveness of new and older drugs taking into account;
    - Drugs now with generic prices
    - That the large majority of studies are sponsored and biased studies and that the independent studies are now dated (8 years old).
- Prevention
    - Public health measures to encourage physical activity and weight control, including governmental measures such as tax on calories or fats, encouraging cycling, etc.
    - Targeted intervention at high risk individuals such as those with IGT, where the research need is around motivation. We know that preventive measures work if adhered to.
    - There is limited economic evidence regarding identification of pre-diabetes in otherwise healthy community-living adults.
- Treatment
    - Intensive intervention at diagnosis (e.g. 2 week on an intensive insulin regimen which Chinese studies have shown can restore normal glucose levels for a year without treatment in many patients; or low calorie diets)
    - The use of Sodium-glucose transport proteins (SGLT2) inhibitors, alone or in combination with Metformin, in type 2 diabetes mellitus (T2DM).
    - Captopril (T1DM), Irbesartan (T2DM) and Losartan (T2DM) appear to be cost-effective in management of diabetic nephropathy, but a Quality Adjusted Life Years (QALY) study is needed directly comparing Angiotensin-Converting Enzyme (ACE) vs. Angiotensin Receptor Blocker (ARB) as generic drugs in T2DM with microalbuminuria.

- Lifestyle intensification versus starting insulin in people failing to achieve glycaemic control on 2 or 3 oral drugs.
- The meglitinide analogues

7.2.9 Osteoporosis

There is a scarcity of non-pharmacological health economic evidence, except for calcium and vitamin D supplementation, and the economic impact of behavioural, physical exercise and other nutritional interventions on osteoporosis is unknown. There is a paucity of health economic evaluations regarding devices for osteoporosis, however this is largely due to a lack of clinical effectiveness studies.

Although clinical studies have been conducted and there is adequate data, there is a current lack of head-to-head comparisons or multi-intervention studies to evaluate pharmacological interventions and cost-effectiveness comparisons across treatments. There is additional need for economic evaluation of second- and third-line treatments, entire clinical pathways and generics. Finally, there is a need to better assess the cost-effectiveness of screening (ultrasonometry, muscle function, bone densitometry-blood tests, etc.) and adherence – both in terms of patients adhering to treatment and professionals adhering to guidelines.

Two significant methodological issues pertaining to cost-effectiveness analysis of osteoporosis treatments were identified. Firstly, drug evaluation and supplementation interventions rely on two very well established methods: Micro simulation methods and Markov models. However, there are no well-established methods for assessing behavioural interventions and physical exercise. Second, an integrated approach to bone health across the life cycle should be promoted, with a focus on children and adolescents

Early economic evaluations of novel treatments and dialogue with healthcare payers through Health Technology Assessment (HTA) agencies would benefit both manufacturers and payers by clarifying the level of efficacy new drugs must reach to be considered cost-effective within the willingness-to-pay (WTP) threshold.

7.2.10 Osteoarthritis

Health economic evidence underpinning the use of lifestyle interventions such as weight reduction; physiotherapy interventions such as heat application; intra-articular injections; and cartilage stem cell replacement is lacking. Furthermore, cost-effectiveness analysis of patient stratification approaches and phenotype assessment would highlight which patient groups could experience the greatest treatment effects and thereby influence cost-effectiveness.

Regarding methodological issues, the hard clinical endpoint of joint replacement is atypical, being the point in time where the patient starts to improve due to the joint replacement rather than deteriorate further. Consequently quality of life gains are missed if follow-up does not extend beyond the clinical endpoint, and medications that delay or prevent the need for joint replacement may appear to be less cost-effective. In addition, since an appropriate model for economic assessments of osteoarthritis is not yet available, most of the currently available data can be considered to be of inadequate quality. A model that integrates the various locations

of osteoarthritis (hip, knee, etc.) is needed to incorporate different disease progressions and clinical procedures.

7.3 Methodological evidence gaps

The following sections highlight areas where further research is needed to address broader methodological issues which are relevant across diseases.

7.3.1 Clinical evidence and study design

7.3.1.1 Quality of evidence

The quality of clinical data will influence any economic evaluations resulting from it. To improve adherence to quality guidelines across Europe and globally, guidance for low- and middle income countries should be available taking into account structural challenges such as weaker information infrastructure which makes long-term follow-up and routine data collection difficult.

