Cost-Effectiveness of Very Brief Interventions Promoting Physical Activity: An Application of the Iterative Approach in Decision Making

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Abstract

Economic evaluations are increasingly used in healthcare decision-making. An iterative approach to economic evaluation has been proposed as good practice in which economic evaluations are re-performed as new evidence becomes available throughout the lifecycle of health technology. Decision analytical models play a key role within this process as they provide a structure in which evidence from a range of sources can be synthesised along with Bayesian updating in order to answer the cost-effectiveness problems. This allows the use of the value of information (VoI) methods that help inform further research priority setting.

Physical activity (PA) interventions, in general, are considered good value for money however little is known about the cost-effectiveness of very brief interventions (VBIs) in PA promotion. The thesis aims to explore the feasibility of using an iterative approach to decision-making in the context of the cost-effectiveness of VBIs to promote PA. Using VBI as a case study, this thesis explores the practical and methodological issues of applying an iterative approach to economic evaluation and considers potential reasons as to why the framework has not been widely implemented to date.

Using VBI as a case study provided the opportunity to examine the challenges involved in undertaking an economic evaluation of very brief PA interventions in real time. This thesis explored the feasibility of applying the iterative process to evaluate the cost-effectiveness of VBIs in PA promotion in a time-constrained setting. A decision analytic model was developed at the outset of the thesis and employed iteratively to handle the evolving evidence base of VBIs in PA promotion. Although there are several merits of applying such a framework in real life economic evaluation, in the case of the VBI study, it was not viable to fully exploit VoI analyses and follow the process iteratively.

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List of Abbreviations

BI	Brief Intervention
CBA	Cost Benefit Analysis
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CMA	Cost-Minimisation Analysis
CUA	Cost-Utility Analysis
CVD	Cardiovascular Disease
DALY	Disability-Adjusted Life Year
ENBS	Expected Net Benefit of Sampling
EQ-5D	EuroQol 5-Dimension
EVPI	Expected Value of Perfect Information
EVPPI	Expected Value of Perfect Parameter Information
EVSI	Expected Value of Sample Information
GP	General Practitioner
HSE	Health Survey for England
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IHD	Ischaemic Heart Disease
LYG	Life Years Gained
MET	Metabolic Equivalent of Task
MVPA	Moderate to Vigorous Physical Activity
NB	Net Benefit
NHB	Net Health Benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PA	Physical Activity
PSA	Probabilistic Sensitivity Analysis

PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
RR	Relative Risk
SBP	Systolic Blood Pressure
SMD	Standardised Mean Difference
T2DM	Diabetes Mellitus Type 2
UK	United Kingdom
VBI	Very Brief Intervention
VoI	Value of Information
WMD	Weighted Mean Deviation
WPAI	Work Productivity and Activity Impairment
WTP	Willingness to Pay

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Author's Declaration

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2. Gc V, Wilson E, Suhrcke M, on behalf of the VBI Programme Team. *Development and validation of a decision model for very brief interventions promoting physical activity*. Presented at the 10th World Congress in Health Economics: iHEA and ECHE Joint Congress in Dublin, Ireland, 15 July 2014.
3. Gc V, Wilson E, Suhrcke M. *Are brief interventions promoting physical activity in primary care cost-effective?* Poster presented at the first EuHEA PhD Student-Supervisor and Early Career Researcher Conference (ECR) in Manchester, 2 September 2014.

The research in Chapter 5 has been presented at the following conference:

1. Gc V, Suhrcke M, Mitchell M, Hardeman W, Wilson E, on behalf of the VBI Programme Team. *Cost-effectiveness of a very brief pedometer-based intervention delivered in the NHS Health Checks: economic analysis alongside a randomised controlled trial*. Poster presented at the Public Health England Annual Conference, University of Warwick, 13–14 September 2016.

I declare that this thesis is the original work of the author and that none of the materials contained in this thesis has previously been submitted for a degree in this, or any other, awarding institution. The research contained in this thesis has been undertaken under the supervision of the Research Advisory Group, as direct by the University of East Anglia.

Chapter 1 Background

1.1 Introduction

Economic evaluation provides a framework in which to measure costs and benefits in order to inform decision makers to make informed decisions about the adoption of new technologies, intervention or to decide what represents acceptable value for money (1). In the face of scarce resources, economic evaluation enables decision makers to maximise health gain to the population by ensuring the efficient allocation of resources. Health technology assessment (HTA) organisations such as the United Kingdom (UK) National Institute for Health and Care Excellence (NICE) require cost-effectiveness data in decisions about the reimbursement of health technologies (2). Although the requirement for cost-effectiveness data provides challenges, they provide an opportunity to demonstrate the value for money. In recent years, the use of economic evaluations in healthcare decision-making has increased (3).

Decision making in health care is a dynamic process. The process of decision-making is based on existing information and new information affecting the decision which becomes available throughout the life cycle of all technologies. An iterative framework to economic evaluation has been proposed for the evaluation of health technologies (4,5). Decision modelling is a key process within this framework. The premise underpinning the iterative framework is that rather than using one-off economic evaluation, the process should be iterative throughout the research process. That is from the process of synthesising evidence from a range of sources to populate the decision model and continually updating in order to answer the decision problem (5,6). The use of the value of information (VoI) methods in decision analysis provides the justification for whether future research ought to be conducted and if so, on which uncertain parameters that research should focus (7-10).

This opening first chapter introduces the main academic disciplines underpinning the thesis: the use of economic evaluation to inform decision-makers with a particular focus on decision analytic modelling as a vehicle to economic evaluation and the use of the iterative approach in decision-making. This is followed by a brief background on the applied topic, very brief interventions (VBIs) in physical activity (PA) promotion, used as a case study in this thesis. The following sections explore the grounds for economic

evaluation, both alongside a clinical trial and using a decision model, of healthcare interventions and the use of the iterative framework in economic evaluation. The first section describes economic evaluations, discusses the types of economic evaluations, and a ten step framework for conducting economic evaluations. The subsequent sections describe 'trial based' vs 'decision model' based economic evaluation, use of the iterative framework in decision making, and finally provides an overview of brief interventions in PA promotion.

The main aim of this thesis is to examine the feasibility of using an iterative framework for economic evaluation using the case of VBI study. This thesis further explores the practical and methodological issues while applying the iterative framework in practice to assess the merits and limitations of the framework.

1.2 Economic evaluation in healthcare

There are finite health resources, and the demands for health services are increasing because of unlimited wants or needs of patients. In the face of limited resources (budgetary constraints), decision makers have to decide between alternative interventions or health technologies, deciding which intervention or health technology to adopt. There is often a trade-off between efficiency (how best to allocate resources) and equity (fairness) in allocating resources (11). Economic evaluations facilitate the comparison of two or more alternative interventions that consider both the costs and consequences of alternative interventions (1). They assist decision makers in setting priorities, making resource allocation decisions and designing health services by efficient use of scarce resources.

Economic evaluations are becoming an integral part of modern healthcare evaluation, and their use in healthcare decision-making has increased over recent decades (3,12). They provide a valuable framework to evaluate alternative options or healthcare interventions and enable decision makers to maximise health gain to the population by efficient allocation of scarce resources (13). Economic evaluation can take a number of forms, and the selection of the type of economic evaluation mainly depends on the purpose of the study and may also be influenced by factors such as availability of data on outcomes or target audience.

1.2.1 Types of economic evaluation

There are four types of full economic evaluation used (1: p.11). They are cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-minimisation analysis (CMA). These four forms of economic evaluations approach costs in a common format but vary in terms of how they measure health benefits (outcomes).

In CBA, both costs and benefits are measured in monetary terms, and the analysis reports a net monetary gain (or loss) or a cost-benefit ratio. The CBA decision rule, as to whether or not to select the intervention, rests in the principle of whether the monetary value of additional benefit exceeds the additional cost. That means the intervention in question should be selected if the health outcome benefits are greater than the resource use cost. This type of analysis overcomes the problem of comparing interventions with multiple outcomes as both costs and outcomes are measured in monetary terms. Although this type of analysis offers a sound theoretical form of economic evaluation, its use in healthcare is limited due to practical issues with placing monetary valuations on health outcomes (14).

Cost-effectiveness analysis attempts to identify whether more health benefits can be achieved for a lower cost. Unlike CBA, CEA measures health outcomes in natural units, for example, life years gained (LYG), moving one inactive adult to an active category, or reduction in blood pressure. The results in CEA are presented in terms of incremental costs per unit of health gain known as an incremental cost-effectiveness ratio (ICER). The ICER is calculated by dividing the difference between the costs of two interventions by the difference in the health effects. Although CEAs are relatively simple and straightforward to carry out, this approach is not comprehensive. The analysis cannot incorporate other aspects of health effects such as quality of life into the cost-effectiveness ratio. For example, cost per life-year saved will not capture potentially important aspects of patients' quality of life. A further limitation of this approach is that health interventions with different outcomes cannot be compared. For example, cost per metabolic equivalent of task (MET) -hour gained cannot meaningfully be compared with the cost per cardiovascular event avoided.

The CUA is often seen as an extension of CEA where the health benefit is measured in quality-adjusted life-years (QALYs) gained or disability-adjusted life-years (DALYs) avoided. QALYs and DALYs adjust life expectancy for morbidity, using quality of life and disability weighting respectively (15,16). The advantage of using CUA over CEA is that it allows comparison between, as well as within, healthcare interventions. In CEA, if we are comparing interventions, for example, deaths averted, we can only compare interventions

designed to prevent deaths. However, using generic measures of health-related quality of life such as QALYs, we can make comparisons between interventions, for example, an intervention designed to prevent deaths and intervention designed to increase PA levels. This type of economic evaluation is extremely useful for decision makers because the outcome measure is comparable across disease conditions and interventions. The ICER outcome would be the incremental cost per QALY gained or DALYs averted. However, this approach has challenges, in particular, deriving the health state utilities (17-20) used to facilitate generalised comparison between health states.

CMA is a specific subset of CEA which is utilised in situations where the outcomes of comparator interventions have been proven to be equivalent. Therefore, the least expensive comparator intervention is preferred (21). However, this method has been criticised mainly because it can only compare input costs and has often been used assuming outcomes to be equivalent (22,23). In practice, it ought to be used where there is clear evidence demonstrating clinical equivalence between comparator interventions. Given the heterogeneous nature of study populations and health outcomes, it may not be possible to determine the exact clinical equivalence.

1.2.2 Steps for conducting an economic evaluation

Drummond et al. (24) provide the most well-known and popular framework in health economic evaluation. In the framework, they define ten elements of conducting an economic evaluation. The elements are described below:

1.2.2.1 Define the question in answerable form

A well-designed economic evaluation must define the study question in an answerable form by specifying the interventions being compared, study population, the perspective of the analysis and timeframe of interest. The study perspective is the viewpoint from which costs and benefits of an intervention are evaluated. Specifying the study perspective is important because it defines the basis of analysis and determines the relevant costs that need to be accounted for (25). There are a number of alternative perspectives but can be broadly categorised into healthcare providers, patients and society. The societal perspective is the preferred perspective for an economic evaluation. It involves broader consideration of costs and benefits (26) taking into account both direct, i.e. medical and non-medical, and indirect costs such as productivity costs due to mortality and morbidity, potentially capturing all the financial consequences of the different interventions. The healthcare provider perspective concerns with the costs related to health service delivery whereas patients' perspective include costs incurred by the patient. Although the societal

perspective is recommended for economic evaluation, the choice of the perspective depends on the aim of the study.

1.2.2.2 Provide a comprehensive description of competing alternatives

As the economic evaluation involves a comparison between two or more competitive options (interventions), it is necessary to specify what is being compared with what. A clear description of the relevant comparators included within the analysis allows the decision maker to understand what is being evaluated. Relevant comparators may include the 'current standard practice', 'usual care', or 'do nothing'. The NICE requires the use of the 'best alternative practice' as the most appropriate comparator in economic evaluation (2).

1.2.2.3 Establish the effectiveness of each competing alternative

The evidence on the effectiveness of an intervention may come either from a single study such as a clinical trial or from a good quality systematic review. This depends on the implementation of the economic evaluation that is whether the analysis is trial based or model-based. When the economic evaluation is carried out alongside a clinical trial, the effectiveness evidence is derived from the clinical trial itself. In the model-based economic evaluation, effectiveness evidence is taken from the systematic review or meta-analyses. While establishing the effectiveness of all relevant comparators, particular attention should be given to the risk of bias in the estimate of intervention effectiveness. For example, when the effectiveness evidence of intervention is based on a single study, it is essential to check whether the evidence base is representative of the whole body of the evidence base for the comparators concerned (24). Likewise, when the effectiveness evidence is taken from a systematic review or meta-analysis, it is essential to clearly state the reasons for inclusion or exclusion of a particular source of evidence. A well-designed randomised controlled trial (RCT) provides less biased evidence than observational studies. Further details on trial and model-based economic evaluations are provided in sections 1.3 and 1.4 respectively.

1.2.2.4 Identify all the important and relevant costs and consequences for each comparator

The choice of the perspective of the economic evaluation determines which costs and benefits to include in the analysis. All likely costs and benefits of an intervention should be defined as comprehensively as possible and be consistent with the chosen perspective. The costs can be divided into direct (health service), indirect (non-health

service) and intangible costs. Direct costs are those immediately associated with an intervention such as nurse time, consumables, treatment, hospitalisation and medication as well as may include patients' out-of-pocket expenses (e.g. travel costs). Indirect costs are those incurred by the reduced productivity resulting from illness (morbidity cost), death or treatment (mortality costs). Intangible or non-resource costs are the costs related to issues such as pain, anxiety, deterioration of the quality of life in a patient. The benefit, or intervention effect, could be an intermediate effect (number of sedentary people becoming active, lowering blood pressure), survival effect (life-year saved), utility effect (QALYs, healthy-year equivalents) or an economic benefit.

1.2.2.5 Measure all costs and consequences accurately in appropriate physical units

Once the costs and effects of the intervention are identified, the next step is to approach measuring the likely costs and benefits of intervention as comprehensively as possible. All the relevant costs and benefits of an intervention must be measured in an appropriate physical unit such as hours of staff time and number of General Practitioner (GP) surgery visits. If the economic evaluation is being conducted alongside clinical trial prospectively or retrospectively, healthcare resource use data can be collected using mechanisms such as resource use questionnaires, medical records, case report forms, interviews or diaries. Resource use questionnaires are either filled in by patient themselves or completed by research staff. To assess patient medical notes, appropriate approvals should be in place. When the economic evaluation is conducted in retrospect, cost data are estimated using questionnaires.

1.2.2.6 Value the cost and consequences credibly

When prices are available, it is relatively easy and straightforward to value resource use. The cost of an intervention is simply the amount of resources used multiplied by the unit cost (27). Various sources exist for standard costs related to health service delivery such as the National Health Service (NHS) reference costs, and the Personal Social Services Research Unit (PSSRU) unit costs for GP and community-based services (28). These standard costs are usually the average costs and should be used with care, for example by carrying out sensitivity analysis (further discussed in section 1.2.2.9). However, sometimes the prices for goods and services may not exist (for example leisure or volunteer time), and the prices available may not reflect the societal value of resources. In such a case, there needs to be some sort of adjustment made to approximate market values. This is especially important while making comparison across studies. One method

of valuing these items is to use market wages however this could be problematic while valuing leisure time as people are not generally paid for their leisure.

One strategy is to value the changes in resource use however this approach requires substantial time and efforts and runs the risk of being specific to the particular context. Another approach is to use gross costing, the top down costing, which simply divides the total budget allocated by the number of participants to arrive cost per participant.

1.2.2.7 Adjust costs and consequences for differential timing

The measurement of costs and benefits may not occur within one time period. There may be more than one intervention and may have different time profile for costs and benefits, for example, the costs of PA intervention are incurred in the present but the benefits of PA interventions such as reduced risk of stroke will occur mostly in the future. Thus there needs to be an adjustment for timing between costs and benefits. Moreover, individually and as a society, we prefer to have money or resources now, as opposed to later (24). Adjusting costs and benefits for differential timing allows comparability between competing interventions. The concept of discounting allows adjustment of all future costs and benefits to their present value. In the UK, the Treasury recommends that the costs and benefits of the programme be discounted at an annual rate of 3.5% (29).

1.2.2.8 Perform an incremental analysis of costs and consequences of alternatives

In economic evaluation, an incremental analysis of costs and benefits is necessary to make a comparison between competing interventions. The incremental analysis examines the additional costs and benefits between two interventions and combined into an incremental cost-effectiveness ratio (ICER). The ICER is calculated by dividing the difference in costs between two interventions by the difference in health benefits (Equation 1-1).

$$\text{ICER: } \frac{C_1 - C_0}{E_1 - E_0} = \frac{\Delta C}{\Delta E} < \lambda \qquad (1\text{-}1)$$

Where C_1 is the cost of new intervention; C_0 is the cost of usual care or a comparator intervention; E_1 and E_0 are the consequences (health benefits) of new and the comparator intervention respectively; ΔC and ΔE are the increments (changes) in cost and health benefits respectively; λ is the society's willingness to pay threshold.

A larger ICER value equates to a greater cost per unit of health benefit; therefore the intervention is less cost-effective in comparison to the comparator intervention. This value should be compared against a monetary threshold of maximum willingness to pay (λ) for a unit of health benefit. If the ICER value is less than or equal to the threshold value (λ) then the intervention is considered to be cost-effective in comparison to the alternative intervention. In the UK, NICE strongly recommends a cost per QALY threshold value of £20,000 to £30,000 (2). There have been debates, and a number of calls for further research on the value of threshold (30,31) as the current threshold has not changed in the NICE methods guidance since 2004. Recently Claxton et al. (32) estimated the threshold value to be just under £13,000 per QALY in the English NHS in 2008-09. However, the methods used for new estimates of the threshold ICER have been debated (33).

A fundamental principle of decision theory is that an individual seeks to maximise his or her expected utility or payoff (1). The policymakers and health economists within the context of economic evaluation use similar criteria putting forward net benefit (NB) as the appropriate measure of this payoff (34). This can be shown by a simple rearrangement of cost-effectiveness decision rule as presented in Equation (1-2). The net benefit is the value of the benefits of a course of action less the cost of any consequences; the incremental net benefit (INB) is the difference in net benefit between two courses of action. In other words, the net benefit approach monetises the health benefit by multiplying the measurement of health benefits by a threshold value. Alternatively, if we rearrange the ICER to express inequalities on effect, it gives the net health benefit (NHB) (35,36) as illustrated in Equation 1-3.

$$\text{INB: } (\lambda \times \Delta E) - \Delta C > 0 \qquad (1\text{-}2)$$

$$\text{NHB: } \Delta E - (\Delta C/\lambda) > 0 \qquad (1\text{-}3)$$

The net benefit framework makes comparisons between more than two interventions easier because the NBs for individual interventions can be calculated. In addition, it overcomes the difficulty in calculating confidence intervals for the ICER (36). The decision rule is to adopt the new intervention if the INB is positive. When more than two interventions are being compared, the decision rule is to adopt the intervention with the highest NB.

1.2.2.9 Undertake analysis of uncertainty

Regardless of whether the economic evaluation is based on a single clinical trial data or a decision analytic model, the results will be subject to uncertainty. Analysis of uncertainty

is thus essential to give confidence in the results. The uncertainty can arise from many sources and can relate to individual variability, heterogeneity, or uncertainty in methodology, model structure, model parameters or in decision itself (37,38). Variability which is also called the first order uncertainty refers to differences that are found by chance. Heterogeneity refers to differences between characteristics of the study population that can be mostly explained such as age, gender and ethnicity.

In economic evaluations, decision models aim to capture uncertainty in the estimates of means and associated standard error of the mean. Variability and heterogeneity are not the subjects of analysis of uncertainty. In RCTs, sampling variation is typically dealt through randomisation and analysis of baseline statistics such as calculation of 95% confidence intervals (CIs). Heterogeneity is assessed by considering various study population subgroups. It allows an assessment of whether the study outcome is influenced by these subgroups.

Uncertainty within decision models can be classified into parameter uncertainty, methodological uncertainty and structural uncertainty (39). Parameter uncertainty refers to uncertainty in the point estimates used to reflect specific parameters in the model such as intervention effect. On the other hand, structural uncertainty refers to uncertainty in the relevant clinical pathways included in the model which is associated with costs and outcomes. The methodological uncertainty exists in at least two levels, first in the process of synthesising the evidence to inform decision models and second in the choice of modelling methods.

Sensitivity analyses are performed to examine the impact of uncertainty in model inputs. Sensitivity analysis refers to the process of varying model input values and recording the impact of those changes on the model outcome i.e. cost-effectiveness results. Five different types of sensitivity analyses are reported in the literature: one-way (univariate) sensitivity analysis, multivariate sensitivity analysis (scenario analysis), threshold analysis, analysis of the extreme case (worst-and best-case scenario), and probabilistic sensitivity analysis (40,41). Details on handling uncertainty in the decision model are further discussed in section 1.4.5.

1.2.2.10 Presentation and discussion of study results

While presenting the results of an economic evaluation, it is important to evaluate whether the conclusions of the analysis incorporated all relevant considerations. Cost-effectiveness results can guide decision-making but are not a decision itself. Decision making is a complex process which needs to take into account several aspects while

evaluating the economic evaluation results. The summary indices from the economic evaluations such as cost-effectiveness ratios are helpful in decision-making process but should be used with care by critically examining the output. Some economic evaluations may report more than one summary index, e.g. cost per additional person being active, and cost per QALY gained for a PA intervention.

The above mentioned Drummond et al. (24) framework provides a guide to how to organise an economic evaluation. However, there are limitations to this approach. Firstly, this approach does not take into consideration the costs and consequences of a wrong decision (42). Economic evaluations also often exclude the importance of distribution of costs and consequences among different patient groups into the analysis. In addition, there are various forms of economic evaluation (as described in section 1.2.1) which value health outcome differently. Decision makers should be aware of these considerations when selecting a particular type of analytic technique (1).

In healthcare, economic evaluations can be undertaken by taking a prospective or retrospective approach. In the trial based evaluation, economic evaluations are conducted prospectively alongside RCTs whereas in decision modelling, mathematical models are used to synthesise existing evidence retrospectively in order to evaluate the interventions. The following sections describe these two approaches to economic evaluation in healthcare.

1.3 Trial based economic evaluation

Clinical trials are often viewed as the ‘best vehicle’ for economic evaluation (43,44). They not only provide the best chance of ensuring internal validity through a prospective collection of patient-specific data but also provide an opportunity to collect additional data, for example, economic data, with a low marginal cost alongside clinical data (45). Use of intervention effectiveness data directly from a rigorously designed clinical trial helps overcome the issue of selection bias (46). To maximise the potential benefit of conducting economic analyses alongside clinical trials, it is essential to incorporate an economic component into the study protocol. This allows statistical analyses on cost, effectiveness and quality of life data. Glick et al. (27) set out a methodology for undertaking economic evaluation alongside clinical trials and specify some ‘gold standard’ characteristics for an economic evaluation as part of a clinical trial to strengthen the design of research and improve the quality of an economic evaluation.

In recent years, there are advances in design, conduct and analysis of trial-based economic evaluation such as developments in improving external validity of trial-based cost-effectiveness analysis, use of VoI analysis for sample size calculations. In addition, there are various guidelines available for conducting and reporting such studies (45,47). However, there remains a great deal of variation in methodology and reporting of such studies (48,49). In experimental studies, economic analysis is rarely the primary purpose of the study. Sample size in clinical trials is determined to detect primary clinical intervention effects; and as a consequence, a trial may not be powered enough to detect economic outcomes (intervention cost-effectiveness) (50).

It may not be possible to compare all relevant alternatives from a single trial. For example, PA interventions have both short-term (e.g. improvements in mood) and long-term (e.g. reduction in stroke risk) health benefits (51). It may be difficult to measure these benefits from a single trial thus often requires a modelling component to estimate the overall change in health-related quality of life and quantity of life as a result of the change in PA level to extrapolate primary data beyond the short-term endpoint of a trial (46).

1.4 Decision analytic modelling

In contrast to trial based economic analysis, economic evaluation can be conducted retrospectively by utilising the existing evidence on resource use, cost, intervention effectiveness and quality of life. Decision models provide a framework to synthesise evidence on health outcomes and costs from a range of sources. A decision model can be defined as a logical mathematical framework that synthesises evidence on clinical and economic outcomes, and aids decision making about clinical practices and healthcare resource allocations (52). They play an important role at each stage of the economic evaluation process (53). Briggs et al. (54) proposed six distinct stages of a framework incorporating decision analytic modelling into economic evaluations. These involve specifying the decision problem, defining the model boundaries, specifying the model structure, identifying and synthesising evidence, dealing with uncertainty, and assessing the value of additional research. These key components are discussed below:

1.4.1 Specifying the problem

The first step involves clearly defining the question that needs to be addressed in the analysis. Usually, in an economic evaluation, the new intervention is compared to a control or ‘current practice’ or ‘standard care’, however, the evaluation may involve more than two

interventions which should be clearly specified. The outcome measure of the study should be defined.

Moreover, disease area of interest, study population and the study setting to which it relates should be specified. The perspective chosen should be specified as this affects the type of costs and outcomes to include in the analysis. For example, the health system perspective includes costs related to health service delivery but societal perspective includes indirect costs incurred by patients and carers on top of the healthcare costs.

1.4.2 Defining model boundaries

This stage involves considering what is relevant and not relevant to be included in the analysis. Decision models are simplified reflection of reality, and it is not possible to include all the potential consequences of the particular option being considered (54). Thus, it is essential to clearly state the scope of the model which refers to its limitations or boundaries. For example, either the outcomes are modelled over the patients' lifetime or shorter duration. This also influences what disease conditions to include in the model. While defining the boundaries, the potential impact of inclusion or exclusion of relevant factors on costs and outcomes should be considered.

1.4.3 Structuring a decision model

Once the decision problem is specified, and model boundaries are defined, an appropriate model structure should be determined. The availability of data plays a significant role in determining the structure of the model (55). Brennan et al. (56) suggested that practical considerations such as availability of data (e.g. natural history of the disease, clinical pathways, intervention effectiveness evidence, health state utilities and costs), the background skill of the researcher and type of software available also have a considerable role in determining the model structure. There are several guidelines for good research practices in modelling (55,57-61), and these guidelines focus mainly on transparent structure, appropriate and systematic use of evidence, and handling uncertainty.

Economic models use two common approaches, aggregate or 'cohort' models and individual-level models also called patient-level simulation, to estimate the expected costs and outcomes (56,58). In a patient-level simulation, the cost and health outcomes are modelled for individual patients. While in a cohort-level model, the health and cost outcomes are modelled for the cohort as a whole, and this does not consider the outcomes for individual patients within that cohort. The patient-level simulation accounts for variability in all included parameters which can be characterised with empirical

distribution. The models often used in the economic evaluation are the former cohort models. Microsimulation models use mathematical equations to simulate the behaviour of an individual taking into account the heterogeneous composition of the target population without focusing on a representative or average individual.