In some diseases, the majority of economic evaluations come from the manufacturers of the products being evaluated. For example a recent review of cost-effectiveness studies in type 2 diabetes found 81 studies, of which 79 were sponsored by the manufacturers and found in favor of their products, and two were independent and found in favor of older cheaper products.

7.3.1.2 Comparators

Selection of comparator(s) can influence the apparent cost-effectiveness of an intervention and limit comparability between studies. Therefore, when feasible and appropriate, a portfolio approach encompassing all relevant treatment options should be considered. Although not a realistic clinical option, including “doing nothing” as comparator allows evaluation of whether current clinical care is cost-effective, and doing so would be a significant step towards disinvestment in non-cost-effective care.

7.3.2 Real world evidence and early HTA

7.3.2.1 Real-world evidence

Promising results in controlled clinical trial settings often are not directly reflected in routine care. Real-world evidence from registry data and pragmatic trials can be used to offset issues of external validity, but at a cost to internal validity. It is the real-world application that ultimately determines the cost-effectiveness of an intervention, and such data is needed to elucidate which population groups benefit from interventions in real life and which do not.

Methods are needed for generating, synthesizing and incorporating real-world evidence together with other clinical evidence in economic evaluations. The acceptability of such evidence to key stakeholders, including reimbursement agencies, should be explored, particularly if the results of real-world studies contrast those of randomized controlled trials. The sharing of efficacy data and, where possible, real world effectiveness data with reimbursement agencies should be encouraged, in order to facilitate early assessment of whether a given therapy is expected to be cost-effective for the suggested indication. This would be an

opportunity for manufacturers to further explore relevant subgroups or other treatment parameters that could improve clinical and cost-effectiveness in practice, prior to investing in large scale clinical trials.

7.3.2.2 Adherence

Lack of adherence can reduce the effectiveness of treatments and is a particular challenge in long-term treatments and prevention strategies. Qualitative research on contextual factors can provide insight into adherence issues and guide the development of compliance strategies.

7.3.2.3 Early HTA

Using pre-launch real-world evidence for early HTA is currently uncommon, but would provide an opportunity to assess whether a new treatment is likely to be cost-effective, and to re-orient clinical research and/or identify sub-groups where the technology may be more cost-effective.

7.3.3 Measures of cost and benefit

7.3.3.1 Patents, generics and confidential drug pricing

Incremental Cost-Effectiveness Ratios (ICERs) can vary significantly from an initial assessment to the end of a patent. Consequently unit costs of inputs must be reported transparently to allow adjustments for price changes.

A range of prices should be included in sensitivity analyses to reflect future developments. A study estimating the general percent difference between a patented drug and the generic across a range of therapeutic areas could inform this analysis.

Additionally confidential prices and rebates for reference-priced drugs affect the accuracy of cost-effectiveness evaluations.

7.3.3.2 Productivity and indirect costs

Indirect costs are often neglected when dealing with elderly populations beyond retirement age, who contribute to the economy through e.g. informal care, child care and volunteering. Return to education after illness is often over-looked but can significantly impact the life course. Standard and agreed methods are needed to address these issues.

7.3.3.3 Measuring benefit

Patient reported outcome measures may be a particular challenge in certain patient groups, such as those receiving palliative care, recovering from stroke or other severe illnesses, where small functional improvements can be perceived to be very important. Patients experiencing the most significant impacts on quality of life are often the least able to directly report impacts and improvements. There is a need for a broader set of health outcome measures that goes beyond the outcomes captured by a QALY, e.g. indicators such as the ability to live an independent life, loneliness, maintaining societal status, ability to cope, etc. Such measure can be used to study the impact of interventions in the care sector as opposed to the cure sector.

7.3.3.4 Cost-effectiveness thresholds

The applicability of the most widespread form of cost-effectiveness evaluation, yielding incremental cost-effectiveness ratios of new technologies against existing comparators, hinges on the estimation of a cost-effectiveness threshold which should represent the value of care foregone elsewhere in the health system or societal willingness to pay for health improvements. Such thresholds, if explicit, are currently set arbitrarily and the validity of cost-effectiveness thresholds need to be addressed. There is little evidence to suggest that they reflect the true value of care foregone in health systems or a societal willingness to pay when a new treatment is adopted. A cost-effectiveness threshold rooted in sound analysis is a pre-requisite for policy decisions based on economic analysis to be meaningful.