Decision Trees are the simplest and most familiar structures. They are graphical models that map patient pathways, assign costs and outcomes to alternative pathways throughout the tree and useful for short-term analyses (61). However, they have limited use for modelling complicated disease conditions involving longer time period. As the decision options increase over time, the size of the tree becomes unmanageable. In addition, they lack an explicit time variable.

Markov models are increasingly used in economic evaluation as they overcome the limitations of decision trees. It is possible to model the complicated disease conditions using Markov model over a time period as they can deal with the pattern of recurring disease over time. They involve a transition between various health states and outcomes over time (53). The main limitation with this approach is that they do not account for the history of progression in the model.

Discrete event simulation (DES) models are another type of models that use a stochastic process to simulate time-dependent behaviour of a system. The three components included in the DES are entities, event and time (62). Entities refer to the items that evolve through the simulation such as patient characteristics. These values are defined at the start of the simulation and may be updated as required: for example, age increases, disease severity may increase or decrease. An event is anything that can occur during the simulation such as an adverse event, remission from the disease, and events can occur sequentially, simultaneously or both. Events can be dependent on any attributes such as patient characteristics, and the function of an event can change over time as appropriate. Time is the fundamental component of a DES and makes handling time much more flexible compared to the Markov model.

The selection of the particular type of model structure and complexity requires decisions about descriptive realism, computational burden, data requirement and usability (63).

1.4.4 Identifying and synthesising evidence

This stage involves a systematic approach to synthesise all the relevant evidence from a range of sources in order to inform the decision model. This involves combining data on intervention effects, clinical events, health state utilities, resource use or unit cost

information. Ideally, the evidence on intervention effectiveness should be from an RCT. In the absence of head-to-head randomised controlled trials, evidence from a well-conducted meta-analysis of RCTs with direct or mixed treatment comparison has been proposed as the least biased source of data to inform clinical effect sizes, adverse events and complications parameters in the model (64). Clinical event parameters used in the model tend to be probabilities, which are simply the likelihood of an event occurring in a given time period and the value always lies between zero and one. However, epidemiological studies often report rates rather than probabilities. Rates refer to the number of occurrences of an event for a given number of patients per unit of time and range from zero to infinity. Probabilities and rates differ in terms of how they account time. It is possible to convert rates to a probability over a specified time period. This assumes that the rate to be constant over a time period (65). Equation (1-4) details how the probability (p) can be calculated given the instantaneous rate (r) and time period (t) is assumed to be constant:

$$p = 1 - e^{rt} \quad (1\text{-}4)$$

As the parameters in the model are assigned from various sources, there are issues related to different follow-up times and intervention comparison. To deal with this issue, there are a variety of methods including indirect and mixed comparisons and meta-regression to synthesise the evidence from multiple sources (66).

1.4.5 Handling uncertainty and heterogeneity

Economic evaluations are subject to uncertainty because they are concerned with estimating the expected future costs and outcomes of competing interventions irrespective of whether they are based on decision models or informed by a single clinical trial. It is necessary to identify the sources of uncertainty that can impact upon the cost-effectiveness results. Uncertainty in the decision model presents in many forms, and they need to be dealt with differently (38). Uncertainty can be related to sampling variation, heterogeneity, parameter uncertainty, structural uncertainty, methodological uncertainty and decision uncertainty.

Much of the evidence synthesis in economic modelling is obtained from observational or experimental studies. In these studies, data are captured for a subset of a population of interest. Well designed and rigorously conducted studies such as pragmatic RCTs provide unbiased estimates of clinical outcomes. Randomisation gives an unbiased comparison between intervention groups as it controls for both known and unknown factors which yield

intervention groups that are balanced with regard to prognostic variables (67). Handling variability and heterogeneity were discussed earlier in section 1.2.2.9.

Decision models require input parameters that need to be carefully estimated in order to appropriately characterise parameter uncertainty. Parameter uncertainty refers to the uncertainty in the point estimates used to reflect specific inputs to the model. Uncertainty in parameters can be dealt deterministically through univariate, multivariate or probabilistic sensitivity analysis.

In univariate (one-way) sensitivity analysis, the value of a single parameter is changed at a time whilst holding the values of other parameters constant, and the impact on the predicted costs and outcomes are observed. However, this approach assumes that there is no causal relationship between the value taken by one parameter and the value taken by other parameters. Threshold analysis is a specific form of one-way sensitivity analysis. It considers what value a specific parameter must take in order to achieve a target result, for example changing values of treatment effect to set an ICER equal to the threshold value.

In multivariate sensitivity analysis, two or more parameters are varied at once, and the impact of the different combinations of changes on the model output is examined. Although this approach allows more than one parameter to change at a time, it becomes infeasible as the number of parameters used in the model increases. In addition, multivariate sensitivity analysis treats all possible combination of parameter values as equally valid which is likely to be conflict with the underlying relationship. As a result, there is a chance of misleading decision makers unless a set of specific parameter values are accessed for their face validity and are relevant to the decision problem. This is also called a scenario analysis. Another form of this analysis is the analysis of extremes, also known as worst-best case analysis which looks at the impact on results by setting one or more parameters at the highest or lowest possible value.

Probabilistic sensitivity analysis (PSA) is used to adequately address parameter uncertainty in the model (38). This method assigns an appropriate distribution to each parameter used in the model and allows the value of each parameter to be varied simultaneously. The values of parameters are drawn randomly from each distribution. Then the outputs of the model for each draw are recorded. By repeating the process of drawing parameter values from the distributions and capturing the model outputs gives the probability distributions for costs and outcomes of the interventions being compared.

Methodological uncertainty arises due to the choice of the modelling approach. In cost-effectiveness models, this exists at least two levels: first in the process of synthesising evidence to populate the model, and second in the choice of modelling methods. There are good practice guidelines for decision analytic modelling (55,57) which help to address methodological uncertainty. Structural uncertainty relates to the uncertainty associated with structuring the model (68,69). It refers to the differences in the model output as a result of the inclusion or exclusion of a clinical pathway in the model.

Handling decision uncertainty using PSA is discussed in more detail in Chapter 3.

1.4.6 Assessing the value of additional research

Decision models provide a framework within which it is possible to begin an assessment of the cost-effectiveness of additional research. Assessing the value of additional research is also an important component of the modelling process. The value of information (VoI) analysis is an economic approach to setting research priorities that puts a value on reducing uncertainty. The VoI analysis has its origins in the work of Raiffa and Schlaifer (70) in statistical decision theory.

Decisions based on existing information will be uncertain, and there will always be a chance of making the wrong decision. If the wrong decision is made, there will be costs in terms of health benefits forgone. The expected cost of uncertainty is determined jointly by the probability that a decision based on existing information will be wrong and the consequences of a wrong decision (71,72).

In recent years, interest has grown in healthcare decision making to apply the VoI concept (73). Pilot studies have been undertaken to inform the prioritisation process within the NICE Health Technology Assessment (HTA) programme (72,74), and published economic evaluations are increasingly reporting VoI analyses (75-81).

1.5 Overview of using an iterative approach in decision making

The above sections provide an overview of economic evaluation and decision analytic modelling. Decision models play an important role in evaluating the cost-effectiveness of a healthcare programme or intervention beyond the duration of a clinical trial. The process of decision making in health care is based on currently available information, and new

information affecting the decision becomes available throughout the life cycle of all technologies (5). The process of decision making in health care is not static because each decision has to be reviewed once new information is available. An iterative framework to economic evaluation of health technologies has been suggested beginning with early indicative studies and progressing towards more rigorous assessment as data become available (4,5,43).

Sculpher et al. (4) and Fenwick et al. (82) outlined an iterative framework for economic appraisal and the use of models to prioritise research. They outlined an iterative process that starts with defining a decision problem, followed by a review of existing evidence on cost and effectiveness. The synthesis of evidence from the literature review leads into a decision model. The decision model requires input parameters that need to be carefully estimated in order to appropriately characterise parameter uncertainty. Probabilistic sensitivity analysis for exploring uncertainty in parameter estimates and the model (38), and the VoI analyses (8,42) are ideal tools for facilitating such an iterative process.

The VoI statistics are the expected value of perfect information (EVPI), the expected value of sample information (EVSI), and the expected net benefit of sampling (ENBS). The expected value of information approach uses a decision analytical framework in order to prioritise further research through identifying those areas in which additional data collection and hence the reduction of uncertainty (13) would be of most value. The expected benefit of eliminating all parameter uncertainties, since perfect information would eliminate the possibility of making the wrong decision, is called EVPI. In other words, EVPI is the difference between the expected value of decision with and without perfect information (36). EVSI is the technique used to estimate the value of obtaining information from a study of sample size n (83). It is the difference between the expected value of a decision after the purposed research with sample information and the expected value of the decision made with current information (7). ENBS is the difference between EVSI with sample size n and the cost of conducting the research with sample size n (42,83). The data collection is only valuable though if the expected cost of the data collection is less than the expected value of the information it yields, i.e. if the ENBS is greater than zero.

The EVPI places an upper bound on the returns to future research. The EVPI surrounding the decision problem can indicate whether further research is potentially worthwhile. The data gathered from primary research are then fed back into an updated systematic review, and the cycle is then repeated (42,83,84). The VoI methods play an important role within an iterative framework of economic evaluation as they help in identifying the focus of further research (research prioritisation) and the appropriate research design (82).

However, methodological and technical challenges such as high computation demands have limited the use of VoI methods in future research prioritisation (85). In addition, it is not clear how this iterative process has been applied in real life economic evaluation where decision makers (such as NICE) and research funders are separate bodies.

The section below now provides an introduction to VBIs in physical activity promotion and the VBI study used as a case study in this thesis.

1.6 Very brief interventions promoting physical activity

Physical inactivity is one of the leading risk factors for global mortality, accounting for 6% of deaths globally (86). Incorporation of physical activity into daily life is known to lead to health benefits such as reduced risk of coronary heart disease (CHD), stroke, type 2 diabetes, cancers, and premature death (87-91). In developed countries these diseases and conditions attributable to physical inactivity account for 1.5–3% of total direct healthcare costs (92). In their recent systematic review on the economic burden of physical inactivity in populations, Ding et al. (93) estimated that healthcare costs attributable to physical inactivity range from 0.3% to 4.6% of national healthcare expenditure. The UK Department of Health and Social Care estimated the societal cost related to physical inactivity in England at £8.2 billion a year (87). This estimation includes the direct costs of treating diseases linked to physical inactivity such as type 2 diabetes and cardiovascular diseases and indirect costs caused through sickness absence.

There are a wide range of interventions to increase PA across the life course (94-96), and some of these interventions are considered cost-effective (97,98). In recent years, there has been substantial emphasis on efforts to promote PA along the continuum of individual-level and population-based interventions (99). Recent systematic reviews and meta-analyses of both randomised and non-randomised studies have shown that PA interventions such as brief exercise advice and physician counselling can significantly increase PA behaviour and fitness in the longer term (100-102).

Brief intervention (BI) is a generic term used to define an intervention delivered in a relatively circumscribed time and is considered an important tool to prevent multiple risk behaviours (103). However, the nomenclature for BIs vary in the literature (104). Usually, they refer to simple advice, brief advice, brief counselling or minimal intervention. Brief interventions are well researched in substance misuse (alcohol consumption, tobacco and

other substance misuses) and provide evidence that BIs work for these conditions (103-106) and are cost-effective (107-109). BIs range from a single session providing brief advice to multiple brief sessions of motivational interviewing or behaviour change counselling and are of short duration lasting between 5 to 30 minutes (110,111). BIs are typically conducted in face-to-face sessions with or without the addition of written materials. NICE (112) defines BIs as “those involving opportunistic advice, discussion, negotiation or encouragement”.

VBIs are very short in duration taking up to five minutes although there is no clear definition as such. VBIs need not take extra time and can be delivered as a part of a routine healthcare consultation. The evidence base for BIs in PA promotion suggests that brief exercise advice delivered in primary care (101) setting increases physical activity. In their systematic review of reviews Lamming et al. (113) reported that BIs can increase short-term self-reported PA, but there was uncertainty about the long-term impact of BIs on PA level.

Currently, in England, all adults with no diagnosis of chronic disease, i.e. those without a pre-existing condition of stroke, heart disease, type 2 diabetes or kidney disease, and who are not currently being treated for certain risk factors (114), and aged 40-74 years are invited to receive a free ‘health check’, referred as the NHS health check. Eligible participants receive a letter from their General Practitioner (GP) or local authority inviting them for an NHS Health Check every five years. The health check is delivered either by a GP, a practice nurse or an alternate provider, e.g. pharmacist (115). The NHS Health Check is free of charge including any follow-up tests or appointment and takes about 20 to 30 minutes (114).

The main aim of the Health Check is to prevent the risk of developing vascular diseases and raising awareness of dementia for those aged 65 to 74 (116). During the Health Check, healthcare professional performs basic checks by asking questions related to family history of illness being checked for, smoking, alcohol risk assessment, diet and physical activity assessment. In addition, healthcare professional measures participant’s body mass index (BMI), blood pressure, and takes a small sample of blood to check cholesterol and blood sugar levels. After the Health Check, participants are given a risk score, i.e. the risk of developing a heart or circulation problem over the next ten years. The risk score is calculated using the QRISK2 algorithm (117).

The majority of people in the 40-74 age group do not meet the minimum recommended level of PA, i.e. 150 minutes of moderate intensity or 75 minutes of vigorous intensity activity per week (118). NHS Health Check thus provides an ideal opportunity to deliver

brief advice or other BIs to a larger proportion of the population. VBIs to increase PA are likely to be beneficial for all adults eligible for NHS Health Check in the UK (115,119). Although (very) BIs may have a small effect at the individual level however if a large population is positively affected, this could translate into a significant public health benefit (120).

The VBI Programme was a five-year research programme funded through a programme grant from the National Institute for Health Research (NIHR). The programme aimed to develop and evaluate VBIs to increase PA that could be delivered by a practice nurse in a vascular check or other primary consultation.

1.7 Statement of study problem

Sections 1.2 to 1.5 outlined the iterative framework in decision making and section 1.6 provided an overview of the VBIs in PA promotion. The iterative process of decision making provides the justification for whether future research is conducted and if so, on which uncertain parameters, and provides an estimate of the appropriate sample size for such a study. However, practical application of this in the area of VBI is limited. Although BIs are considered cost-effective in other domains of public health such as smoking cessation and alcohol misuse, there is a dearth of economic evidence in PA promotion (121). Compared with more complex PA interventions, VBIs can be easily integrated into routine healthcare consultation and are inexpensive to implement on a large scale.

The VBI study provided an ideal opportunity to start further research by applying iterative decision-making theory in practice. This will allow using VoI methods to determine the value of future research in this area. The main aim of this thesis is to examine the feasibility of using an iterative framework for economic evaluation using the case of the VBI study. This thesis further explores the practical and methodological issues while applying the iterative framework in practice, merits and limitations of the framework, and consider potential reasons as to why it has not been widely implemented. To answer these questions, this thesis uses:

a. decision analytic modelling and PSA to assess the relative cost-effectiveness of promising VBIs in terms of incremental cost per QALYs gained,
b. expected VoI techniques to determine the value of collecting further data on input parameters, to help guide the design of a primary data collection exercise, and

c. update the decision model with the data gleaned from the VBI trial, and so update the policy recommendations regarding the most cost-effective VBI and the value of future research.

1.8 Thesis overview

This thesis is organised into six chapters. The first chapter introduces the key concepts in economic evaluations of health interventions including the background of an iterative approach in economic evaluation and brief interventions in PA promotion, the rationale of the study, the aim and objective and the way the thesis has been organised. Hereunder a brief description of the subsequent chapters is provided.

Chapter 2 presents a background and overview of the literature regarding the cost-effectiveness of brief PA interventions. The chapter discusses the current evidence on the cost-effectiveness of brief PA interventions in primary care or community setting. This literature review chapter summarises economic evidence – both within trial and model-based economic evaluations – relating to BIs promoting PA. The particular issues with existing economic evidence are drawn out, about the long-term costs and health outcomes associated with such BIs.

Chapter 3 starts expanding section 1.5 that is describing the stages of the iterative approach in decision making followed by a critique of such approach. The second part of the chapter includes a literature review on the use of VoI in an iterative framework in decision making to inform further research. The review aims to explore how the VoI methods are used within an iterative framework to inform further research. Finally, the chapter ends with a summary of how VoI methods are used in real life economic evaluations within the iterative framework.

Chapter 4 uses the modelling approach to evaluate the cost-effectiveness of VBIs in PA promotion. This chapter corresponds with stages 2 and 3 of the iterative approach in economic evaluation, involving the development of a decision analytic model-based on existing evidence to undertake an economic evaluation of VBIs. This analysis determines whether VBIs in PA promotion are cost-effective or whether further research is needed to make an informed decision. This builds on the systematic review of existing evidence on effectiveness and cost-effectiveness of brief PA interventions presented in Chapter 2 and aims to estimate the cost-effectiveness of VBIs in PA promotion using a modelling approach based on the best available evidence.

Chapter 5 presents the results from a cost-effectiveness analysis of the VBI trial. This chapter follows on designing trials following an iterative approach and demonstrates the practicalities of designing clinical trials from an economic perspective. This chapter undertakes the re-analysis of the study from Chapter 4 (model update) in line with the iterative framework to compare the subsequent research priorities based on the VoI analysis.

Chapter 6 presents the discussion and conclusion chapter. The chapter starts by reflecting on the application of the iterative framework in real life economic evaluation. Based on the findings of the study, the chapter provides a summary of the main findings acknowledging the limitations of the thesis and setting out an agenda for future work. This chapter pulls together the findings from Chapter 2 to Chapter 5 providing a reflection from the VBI study.

Chapter 2 Systematic literature review on the cost-effectiveness of brief physical activity interventions

2.1 Introduction

Chapter 1 introduced the methods and the applied case study. This chapter develops the latter further by presenting a review of economic evidence for promoting physical activity via brief interventions. The primary motivation behind this review was to assess the current economic evidence on BIs promoting PA and inform the development of this thesis work. In turn, this chapter starts with an overview of the literature review followed by the methods section which describes the search strategy, study inclusion/exclusion criteria and methods employed to synthesise the evidence. The results section presents the findings of the review followed by a discussion.

This chapter acts to provide the context for the case study to be used in the remainder of the thesis, showing how the work in this thesis builds upon existing literature in this clinical area. In other words, this chapter contributes to the research aim by answering the question: what is the current economic evidence for the brief physical activity interventions in primary care or the community setting?

Current intervention strategies based in primary care or the community have provided convincing evidence that such strategies can effectively increase PA (122-124). Moreover, recent systematic reviews and meta-analyses of randomised and non-randomised trials have shown that PA interventions such as brief advice, exercise on prescription and physician counselling significantly increase PA behaviour and fitness in the longer term (94,100,101) and these interventions are considered good value for money (97,98). Furthermore, there is growing interest in evaluating cost-effectiveness PA interventions as evidenced by a series of relevant systematic reviews published in the last few years (98,125-127). These economic reviews looked at PA interventions in general, for example, in their review Garrett et al. (98) looked at the cost-effectiveness of PA interventions among the adult population based in primary health care or community, or specific interventions such as exercise referral scheme. Exercise referral scheme refers a person from primary care to a qualified exercise professional who develops a tailored programme (exercise regimen) based on individual's medical information (125).

Brief interventions are well researched in other domains of public health such as smoking cessation and alcohol misuse and are considered highly cost-effective (107-109). However, little economic evidence exists about their cost-effectiveness in physical activity (121). Although previous systematic reviews indicated that PA interventions are effective at increasing activity levels and are cost-effective in general, these studies are not specific to BIs, as they include varieties of interventions such as extended BIs. In addition, the lack of economic evidence for BIs in PA has been recognised (121,128). This review thus aims to summarise the current evidence on the cost-effectiveness of BIs in PA promotion for adults in primary care or community settings.

2.2 Methodology

2.2.1 Search strategy

A literature search was carried out in several databases for articles published up to 31 December 2017: Medline, Embase, PsycINFO, CINAHL, EconLit, SPORTDiscus, Physiotherapy Evidence Database (PEDro), the Cochrane library, the NHS Economic Evaluation Database and Tufts Cost-Effectiveness Analysis (CEA) Registry. The search consisted of keywords and medical subject heading (MeSH) terms related to physical activity, brief or minimal intervention, and economic or cost analysis and was limited to English language. The search strategy used is described in Appendix A1. References of retrieved articles were examined manually after reviewing the title and abstracts. A cross reference search was carried out using Web of Knowledge to identify any economic studies alongside clinical trials and other pertinent studies.

2.2.2 Eligibility criteria

Studies were eligible for inclusion if they met the following three criteria listed in Table 2-1.

Table 2-1: Criteria for study selection

Component	Inclusion criteria
Population	Inactive (i.e. not meeting the government recommended minutes of PA per week) adults aged 16 years or over
Intervention	The NICE definition (as described in section 1.6) was used to define BIs. Briefly, interventions were included if they: a. involved verbal advice, encouragement, negotiation or discussion, delivered face-to-face in a single session or multiple brief sessions, with or without additional non face-to-face contacts (e.g. leaflets or phone calls) or reported as 'brief' or 'minimal', and b. aimed to increase physical activity or fitness levels (or both) at individual-level that is BIs delivered to individuals or groups
Comparator	Usual care or other interventions
Outcome	Information on both cost and health outcomes
Study design chosen	Economic analyses alongside RCTs or non-experimental designs, or modelling studies of physical activity interventions which were based in either primary care or the community.

Studies focusing on specific populations or those that recruited participants on the basis of the pre-existing disease condition(s), such as patients with severe mental disorders or osteoarthritis were excluded because these populations require tailored interventions. Interventions were included if the primary focus of the study or one of the comparator intervention was physical activity as PA interventions are often used in combination with other types of intervention, for example, PA plus dietary advice, for its physical well-being benefits.

2.2.3 Data extraction and methodological quality assessment

The search results from electronic databases were downloaded into EndNote and screened by titles and abstracts against the inclusion criteria. Papers likely to fulfil inclusion criteria were examined and their quality assessed by two reviewers. Based on the Consolidated Health Economics Evaluation Reporting Standards (CHEERS) checklist (129), a standardised proforma (Appendix A2) was developed to extract data from full texts on type of economic analysis and perspective, interventions and comparison, participants, follow-up duration, outcome and cost-effectiveness results. Having screened and extracted data from included studies, a second reviewer double checked the data extraction table for all studies. There are a number of checklists for example (1,55,130-132) to assess reporting and or methodological quality. In this review, Drummond's ten-point checklist (24) was used to guide the critical appraisal of full economic evaluation. The Drummond checklist includes ten questions with four possible responses: yes, no,

not clear and not appropriate. One point was assigned for each 'yes' response giving the lower and highest possible scores 0 and 10 respectively. Based on the checklist criteria, a rating of 'high' (9-10), 'good' (7-8), 'fair' (5-6) or 'poor' (1-4) was assigned.

2.2.4 Statistical analysis methods

To make economic results of individual studies included comparable, all costs were converted to 2011 UK pounds sterling (£) by applying Gross Domestic Product deflator index and purchasing power parity conversion rates using the CEMG-EPPI-Centre Cost Converter (v1.4) (133,134). The economic results of the studies were grouped into two categories (a) those reporting intermediate outcomes such as the incremental cost of moving one inactive adult to an active category; and (b) those reporting final outcomes such as incremental cost per incremental QALY gained, disability-adjusted life-year (DALY) averted or life years gained (LYG). The activity level is defined as those meeting the Department of Health physical activity recommendations, that is at least 150 minutes of moderate intensity activity per week (135).

2.3 Results

2.3.1 Characteristics of included studies

Figure 2-1 presents the PRISMA flow diagram of the study selection. A total of 2,356 records were identified through database searches and cross-referencing search, of which 1,731 were unique records. After excluding 1,698 records based on reading the title and abstract, full text of the remaining 33 studies were examined. A total of 20 studies were excluded because either these studies were not brief, targeted multiple behaviour, not delivered face-to-face, were exercise referral scheme, did not report cost or PA outcome. The thirteen studies included in this review described 30 intervention strategies or scenarios, of which 14 met the definition of BIs. The initial search included studies published up to August 2014 which has been updated to include studies published up to December 2017. The updating of the search did not result in any additional studies being included.

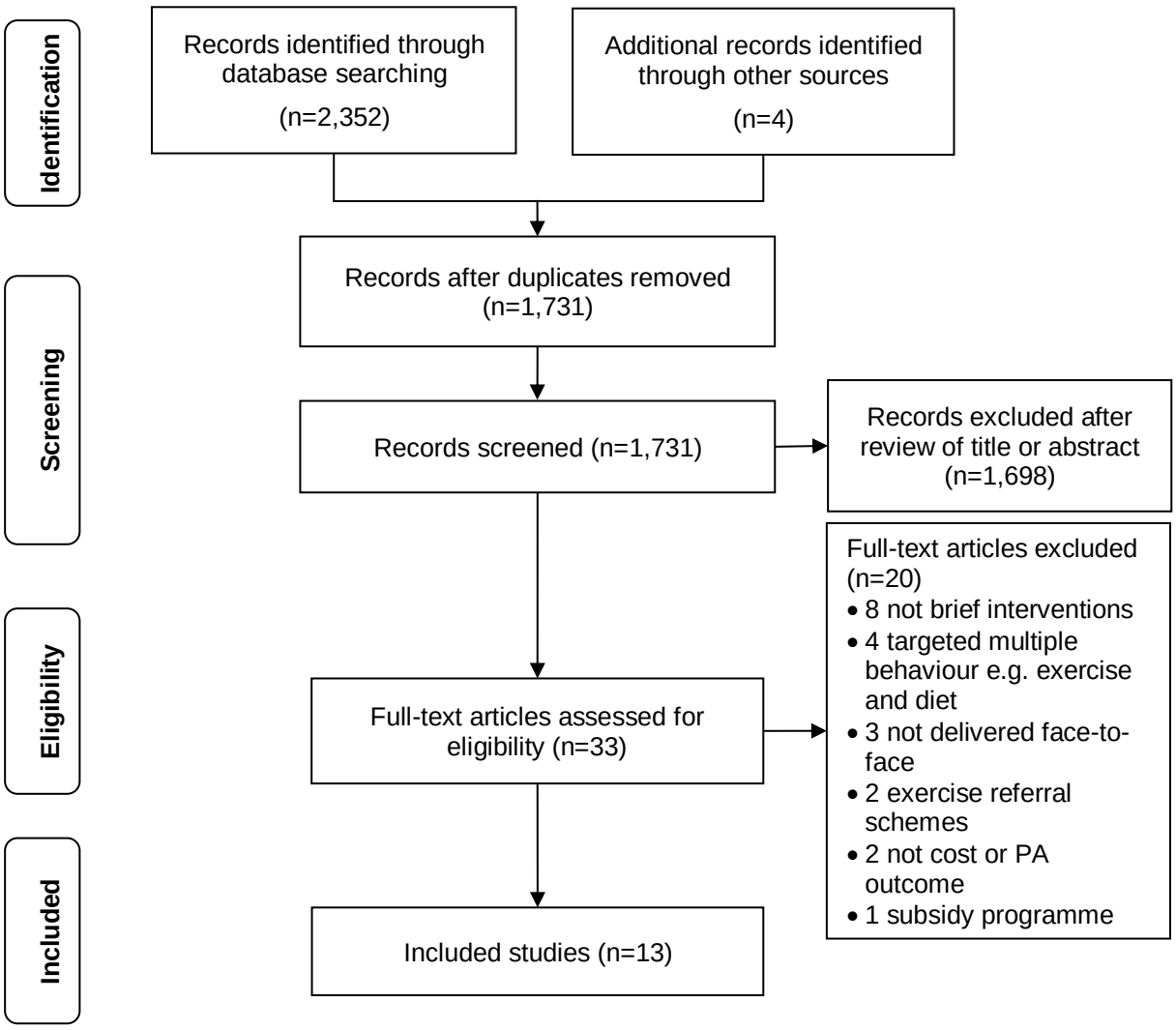

Figure 2-1: PRISMA flow diagram of study selection

Table 2-2 presents the grouping of BIs along with the source of effectiveness data used in cost-effectiveness analysis. These BIs were typically compared with usual care or the current practice (n=10).