7.3.3.5 Societal perspective

Consensus on what constitutes a societal perspective, and what methods should be used to quantify externalities, requires strong value judgments and is difficult to achieve on an international scale. It would be beneficial to have decision-makers involved in early cost-effectiveness research to ascertain from the beginning what type of information is needed.

7.3.4 Standardized and validated models

A lack of standardization in economic modeling leads to comparability issues across studies. It is also unclear whether outputs from more complex models better predict the impacts of new interventions than simpler and more transparent models, given that data requirements of more complex models are often beyond what is available, which introduces more uncertainty in the results. Simpler models would facilitate transferability and continual updating to include new clinical data.

In addition, a significant body of economic evidence is focused on commercial products and funded by manufacturers, and structural and parameter variations are known to significantly affect cost-effectiveness results. Publicly funded, validated, open-access and open-source economic models would reduce the risk of bias, provide a common platform for economic evaluations across countries, provide a reliable source of information for reimbursement submissions and reduce duplication of effort across countries.

7.3.5 Complex interventions

Similarly treatments which are well studied individually are often not studied as part of complex regimens, either consisting of several treatments for the same condition, or of treatments for multiple, comorbid conditions. The sequence in which individual treatments are given along a pathway of care and cut-off points for changing therapies are often not well understood. There is a need for methods to address the cost-effectiveness of treatments given under these complex conditions.

7.3.5.1 Palliative care

Palliative care is ethically complex and not clinically well defined, which is a challenge for economic evaluation. Methods of assessing palliative care are being explored, including Multiple-Criteria Decision Analysis, but it is unclear what the

acceptability of such methods is to key stakeholders including reimbursement authorities.

7.3.5.2 Prevention, public health and the non-health sector

Health in all policies is promoted as a policy principle, but in many cases health benefits are not modelled as part of interventions with an impact on health either directly or through determinants of health, such as social housing and education. Prevention and public health programs often require multi-sector involvement, which can lead to breaks in circuits of investment and benefit. The economic methods used in other sectors, often cost-benefit or return-on-investment, are generally different from methods used within the health sector, mostly cost-effectiveness including cost-utility. Developments to bridge the gaps between the technical approaches of health and other sectors could encourage wider consideration of health benefits in wider policy evaluations.

Research is needed on whether different sub-groups of patients experience different levels of risk-reduction in public health interventions.

7.3.5.3 Multi-factorial interventions

Interventions with several components such as mixtures of pharmacological and non-pharmacological treatments, and interventions directed at both the patient, healthcare providers and the organization, such as integrated care programs or disease management programs, require a systematic framework for economic evaluation. Multiple-Criteria Decision Analysis could be one approach to evaluate such programs.

7.3.6 Individualized medicine

Discussions from most disease areas highlight that care needs to be targeted to patients that benefit the most, using appropriate risk scores, pathological traits, patient characteristics or other methods of stratification. This improves both clinical outcomes and cost-effectiveness of treatment.

7.3.6.1 Optimizing management of complex cases

For multi-morbid patients receiving multiple interventions concurrently, there is little evidence on the most clinically and cost-effective combinations of treatments. There is a need to develop more sophisticated characterization of complex patients, and to evaluate best treatment strategies rather than drug A versus drug B.

7.3.6.2 Sequencing of interventions

Patients often receive multiple treatments over the course of their conditions, however cost-effectiveness of the overall treatment pathway is rarely considered. There is a need to quantify the stream of costs and benefits for chronic conditions, including sufficient data to determine which patients benefit more from particular sequences.

7.3.7 Operational research

7.3.7.1 Guideline recommended treatment

Cost-effectiveness is often not included, is not transparent, or is not comprehensive in published clinical guidelines. Standardized methodology for incorporating economic evidence into clinical guidelines is needed, and operational research may help generate understanding of how to improve its uptake. Discussions have also highlighted the need to determine cost-effectiveness of current guideline recommended treatments.

7.3.7.2 Service delivery

Operational research could provide valuable input to cost-effectiveness studies in service delivery. There is a reasonable body of evidence on clinical effectiveness in this area, however health economic evidence is often rudimentary. Platforms to combine operational research and economic evaluation could be beneficial.

7.3.8 Disinvestment

The cost-effectiveness of interventions that are already part of health systems can be assessed e.g. in economic evaluations of new technologies by including a hypothetical “doing nothing” or “best supportive care” scenario.