Table 2-2: Overview of interventions

Interventions	#	Short description	Source of effectiveness data
Exercise advice (136-140)	5	Brief exercise advice or counselling by a GP or trained health professionals	CS, MA, OS, RCT
Exercise on prescription (141-144)	4	Verbal and written PA advice by GP or practice nurse	MA, RCT
Pedometers (141,145-147)	4	Pedometer-based PA counselling with step-related goal or walking programme	MA, RCT
Motivational interventions (148)	1	Motivational interviews to increase PA	Pre-post intervention

Note: CS, cross-sectional population surveys; GP, General Practitioner; MA, meta-analysis of RCTs; OS, observational study; RCT, randomised controlled trial

Of the 13 economic evaluation studies, two studies were based on quasi-experimental designs (137,148), four were 'piggybacked' economic evaluations conducted alongside clinical trial (143-145,147) and seven were model-based economic evaluations (136,138-142,146). These modelling studies used data from a single clinical trial (139,141,142), a meta-analysis of RCTs (138,141,146), a systematic review of randomised and observational studies (136), or a cross-sectional and observational study (140) to evaluate the cost-effectiveness of BIs.

Characteristics of included study are summarised in Table 2-3. Economic evaluations conducted alongside the clinical trial had a follow-up ranging from 3 months to 2 years. Of the 13 studies, only six studies reported the face-to-face duration of BIs. The duration of face-to-face contact lasted between 4 to 30 minutes (137,140,142-144,147). The measurement of PA varied between studies. Studies using a time-based outcome used a target of ≥150 minutes of moderate activity per week or ≥60 minutes of vigorous intensity activity per week. Pedometer-based studies, however, used a common threshold of ≥10,000 steps per day while Shaw et al. (147) used a target of a weekly increase of ≥15,000 steps.

The economic studies either reported an intermediate outcome such as cost of moving one additional inactive person to active category (137,143,144,147), or a final outcome, i.e. cost per QALY, DALY or LYG (138,139,141,142,146), or both outcomes (136,140,145,148). The following sections first summarise the studies reporting intermediate outcomes followed by the final outcomes.

2.3.2 Studies reporting intermediate outcomes

Eight studies reported the cost of converting one sedentary adult to an ‘active category’, and the value ranged from £96 to £986 (Figure 2-2). Sims et al. (140) evaluated an organised approach to exercise counselling by GPs in Australia (called an ‘active script programme’) which was the most cost-effective intervention considered, i.e. incremental cost of £96 for making a person active. They compared the active script programme with usual care. In their study, Boehler et al. (137) reported that delivering brief exercise advice using disease register screening compared to opportunistic patient recruitment had the additional cost of £986 to convert one inactive adult to an active state. Likewise, Elley et al. (144) evaluated the cost-effectiveness of nurse-delivered exercise counselling and written prescription with telephone support (called ‘enhanced green prescription’). Their cost-effectiveness results showed that the cost-effectiveness of a PA intervention decreases over the time of follow-up (£308 at 12 months versus £630 at 24 months).

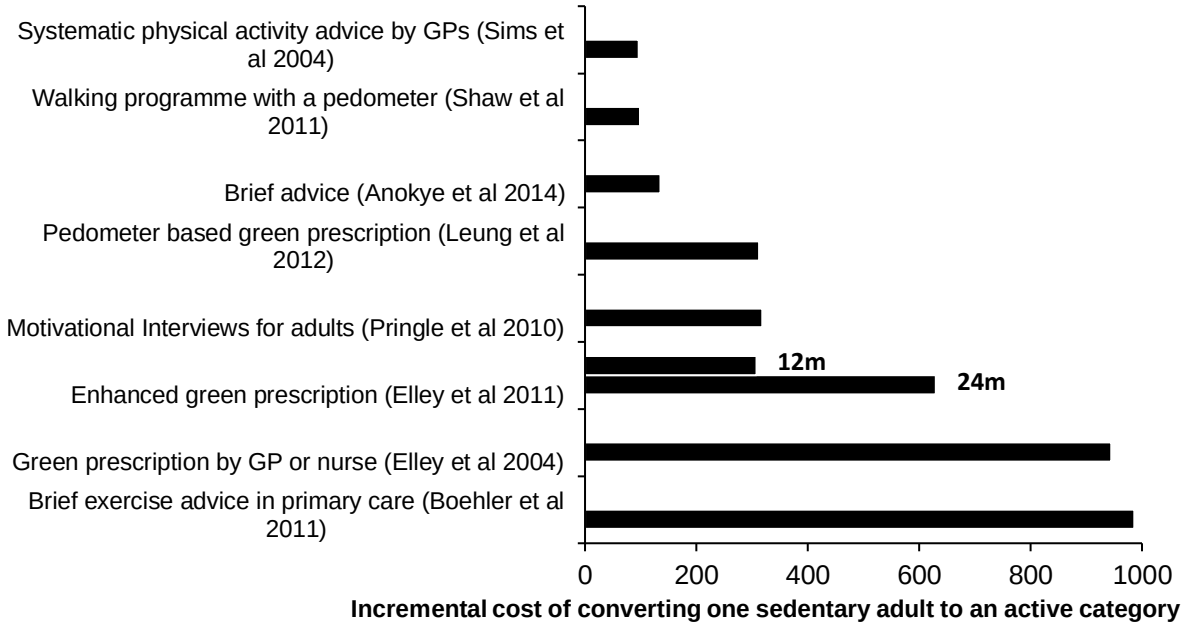

Figure 2-2: Incremental cost of converting one sedentary adult to an active category

Source: Adapted from Figure 2, Gc et al. (149). Costs are 2011 equivalent £ sterling.

Table 2-3: Characteristics of included studies

Study, Setting, quality	Objective; economic perspective, cost year	Study type; economic analysis type	Interventions compared	Participants	Follow-up duration	Definition of physically active person	Mean time to deliver intervention per person	Outcome	
								Cost of converting to an 'active category' (£ at the time of study) [£ inflated to 2011]	ICER (£ at the time of study) [£ inflated to 2011]
Anokye 2014 (136) UK: Good	Brief exercise advice in primary care; NHS, 2010/11	Economic modelling; CUA	I: brief advice C: usual care (no active intervention)	Cohort of 100,000 physically inactive but healthy adults aged ≥33 years	Modelled for lifetime	150 min of MPA or 75 min of VPA per week	Not mentioned	£ 136 (brief advice compared with usual care)	£1,730 per QALY gained
Boehler 2011 (137) UK: Fair	Physical activity promotion in primary care; Health service (NHS), 2007	PA care pathway pilot based regression model; CEA	Brief exercise comparing two recruitment strategies: I1: patients recruited opportunistically I2: patients on the hypertension disease register 'disease register sites'	Insufficiently active, 16-74 years old	3 months	150 minutes of MPA per week	I1: 4 min I2: 18 min Total across intervention: I1: 28 min I2: 76 min	£886.50 [£986] disease register vs. opportunistic recruitment	
Cobiac 2009 (141) Australia: High	Physical activity promotion in community; Health sector, 2003	Economic modelling study; CUA	I1: GP prescription – exercise prescription with follow-up phone call I2: GP referral for PA counselling to an exercise physiologist I3: mass media I4: TravelSmart (active transport) I5: pedometer I6: internet advice C: do nothing	I1: 40-79 years old less active patients I2: 60+ years sedentary patients I3: 25-60 years 14: 18+ years I5: 15+ years I6: 15+ years	Modelled for lifetime	150 minutes of moderate intensity of 5 METs per week	Not mentioned		I1: AUD 11,000 (£5,374) [£6,500] per DALY I2: AUD 75,000 (£36,638) [£44,315] per DALY I3: dominant I4: AUD 18,000 (£8,793) [£10,636] per DALY I5: dominant I6: AUD 2,000 (£977) [£1,182] per DALY when compared with 'do nothing'
Dalziel 2006 (142) New Zealand: High	Primary care based exercise counselling/ prescription; Health system, 2001	RCT based economic modelling; CUA	I: green prescription C: usual care (no additional exercise advice)	Less active participants; 40-79 years I: 451 C: 427	Modelled over full life expectancy	5×30 minutes of MPA or VPA per week	7 min (GP); 13 min (practice nurse)		NZD 2,053 (£865) [£1,104] per QALY (lifetime)

Table 2-3 (continued)

Study, Setting, quality	Objective; economic perspective, cost year	Study type; economic analysis type	Interventions compared	Participants	Follow-up duration	Definition of physically active person	Mean time to deliver intervention per person	Outcome	
								Cost of converting to an 'active category' (£ at the time of study) [£ inflated to 2011]	ICER (£ at the time of study) [£ inflated to 2011]
Elley 2004 (143) New Zealand: High	Primary care exercise counselling/ prescription; Health funder's and societal, 2001	RCT; CEA	I: green prescription (brief oral or written advice) by a GP or practice nurse with telephone exercise specialist follow-up C: usual care (do nothing)	40-79 years old less active patients in general practice I: 451 C: 427	12 months	150 minutes per week	7 min (GP); 13 min (nurse)	NZD 1,756 (£740) [£938]	
Elly 2011 (144) New Zealand: High	Primary care exercise counselling/ prescription with on-going support; Societal, 2008	RCT; CEA	I: enhanced green prescription (nurse delivered brief advice and a written exercise prescription, counselling in primary care with telephone follow-up) C: usual care (do nothing)	Physically inactive women aged 40-74 years I: 544 C: 545	24 months	150 minutes per week of at least MPA	10 min brief advice and a written prescription	NZD 687 (£285) [£308] sustained at 12 months; NZD 1407 (£584) [£630] sustained at 24 months	
Gulliford 2013 (138) UK: Good	Universal strategy to promote PA in primary care; Healthcare service, 2010	Economic modelling; CUA	I: brief GP advice in primary care C: standard care (do nothing)	262,704 healthy participants aged 30-100 years from GPRD	Modelled for lifetime	150 min of moderate PA per week	Not mentioned		Net health benefit of 3.2 QALYs per 1,000 participants (at a threshold of £30,000 per QALY); £13,686 [£14,002]/QALY
Leung 2012 (145) New Zealand: High	Pedometer based exercise advice to increase PA; Societal, 2008	RCT; CUA	I1: pedometer based green prescription I2: standard green prescription (exercise advice & time-related goal)	Healthy inactive adults aged ≥65 years I1: 165 I2: 165	12 months	150 minutes of at least MPA per week	Not mentioned	AUD 667 (£290) [£313]	
Lindgren 2003 (139) Sweden: Good	Dietary and exercise advice; Societal and payer's, 2000	RCT based economic modelling; CEA	I1: dietary advice by dieticians I2: exercise advice by physician I3: exercise & diet C: usual care (no intervention)	Men aged 35-60 years I1: 40; I2: 39 I3: 39; C: 39	Modelled for lifetime	Regular PA of an aerobic type 2-3 times/week lasting 30-45 min	Not mentioned but included 3 visits to a physician		SEK 180,470 (£12,263) [£15,873] per LYG for exercise compared to no intervention

Table 2-3 (continued)

Study, Setting, quality	Objective; economic perspective, cost year	Study type; economic analysis type	Interventions compared	Participants	Follow-up duration	Definition of physically active person	Mean time to deliver intervention per person	Outcome	
								Cost of converting to an 'active category' (£ at the time of study) [£ inflated to 2011]	ICER (£ at the time of study) [£ inflated to 2011]
Over 2012 (146) Netherlands: Good	GP counselling in addition to pedometers to increase PA; Health care, 2009	Economic modelling; CUA	Two scenarios: S1: Pedometer use with diary and GP counselling S2: current practice (no additional advice)	Insufficiently active 20-65 year olds	Modelled for lifetime	150 minutes of moderate intensity PA per week	Not mentioned but included 10 min GP counselling		EUR 11,100 (£8,401) [£8,858] per QALY
Pringle 2010 (148) UK: Fair	Community-based interventions to increase; NHS, 2003	Alongside single clinical and cost study; CEA, CUA	Seven intervention categories: campaigns, exercise classes, exercise referral, motivational interviews, outdoor activity, peer-mentoring, training of PA leaders	inactive; 343 young people and 641 adults particularly aged 65 years and over	Modelled for lifetime using Matrix model (150)	150 minutes of moderate intensity PA per week	Not mentioned	£260-£1,253 [£318-£1,531] per completer improving MPA	£47-£229 [£57-£280] per QALY
Shaw 2011 (147) Scotland: Fair	Pedometer based walking; Health services, 2008	RCT; CEA	I1: minimal intervention (walking programme and pedometer) I2: maximal intervention (PA consultation, pedometer and individualised walking programme) C: 'usual behaviour'	18-65 year olds I1: 40 I2: 39	12 months	weekly increase of ≥15,000 steps	30 min	£92 [£99] (minimal versus control) £591 [£637] (maximal versus minimal)	
Sims 2004 (140) Australia: Fair	Active script in general practice; Health service, 1996	Economic modelling; CEA, CUA	I: active script program (ASP) – improving systematic PA advice by GPs C: routine GP care (no PA advice)	less active adults aged 20-75 years, 670 GP advising sedentary patients I: 40,258; C: 10,437	Unclear time horizon	150 minutes of MPA per week	4 min GP consultation	AUD 138 (£70) [£96 per patient to become active	AUD 3647 (£1,838) [£2,542] per DALY saved

Note: BI, brief intervention; C, control group; CEA, cost effectiveness analysis; CUA, cost utility analysis; GP, general practitioner; GPRD, general practice research database; HCA, healthcare assistant; I, intervention group; ICER, incremental cost effectiveness ratio; METs, metabolic equivalents; MPA, moderate intensity physical activity; NHS, national health service (England); PA, physical activity; RCT, randomised controlled trial; S, scenario; VPA, vigorous intensity physical activity

Source: Adapted from Table 3, Gc et al. (149)

2.3.3 Studies reporting final outcomes

Three studies reported cost-effectiveness of multiple interventions, of which only a few were relevant (BIs) to this review. For example, Pringle et al. (148) included seven broad categories of community-based PA interventions, Cobiac et al. (141) compared six intervention strategies to promote PA, and Lindgren et al. (139) included three interventions of dietary and exercise advice. Figure 2-3 summarises the cost-effectiveness results for those studies reporting QALY, DALY or LYG outcomes.

Pedometer-based BIs, either as a motivational tool or in combination with brief exercise advice, were dominant, i.e. they were both cost saving and more effective when compared with usual care (141) or standard 'green prescription' (oral or written exercise advice by a GP or practice nurse with telephone follow-up) (145). GP advice in combination with a pedometer had an ICER of £8,858 per QALY when compared with current practice (146).

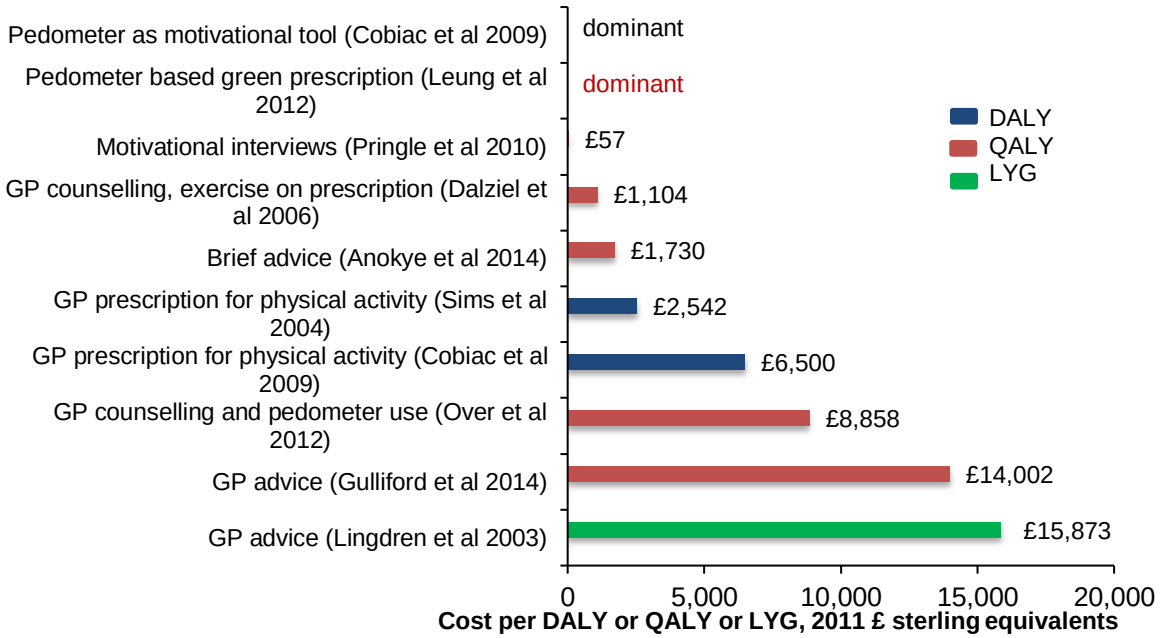

Figure 2-3: Cost-utility (cost per DALY or QALY or LYG) for different PA interventions

Source: Adapted from Figure 3, Gc et al. (149). All costs are 2011 equivalent £ sterling.

The ICER for brief exercise advice or exercise on prescription compared to usual care ranged from £1,104 to £14,002 per QALY (136,138,142); and from £2,542 to £6,500 per DALY (140,141). The lowest ICER, i.e. £57 per QALY was for motivational interviews (148). Exercise counselling by a GP in combination with a pedometer (146) had lower cost-effectiveness ratio than a GP advice or counselling with written materials (138) (£8,858 versus £14,002 per QALY) - both were compared with usual care.

Table 2-4: Critical appraisal of included economic papers using Drummond et al. checklist (24)

Study	Well-defined question posed in answerable form	Comprehensive description of the competing alternatives given	Effectiveness of the programme or service established	All important and relevant costs and consequences for each alternative identified	Costs and consequences measured accurately in appropriate physical units	Cost and consequences valued credibly	Costs and consequences adjusted for differential timing	Incremental analysis of costs and consequences of alternatives performed	Allowance made for uncertainty in the estimates of cost and consequences	Presentation and discussion of study results included all issues of concerns to users
Anokye 2014 (136)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes, PSA	Yes
Boehler 2011 (137)	Yes	Yes	Yes	Yes	Yes	Yes	Not relevant	Yes	Yes, PSA	Yes
Cobiac 2009 (141)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes, PSA	Yes
Dalziel 2006 (142)	Yes	Yes	Yes	Only included programme costs – cost of downstream events not included e.g. CVD, diabetes	Yes	Not all sources cited (e.g. source for overhead costs)	Yes	Yes	Yes, PSA	Yes
Elley 2004 (143)	Yes	Yes	Yes	Yes	Yes	Not all sources cited (e.g. source for overhead costs)	Yes	Yes but excluded lost productivity from calculation (reason given by authors)	Yes, OWSA	Yes
Elley 2011 (144)	Yes	Yes	Yes	Yes	Yes	Yes	Mostly; second year costs not discounted	Yes	Yes, OWSA and hypothesis test but of geometric means	Yes
Gulliford 2013 (138)	Yes	Insufficient detail	Yes	Yes	Yes	Insufficient detail	Yes	Yes	Yes, PSA	Yes
Leung 2012 (145)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes, PSA	Yes

Table 2-4 (continued)

Study	Well-defined question posed in answerable form	Comprehensive description of the competing alternatives given	Effectiveness of the programme or service established	All important and relevant costs and consequences for each alternative identified	Costs and consequences measured accurately in appropriate physical units	Cost and consequences valued credibly	Costs and consequences adjusted for differential timing	Incremental analysis of costs and consequences of alternatives performed	Allowance made for uncertainty in the estimates of cost and consequences	Presentation and discussion of study results included all issues of concerns to users
Lindgren 2003 (139)	Yes	Yes but hypothetical intervention	Yes	Yes	Yes	Authors state time and travel costs not included	Yes	Yes	Yes, PSA and scenario analysis	Yes
Over 2012 (146)	Yes	Yes	Yes	Insufficient detail	Insufficient detail	Not all sources cited (cost, utility)	Yes	Yes	Yes, PSA	Yes
Pringle 2010 (148)	Yes	Unclear if usual practice and all the relevant comparators included, although full details provided in referenced sources	Insufficient detail about source of study	Out of pocket expenditure excluded	Yes	Yes	Yes	Yes	Yes, OWSA	Minimal information about economic model and sensitivity analysis, although references to more details are provided
Shaw 2011 (147)	Yes	Yes	Yes	Restricted to intervention costs	Yes	Sources cited but not clear which relates to which unit cost	Not applicable to within-trial analysis, threshold analysis for £/QALY doesn't appear to take discounting into account	Yes	Mentioned but not described in detail	Discussion limited by broad scope of the paper (qualitative and economic analysis in one paper)
Sims 2004 (140)	Yes	Yes	Yes	Yes	Yes	Not all sources cited	Not clearly mentioned	Yes	Yes, OWSA	Yes but not in detail

Note: OWSA, one-way sensitivity analysis; PSA, probabilistic sensitivity analysis

Source: Adapted from Table 1, Gc et al. (149)

2.4 Discussion

2.4.1 Principal findings

Primary care or the community-based BIs such as exercise advice (136,140), pedometer-based walking (147), pedometer-based exercise advice ('green prescription')(145), and motivational interviews (148) had similar cost-effectiveness ratios for converting one inactive person to an active state. With respect to the final outcomes, use of pedometers (141) pedometer in combination with written exercise advice (145), motivational interviews (148), exercise advice or counselling by a GP (140,142), and brief exercise advice (136) were cost-effective intervention strategies. The reviewed studies also showed that the cost-effectiveness of BIs decreases over time unless there is continued contact so that the activity levels are maintained over time (144). Although the 'active script programme' (140) reported lower cost per additional person active, the economic evaluation used rather optimistic assumptions regarding the uptake of PA. In addition, effectiveness evidence was derived from a pre-post study to model intervention cost-effectiveness and the time horizon was not clear.

Both Leung et al. (145) and Cobiac et al. (141) reported the dominance pedometer intervention, but the pedometers were compared with 'green prescription' and usual care respectively. In contrast, Over et al. (146) reported a considerably higher ICER (£8,858 per QALY) for pedometers when compared with current practice. Although both Cobiac et al. (141) and Over et al. (146) modelled cost-utility using intervention effectiveness data from a meta-analysis of 8 RCTs (151), the higher possible health gains in Cobiac et al. may be a consequences of much larger proportion of inactive people in the Australian compared to the Dutch population, and of the reported programme cost per participant being lower in the Australian estimates than Over et al.

Brief exercise advice delivered by the nurse (144) had a more favourable cost-effectiveness ratio than those delivered by a GP (143) (£308 versus £938 for converting one additional inactive person to an active category over a 12-month period). The nurse delivered 'enhanced green prescription' had a slightly higher proportion of participants who increase their PA at 12 months than the GP delivered 'green prescription'. The nurse delivered intervention had extra telephone support and 6-month face-to-face contact which may explain the higher proportion of participants with increased activity level in 'enhanced green prescription'. The ICER for both QALY and DALY outcomes varied between studies. For example, ICER for exercise advice ranged between £1,104 and £14,002 per QALY.

Of the seven economic modelling studies, few studies adopted previously reported models. For example, Pringle et al.'s (148) model was informed by the NICE cost-effectiveness model (150), while Over et al. (146) used the Chronic Disease Model (CDM) developed by the Dutch National Institute for Public Health and the Environment to estimate the long-term effects of an increase in PA. These modelling studies incorporated multiple chronic conditions which are known to be linked to physical inactivity except Lindgren et al. (139) who only included CHD conditions.

2.4.2 Methodological issues

There were issues where studies did not report sources of evidence used in the analysis and did not justify the potential exclusion of relevant costs. For example, Pringle et al. (148) did not include out-of-pocket expenditures which might be significant and could influence the intervention attendance levels apart from the cost-effectiveness of the intervention. The model-based economic evaluations differed mainly in terms of quality of evidence used, model structure and outcome measure. Only eight studies (136-139,141,142,145,146) properly characterised decision uncertainty by performing PSA while the remaining studies used either scenario-based or one-way sensitivity analysis. Most of the studies used evidence base either from a single RCT or meta-analysed data, three studies (137,140,148) used evidence from non-experimental studies or theoretical scenarios. In addition, assumptions around the maintenance of PA levels beyond BIs were not clearly reported in most of the studies which could determine how cost-effect BIs are over the time.

2.4.3 Comparison with previous reviews

Previous studies (97,98,121) suggested that PA interventions are cost-effective when compared with usual care. The NICE review (121) of PA was limited to three studies and did not include other kinds of BIs promoting PA such as pedometer-based interventions. Garrett et al. (98) included 13 economic evaluations, of PA interventions in primary care, conducted alongside clinical trials and concluded that PA interventions are cost-effectiveness in primary care especially where direct supervision or instruction was not required. The cost-effectiveness ratio defined as the cost of moving one inactive person to an active stage at 12 months varied from £262 to £3,144, and cost-utility estimated in nine studies varied from £276 to £68,798 per QALY gained. However, their review included intensive PA interventions and did not include modelling studies. Another review by Muller-Riemenschneide et al. (97) included eight studies (6 RCTs, 1 cross-sectional and 1 economic modelling) covering a broad range of interventions promoting PA

including workplace-based PA and environmental interventions. The cost per participant to achieve the recommended level of PA over a 12 months period was £662.