Rather than solely considering whole interventions, disinvestment research should be an integrated element in identifying for which patient groups existing interventions are more or less cost-effective. Disinvestment from low value care should focus on determining for which patients a treatment is inappropriate and how patients can be guided away from such treatments on the pathway of care.

Approaches are needed to identify candidate interventions for disinvestment, such as studying practice variation to identify over-use of certain interventions or consulting professional organizations to list and prioritize interventions for potential disinvestment, both of which are being tried in the Netherlands (Zinnige Zorg (9) and SENEEZ projects). However, resources freed up through disinvestment in low value care do not necessarily translate directly to increased investment in more cost-effective care. Methods need to be developed for identifying what resources are needed, and where these might come from.

7.3.9 Communication of results

7.3.9.1 Transferability

Transferability of economic evidence across settings and countries is complicated by setting-specific baselines, costs, clinical management and reimbursement. Resources considered and unit costs used should be specified to facilitate transferability and re-use of analysis.

Transparency in reporting of effectiveness components in disaggregated forms would also facilitate comparison of analyses across countries.

7.3.9.2 Evidence synthesis

Methods for evidence synthesis need to be investigated. Network meta-analysis allows for comparison of the entirety of treatment options available, not only those that have been compared head to head, but often available clinical trials feature key design differences rendering them unfit for indirect comparisons.

7.3.9.3 Dissemination

There is a disconnect between the language and concepts used in health economic evaluation and by those using the data. Economic evidence presented in a more accessible way could improve uptake in practice.

7.3.10 Funding sources and publication bias

7.3.10.1 Bias of results

Bias in the findings of studies is a pervasive risk both in the health economic and underlying clinical literature. Economic modelling studies, where structural assumptions, disease states included, transition probabilities and other parameter estimates give the modeller a wide range of handles to influence results, may be particularly prone to bias which is difficult for reviewers and readers to assess. Various sources of bias from vested interest (i.e. industry, researcher affiliations, government) exist and must be acknowledged when reviewing the results of a study. Publicly funded, open access models which are validated by relevant stakeholders could help limit the influence of bias. In addition, clinical studies often prioritize internal over external validity, where the latter is more appropriate for economic evaluations. Bias from low external validity could be addressed through increased use of real-world effectiveness data.

7.3.10.2 Bias of evidence availability according to commercial interest

A significant volume of health economic research is funded through commercial interests, and consequently public health and other non-commercial interventions tend to be under-studied.

7.3.10.3 Publication bias

Cost-effectiveness analyses of interventions that were previously found to be effective in clinical trials are more likely to be published than those that were found to be ineffective, where economic evaluation adds little value. This results in an evidence-base on the cost-effectiveness of treatments that is highly influenced by publication bias.

8 Conclusions

The following conclusions encompass the salient points of the expert panel deliberations.

8.1 Translation of health economic evidence into practice

The case studies suggest that country capacity and established institutions are important for the use of economic evidence in practice. In England, a dedicated team of economists within the department of health provided custom economic modelling to support the proposed policy, whereas in the Polish case the economic assessment of a regional health program was undertaken based on existing literature without institutional support. Data availability was a major issue across countries, in particular epidemiological data was not readily available in Poland, and was published with a 4-year delay in the case of colorectal cancer statistics in Slovenia. Cost data were not readily available in Poland.

In all cases, published economic evidence was used as background material or to derive parameter estimates for a custom economic model. Only in the case of Poland was a custom economic model not built and published papers used as the only source of evidence.

The Belgian case study highlights the fact that economic evaluation may not be taken into account if there are budgetary silos which prevent overall efficient spending.

To promote uptake, economic evidence must be available within the same timeframe as policy decisions are made. In some cases sufficient infrastructure and institutional processes exist, in other settings there may be a need for robust but user-friendly health economic tools to improve access to relevant and timely economic evaluation. This could be usefully complemented by a resource book or European level database of existing economic evaluations, curated and interpreted for specific applications such as screening programs.

8.2 Broad directions for health economic research

The expert panel deliberations raised a number of broad directions for health economic research based on both the disease specific and methodological discussions (in no particular order):

Individualized medicine should reflect not only an "-omics" approach but encompass all methods of patient stratification incl. e.g. risk scores and prognoses with the aim of targeting interventions to those that benefit the most. Understanding these nuances also allow more efficient **disinvestment** in services that are of little or no benefit in particular patient groups. Evidence for disinvestment may be further improved by determining the cost-effectiveness of existing and **guideline-recommended treatments**.