These economic reviews of PA interventions either considered the cost-effectiveness of PA interventions in general and were not specific to BIs (97,98) or did not include other kinds of BIs such as pedometer-based interventions (121).

2.4.4 Strengths and limitations

This review includes both economic evaluations alongside clinical trials and economic modelling, provides a comprehensive overview of current evidence on the cost-effectiveness of BIs in PA promotion. The included studies vary widely in terms methodology used, for example, the perspective used, discounting of the future value of cost and health outcomes. The source of evidence used to populate the model (e.g. intervention effectiveness) and assumptions underlying (for example, the sustainability of intervention effects over time) differed considerably between studies. Such methodological differences between the studies as well as other context characteristics, for example, variability in funding mechanism, health system and cost structures limit the generalizability of the cost-effectiveness results across different settings (152).

Some of the studies included in this review did not provide intervention details such as time duration and intervention delivery method, i.e. either the intervention is delivered in person or in group(s). This makes it difficult to determine whether or not interventions were truly BIs according to the NICE definition. It is important to describe interventions in sufficient details (153), and this may have an impact on cost-effectiveness. For example, the duration of BIs has implication on resource use cost estimation. This review only included studies that had at least one face-to-face contact as a result PA intervention not delivered face-to-face such as print or telephone-based interventions were excluded. The latter constitutes a growing area of research and especially useful in older adults (154). In addition, due to the heterogeneity among studies, it was not possible to rank interventions based on cost-effectiveness ratios. However, when used current NICE threshold of £20,000 to £30,000 per QALY (2), most of these interventions are considered cost-effective.

2.5 Chapter summary

This chapter has presented a review of the economic literature in relation to brief interventions promoting PA in primary care or community setting. In this regard, the first

part of the chapter provided an overview and justification why this review was conducted followed by the methods used and presenting review results. Overall, the reviewed literature offered relatively richer evidence on PA interventions based in primary care or the community. Results of the review showed that brief PA interventions were likely to be inexpensive and increase individuals' PA at a reasonable cost however there was notable variation between studies. Additionally, there was limited evidence on the longer-term costs and consequences of these interventions.

The review also highlighted the methodological challenges, for example, ranking and prioritising interventions based on the cost-effectiveness ratios was not feasible given variations in interventions, study participants, outcome measures and study design. Ideally, it would be more appropriate to compare each intervention from a list of 14 interventions strategies included in this review in an iterative manner taking into account dominance and extended dominance. An intervention is considered dominated when the comparator intervention strategy accrues more health benefits for less cost. The intervention is extendedly dominated when a combination of two alternative intervention strategies can produce the same health benefit but at a lower cost (1,155). However, this was not possible as the interventions were typically compared with standard usual care, i.e. doing nothing. In order to make a comparison of BIs, this requires a decision analytic modelling framework that transforms short-term costs and health outcomes to long-term costs and health outcomes. This framework helps identifying which brief intervention is the most cost-effective intervention strategy and quantifying the associated decision uncertainty. This is done in Chapter 4 by developing a decision analytic model and evaluating three brief interventions in PA promotion.

As this chapter gives an overview on the economic literature of brief PA interventions, the next chapter lays out the theoretical framework adopted in this study with the aim of assessing the feasibility of using the iterative framework.

Chapter 3 An iterative approach to economic appraisal

3.1 Chapter outline

Following the overview of the economic evaluations in healthcare and methodologies used in decision analytic models for economic evaluations (Chapter 1, sections 1.2 to 1.4), and a review of economic evidence of brief PA intervention (Chapter 2) this chapter now considers the iterative approach to economic appraisal as a framework for undertaking research in the healthcare sector. This chapter starts with an overview of the approach followed by a five-stage iterative framework for economic evaluation. The subsequent sections discuss the merits and limitations of the methods. The last section of the chapter explores how value of information (VoI) methods are being used in decision making to inform further research within an iterative process of analysis. A systematic review of existing VoI literature was conducted to find real life economic evaluations performed that follows the iterative framework to inform further research.

3.2 Introduction

As previously discussed in section 1.2, economic evaluations are useful in informing decisions about the efficiency and allocation of resources to maximise the benefit of healthcare spending. However, the advances in modern medicine and public health bring about incremental innovations (thus improved patient outcomes) that result in an evolving evidence base (156). As new information becomes available during the lifecycle of the health technology, the adoption decision is influenced and could change. Due to this evolving nature of health interventions or technologies, their evidence bases and the effects of this on healthcare decision making this suggests that an economic evaluation should not be a one-off activity.

Sculpher et al. (4) and Fenwick et al. (82) suggested that economic evaluation should be re-performed as evidence bases develop throughout the lifecycle of the technology. This implies that rather than using economic evaluations as one-off analyses, it should be an iterative process conducted alongside all stages of healthcare research. This involves using decision analytic models and updating them regularly as a new evidence base becomes available. The five-step iterative framework (4,43) was proposed as the best

practice for evaluating healthcare technologies. The framework utilises the key methodologies for decision analytic modelling and provides a structure in which evidence from a range of sources can be synthesised along with Bayesian updating in order to answer cost-effectiveness decision problems (6).

The process as outlined in Figure 3-1 starts with defining a decision problem, which is followed by a systematic review of existing evidence. The synthesis of evidence from the literature review leads to a decision model. The decision model requires input parameters that need to be carefully estimated in order to appropriately characterise parameter uncertainty. The next step is the adoption decision based on the availability of current evidence, i.e. choosing the intervention with the highest net benefit.

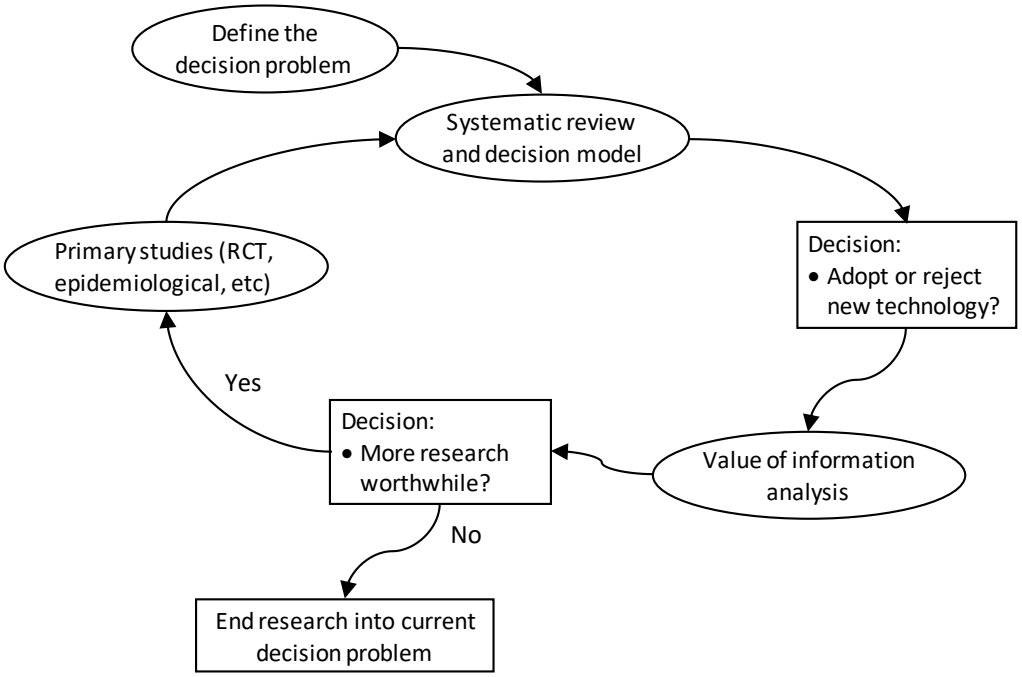

Figure 3-1: The iterative approach to economic evaluations

Source: Wilson and Abrams (83)

Irrespective of the adoption decision made, the next step is to explore the value of further research by using VoI analysis. By using the results from the cost-effectiveness VoI analyses, decision makers can make a decision that is either to collect more information or not. The data gathered from primary research are then fed back into an updated systematic review, and the cycle repeated (42,83,84).

The five stages of the iterative framework outlined by Sculpher et al. (4,43) is discussed below in detail.

3.3 Stages of an iterative approach

3.3.1 Identify decision problems

The first stage of an iterative framework starts with an explanatory stage focusing on identifying the decision problem. This stage needs to clearly define the related aspects of the economic analysis such as comparators, outcome measures, disease area, patient population and perspective of the analysis. This stage is also similar to the first two steps of decision analytic modelling, i.e. 'specifying the problem' and 'defining the model boundaries' (section 1.4). It is essential to formulate an appropriate economic question by defining which patient population is being considered, the treatments or interventions that are currently available to the specified patient population, and the costs and benefits of new treatment or comparator. This involves, for example, identifying different brief physical activity interventions for the NHS Health Check population, their costs and effectiveness, i.e. are brief interventions in physical activity promotion in primary care cost-effective compared with usual care ('doing nothing') from the health service perspective? This stage of the iterative process thus begins by exploring the literature and existing information to identify the decision problem.

3.3.2 Synthesis and modelling given available evidence

Once the decision problem has been identified, the next step (stage 2) is to explore existing and available information, then undertake evidence synthesis and the construction of a decision analytic model. It is crucial to define appropriate input parameters to the decision model and estimate their mean values and characterise uncertainty (83). The aim of the decision analytic model is to estimate the long-term costs and health gains of each VBI identified by a review of existing evidence: to provide an indication of whether VBIs are cost-effective and associated uncertainty. This involves developing a decision model using information synthesised from various sources, fitting distributions to model parameters, and undertaking probabilistic sensitivity analysis (38). The steps involved in developing a decision analytic model are described in section 1.4.

Developing an early decision model can provide an indication of whether the VBIs in PA promotion are expected to be cost-effective and the associated uncertainty.

3.3.3 Setting of research priorities

The adoption decision is determined by the available information and results from the decision analytic model. The intervention option with the highest incremental net benefit (INB) is selected. The uncertainty, i.e. standard error around INB tells us whether we require further information to reduce uncertainty surrounding the cost-effectiveness and to identify the focus of further research and appropriate research design (82).

The VoI is based on the rationale that decisions based on existing information will be uncertain and given this uncertainty, there is always a chance that the wrong decision will be made. This will have costs in terms of health benefits forgone. Expected value of information (EVI) approach uses a decision analytical framework in order to prioritise further research through identifying those areas in which additional data collection (primary research) and hence the reduction of uncertainty (13) would be of most value.

The uncertainty in parameters used in the VoI analysis determines whether new information has a probability of changing the adoption decision, i.e. selecting the VBI with highest NB. If the probability of changing the decision is zero, then no further research into the current decision question should be conducted. However, if earlier, i.e. NB is greater than zero there is a case for conducting further research into the current decision question.

The VoI statistics are Expected Value of Perfect Information (EVPI), Expected Value of Perfect Parameter Information (EVPPI), Expected Value of Sample Information (EVSI) and Expected Net Benefit of Sampling (ENBS) which are described below:

3.3.3.1 Expected value of perfect information (EVPI)

The EVPI represents the monetary value that can be attached to eliminating all uncertainty in decision making. In other words, EVPI calculates the opportunity cost of making the wrong decision. It does this by calculating how the costs and consequences of a decision made with current evidence differ from those made with perfect evidence. Thus, the expected cost of uncertainty is determined by the probability of making the wrong decision multiplied by the consequences of a wrong decision. If the EVPI exceeds the expected cost of additional research (EVPI > 0), then it is potentially worthwhile undertaking further research to gather more information. However this is necessary, but not a sufficient, condition (157,158).

The process of calculating the EVPI follows on from calculating the cost-effectiveness acceptability curve (CEAC) using the results from a PSA. In determining the CEAC from the PSA results, the net benefits can be calculated for each comparator for the number of iterations (*n*) of the Monte Carlo simulation. The average of these is taken in order to determine the optimal intervention. The optimal intervention is the intervention which has the highest expected net benefit across the *n* Monte Carlo simulations.

The EVPI is estimated using the expected costs (C), effects (E) and cost-effectiveness parameters from the decision model and PSA. The NB for intervention j with the ceiling ration λ can be calculated as follows (35):

$$NB_j = E_j\,\lambda - C_j \qquad (3\text{-}1)$$

Assuming, j alternative interventions, θ input parameters to the model and given current information, the adoption decision is made based on the intervention with the maximum expected NB over *n* iterations of the Monte Carlo simulation:

$$max_j\, E_\theta\, NB(j,\theta) \qquad (3\text{-}2)$$

If there was perfect information, the value of θ would be known, and the value of the optimal decision at these known values of θ could be obtained by maximising the NB, $max_j\, NB(j,\theta)$. However, it is not known where the uncertainty around θ will resolve. Thus, the expected value of decision made with perfect information is estimated by averaging the maximum NB in each iteration:

$$E_\theta\, max_j\, NB(j,\theta) \qquad (3\text{-}3)$$

The EVPI for an individual patient (158) is simply the difference between the expected net benefit with perfect information (equation 3-3) and that with current information (equation 3-2), as detailed in equation (1-1).

$$EVPI = E_\theta\, max_j\, NB(j,\theta) - \, max_j\, E_\theta\, NB(j,\theta) \qquad (3\text{-}4)$$

After calculating the EVPI per patient, it is important to account for the relevant population who may benefit from the additional research over the expected lifetime of the technology. The population EVPI is calculated using the estimates of current and future patient number (I), over the lifetime of the new technology or intervention (T) in each time period (t) discounted at a discount rate (r) as follows (36):

$$PopnEVPI = EVPI \sum_{t=1}^{T} \frac{I_t}{(1+r)^t} \quad (3\text{-}5)$$

Determining the estimates of the potential patient who might benefit and the lifetime of the new technology or intervention requires some assumption to be made. It should consider far enough into the future to reflect important differences between alternative interventions, the duration of treatment and the duration of the treatment effect.