Real world evidence is considered a valuable resource for understanding the clinical- and cost-effectiveness of treatments in everyday practice, which is not always evident from clinical trials focusing on optimizing internal validity. There is a need to understand how real world evidence generated pre-launch e.g. through pragmatic

trials can be used by regulatory and reimbursement agencies. **Earlier engagement with HTA agencies** both in the case of real world and traditional clinical evidence would provide an opportunity to assess potential cost-effectiveness of novel therapies, and allow industry to orient additional evidence generation accordingly.

The transferability and generalizability of economic evidence between countries and settings is limited due, for instance, to reporting practices and local inputs. Generalizability is further limited by variations in structure and assumptions of economic models. There are obvious conflicts of interest when economic studies are funded by the manufacturer of a study drug, and there is a risk of **funding bias** particularly in modelling studies where a multitude of design choices and input parameters can significantly affect results. **Standardized economic models**, which are publicly funded, open-access and fully transparent, would help to minimize bias in economic analysis, improve transferability and generalizability of evidence, and reduce duplication of effort for example in reimbursement applications.

Cost-effectiveness thresholds, applied implicitly or explicitly, are intended to reflect opportunity cost when investing in new services under fixed budgets, or societal willingness to pay when there is budgetary flexibility. In practice, however, thresholds tend to be set arbitrarily with little justification. There is a need to determine what such thresholds should be, and how they should be arrived at.

9 Dissemination strategy

The RAHEE dissemination strategy was briefly discussed with the expert panel in order to obtain suggestions of organizations, agencies, individuals and journals with whom project outcomes should be shared. Intended deliverables include a summary report, synthesizing the main results and conclusions from the expert panel, a lay summary of the final report, and an electronic leaflet highlighting key project outcomes. Beginning in May/June, two separate processes of dissemination are planned: an official dissemination to the European Commission, which will also include a meeting with DG SANTE and DG Research, and a parallel stream reaching out to the broader public health community, potentially involving attendance at relevant conferences and scientific publications. Recommendations from the meeting included involving the press for visibility outside of academia, reaching out to patient organizations and special interest groups with MEP members, and preparing papers and/or fact sheets on specific project topics for publication.

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12 Workshop program

Day 1 – Tuesday 3rd February

12:30 - 13:00	**Networking lunch**
13:00 - 13:20	**Introductory remarks**
13:20 - 13:30	**Election of office bearers** • Dr. Roberto Bertollini (WHO Representative to the EU)
13:30 - 13:45	**Adoption of agenda and program**
13:45 - 14:45	**Approach and methods of the RAHEE project** • David Tordrup (Research Fellow, WHO Office at the EU)
14:45 - 15:15	**Break**
15:15 - 17:15	**RAHEE case studies and discussions:** • Slovenia (Nika Berlic, Institute for Economic Research) • Poland (Iwona Damps-Konstanska, Medical University Gdansk) • England (Fiona Thom, Department of Health) • Belgium (Allira Attwill, consultant)
17:15 - 18.00	**Priorities for research emerging from case studies** **Conclusions of day 1**
19.30 -	**Social event**

Day 2 – Wednesday 4th February

9:00 - 9:20	**Summary of day 1**
9:20 - 10.00	**Plenary session: Findings of the RAHEE review and discussion** • David Tordrup (Research Fellow, WHO Office at the EU)
10:00 - 10:15	**Introduction to working groups**
10:15 - 13:00	**Parallel sessions : Identification of evidence gaps and prioritization of research recommendations** **Circulatory and endocrine conditions and depression** (Ischemic heart disease, stroke, diabetes, depression) **Lung conditions, falls and MSDs** (lung cancer, COPD, falls, low back- and neck pain, osteoporosis, osteoarthritis)
13:00 - 14:00	**Lunch**
14:00 - 16:00	**Parallel sessions continue**
16:00 - 16:30	**Break**
16.30 - 18.00	**Plenary session: reports from parallel sessions and prioritization of research priorities**
18:00 - 18:15	**Conclusions from day 2**

Day 3 – Thursday 5th February

8:30 - 9:30	**Summary of day 2**
9:30 - 11:30	**General methodological evidence gaps: identification and prioritization of research priorities for methodology** • David Tordrup (Research Fellow, WHO Office at the EU)
11:30 - 11:50	**Publication and dissemination strategy**
11:50 - 12:30	**Conclusions and Recommendations from the meeting**
12:30	**Sandwich lunch**