The per person EVPI and population EVPI indicate whether further research is potentially worthwhile by providing an upper bound on the value of conducting further research. However, as perfect information is not achievable, EVPI alone is not sufficient to determine the potential for conducting future research. Thus, it is a necessary but not a sufficient condition (157,158).

3.3.3.2 EVPI for parameters (EVPPI)

After the calculation of EVPI and investigating if future research is worthwhile using EVPI, the next question comes about the optimal design for collecting further evidence. One consideration is to establish on which parameter(s) further information will be of most value. The expected benefit of reducing uncertainties surrounding a particular parameter or a subset of model parameters is called the EVPPI. Those parameter(s) with a higher EVPPI value are likely to be more uncertain, and thus further research to get a more precise estimate of its value is likely to be of value.

EVPPI is simply the difference between the expected value of a decision made with perfect and current information about parameter(s) (83,158,159). It provides an upper bound to research expenditure with respect to a particular parameter or set of parameters. In a decision model with uncertain parameters θ, the value of perfect information about the parameter or a subset of parameters (ϕ) are of interest. If there was perfect information, it would be known which value ϕ will take. Then the alternative with the maximum ENB would be chosen by averaging the ENB over the remaining uncertain parameters (ψ), where $\varphi \cup \psi = \theta$. In other words, by taking the value of ϕ and calculating ENB over the remaining uncertain parameters (ψ) the alternative with maximum ENB (j) is selected (equation 3-6):

$$max_j \, E_{\psi|\varphi} NB(j, \varphi, \psi) \quad (3\text{-}6)$$

However, the true value of ϕ is unknown. Therefore the expected value of a decision with perfect parameter information is found by averaging the maximum ENBs over the distribution of ϕ (equation 3-7):

$$E_{\varphi}\, max_j\, E_{\psi|\varphi} NB(j, \varphi, \psi\,) \tag{3-7}$$

The expected value with current information is the same as EVPI because $\varphi \cup \psi = \theta$. So the EVPPI for the parameters (ϕ) is the difference between the expected value of the decision made with perfect information on ϕ and the decision made with current information. (159) as given in equation 3-8:

$$EVPPI_{\varphi} = E_{\varphi}\left[max_j\,(E_{\psi|\varphi} NB(j, \varphi, \psi\,))\right] - max_j\,[E_{\theta}\, NB(j, \theta)] \tag{3-8}$$

Similar to calculating EVPI, the results from the decision model and PSA are used to calculate EVPPI. While calculating EVPPI, the simulation needs to run for the parameters ψ with each value φ. Values for the parameter φ are selected using an outer loop. The simulation is then run for each value of φ to generate the expected costs and QALYs which are used to estimate ENB. This step is repeated until there is sufficient sampling from the distribution of φ.

To compute EVPPI as outlined in equation 3-8, it involves various steps which are described below (159) in Box 3-1.

Box 3-1: Monte-Carlo algorithm for calculation of EVPPI

Preliminary steps (adoption decision)

1) The first step, Set up a decision model comparing different brief PA intervention strategies and set up a decision rule, for example, ICER ≤ λ (where λ is the society's willingness to pay threshold)
2) Characterise the uncertain parameters with probability distributions. For example, normal(θ, σ^2), beta (a, b), gamma (a, b), triangular (a, b, c), . . ., etc.
3) Simulate L iterations (e.g. $L = 10{,}000$) sample sets of uncertain parameter values using Monte Carlo simulation.
4) Work out the baseline adoption decision given current information, that is, the brief intervention giving the highest estimated expected net benefit over L simulations.

Partial EVPI for a Parameter Subset of Interest

The algorithm has 2 nested loops.

5) Obtain a sample value for the parameter of interest, say intervention effect (ϕ) from its prior distribution, given by φ_k. This step corresponds to the outer level simulation. The intervention effectiveness parameter (ϕ) is a subset of the entire set of parameters ($\varphi \cup \psi = \theta$).

6) Run the Monte Carlo simulation which was set up in the preliminary steps to estimate ENB of the intervention given perfect information on ϕ, which is fixed at the sampled value φ_k obtained in the outer loop.

   In running this simulation, all remaining uncertain parameters (ψ) are simulated over say, $j = 10{,}000$ times, allowing them to vary according to their conditional probability distribution (conditional on the parameter subset of interest at its sampled value φ_k). This corresponds to the inner-level simulation.

7) Calculate the conditional ENB of each intervention strategy given perfect information about the treatment effect (ϕ). The brief PA intervention strategy chosen is the one with the highest estimated ENB for the sampled value of φ ($E_{\varphi|\psi}[NB(j, \varphi, \psi)]$).

8) Loop back to step 5 and repeat steps 5-7 (say, j =10, 000 times) and then calculate the average net benefit of the revised adoption decisions given perfect information on treatment effect parameters (φ).

9) Calculate and record the average net benefit of each brief PA intervention strategy across all the inner loop iterations and then calculate the maximum of those average net benefits.

10) Across all *L* outer loop iterations, calculate the average of the average net benefit for each brief PA intervention strategy and the average of the maximum net benefits.

11) The partial EVPI for the parameter subset of interest (treatment effect, φ) across the intervention strategies is estimated by getting the difference between the average maximum net benefit and the maximum average net benefit of each intervention strategy in step 7.

Source: Adapted from Brennan et al. (159)

The EVPPI can be run for a single parameter as well as for groups of parameters where a specified group of parameters such as treatment effects are held constant rather than a single parameter. Additional parameter information is only valuable for those parameter(s) for which additional information would change the adoption decisions. Parameters with more uncertainty will have a higher VoI attached to them. It is important to note that the EVPPI for individual parameters does not sum to the overall EVPI, and likewise, the EVPPI for groups of parameters is not the sum of the EVPPI for individual parameters (36).

The EVPPI measures the sensitivity of the decision problem to uncertainty in particular or a group of parameters. The population EVPPI can be estimated by multiplying the EVPPI value with 'effective population'. The effective population can be determined in the same way as described above for EVPI (section 3.3.3.1).

The EVPI and EVPPI give an upper bound of the expected benefit of doing more research by calculating the improvement in net benefit expected from eliminating uncertainty in all parameters or a subset of parameters respectively. The next step is to determine if further research is worthwhile and identify an efficient research design.

3.3.3.3 Expected value of sample information (EVSI)

Whilst EVPI and EVPPI place an upper bound on the potential value of further research, they provide a necessary but not sufficient condition for acquiring further information (42,160). The VoI framework can be extended to establish the expected value of sample information for a sample of *n* participants for particular research designs (160). It is the societal benefit of acquiring additional evidence from a sample to inform a decision. This allows the marginal benefit of additional sample information for a patient population and the marginal cost of sampling to be examined. The Expected Value of Sample Information (EVSI) is the technique used to assess the value of sample information acquired after the proposed research and the expected value of the decision given current information (75).

The EVSI is estimated using a similar process used to estimate EVPI and EVPPI. However, in estimating EVSI a sample is drawn rather than assuming perfect information about parameter(s). EVSI for a parameter or a subset of parameter φ can be estimated over the remaining parameters ψ.

If φ and ψ are independent then a sample of n on φ provides the sample result D. If D were known, the ENB could be averaged over the prior distribution of ψ and the posterior distribution of treatment effect (φ) given D:

$$max_j \, E_{\psi,\theta|D} NB(j, \varphi, \psi) \quad (3\text{-}9)$$

As D is unknown, so the expectation of the maximum ENB over the predictive distribution of D conditional on φ is taken and averaged over the prior distribution of treatment effect φ:

$$E_D max_j \, E_{\psi,\theta|D} NB(j, \varphi, \psi) \quad (3\text{-}10)$$

As above, the EVSI is the difference between the expected value of a decision with sample information and that with current information (160):

$$EVSI = E_D max_j E_{\psi,\theta|D} NB(j, \varphi, \psi) - max_j E_\theta NB(j, \theta) \quad (3\text{-}11)$$

The various steps for the EVSI estimation (7,71,160,161) are provided below:

Box 3-2: Monte-Carlo algorithm for calculation of EVSI

1) For an assumed new sample size (n), the initial step involves setting up a decision model with parameters θ ($\varphi \cup \psi = \theta$) and setting up a decision rule, for example, ICER ≤ λ. The first step is to draw sample value(s) from a prior distribution of treatment effect (φ).
2) Draw, a random sample to simulate the true event given sample size (*n*) and the estimate of treatment effect parameter, φ. Using this draw and the prior mean for the treatment effect parameter, φ, calculate a posterior estimate.
4) Sample value from pre-posterior distribution of φ and from distribution of remaining parameters,ψ, place back into the model and recalculate the NB for each intervention i.e. $NB(j, \varphi, \psi)$
5) The NB for each intervention is calculated and stored, identifying the intervention with the highest NB.
6) This process is repeated again (steps 1-5), using the second iteration of prior means from the Monte Carlo simulation and continually repeated for all of the posterior estimates. The NB for each intervention is recorded and the intervention that gives the maximum ENB for each is identified
7) Once the process has been repeated for all of the prior iterations in the Monte Carlo simulation, the stored NBs and maximum intervention identities are used to calculate the ENB for each iteration. The intervention with the highest ENB is the expected value of a decision based on current information.
8) Calculate the expected maximum NB (averaging the maximum NBs). This is the expected value of a decision based on sample information for the selected sample size (n).
9) The ENB of a decision under current information is subtracted from the ENB of a decision based on sample information to give the EVSI.

Source: Adapted from Ades et al. (7), Brennan et al. (161) and Wilson (71)

The EVSI calculated is the value per decision. Thus, the population EVSI can be calculated using the same approach used to determine EVPI and EVPPI (equation 3-12).

$$pEVSI = EVSI \cdot \sum_{t=1}^{T} \frac{I_t}{(1+r)^t} \quad (3\text{-}12)$$

The calculation of population EVSI should define the eligible population who can benefit from the results of research. Population EVSI value depends on the definition of eligible population, disease incidence and prevalence (I), and the time horizon (t) over which the additional information is expected to be useful. Thus, the EVSI associated with future patients should be discounted appropriately and the discount rate (r) stated. The calculation of population EVSI assumes that the intervention shown to be cost-effective with sample information for a sample of *n* will be implemented instantly to the entirety of eligible population. However, this assumption is generally unrealistic especially in the healthcare setting (162). Adoption of a new intervention strategy requires time and such strategies do not immediately get implemented perfectly into practice. For example, implementation of new intervention strategies may require new skills which may lead into less perfect or phased implementation of such intervention strategies.

3.3.3.4 Expected net benefit from sampling (ENBS)

With respect to the sample size, the greater n is the less uncertainty around the parameter(s) of interest. However, as n increases so does the cost of the study. Therefore, the optimal sample size can only be determined by comparing the EVSI with the expected cost of sampling (new research). The costs of sampling are defined in terms of financial resource (fixed and variable) costs and the opportunity cost. The expected net benefit of sampling (ENBS) is the EVSI less the cost of conducting a research with sample size n. The ENBS reaches the maximum at the optimal sample size. If the maximum ENBS is greater than the fixed cost of conducting the research, then additional research is warranted (42,160,163). The ENBS of sample size (n) can be calculated given the population EVSI for that sample size and the cost of additional research at that sample size (C_n):

$$ENBS_n = pEVSI_n - C_n \quad (3\text{-}13)$$

3.3.4 Primary research

Based on outcomes of the decision model in stage 2 (section 3.3.2) and the research priorities established in stage 3 (section 3.3.3) using VoI analyses, the next stage is to design and conduct primary studies to detect a difference in the key parameters driving the primary research. For example, if the research priorities identified in stage 3 indicated insufficient data surrounding the treatment effect, then the study should be conducted to detect a difference in effectiveness (6). If an economic evaluation is commissioned alongside a clinical trial, attempts should be made to adhere to the gold standard characteristics (use of appropriate comparator, endpoints, adequate length of follow-up to assess the full impact of treatment etc.) for economic evaluation within clinical trials (27). Use of gold standard economic evaluation within a clinical trial (section 1.3) will strengthen the design of research and improve the quality of economic evaluation.

3.3.5 Synthesis and modelling with updated evidence

In this stage of the iterative approach, new evidence is incorporated into the information set used within the decision model, and any other evidence published during the interim. Having synthesised the primary research outcome with any other relevant information in stage 5, the iterative process then loops back to stage 2 again. This updating of existing evidence or knowledge about each parameter in the model with new information as it becomes available is known as a Bayesian process (164).

Having described the key steps of an iterative approach to economic evaluation, the following section examines its merit and limitations/challenges.

3.4 Merits and criticism of using an iterative approach

The iterative economic framework has been suggested throughout the lifecycle of a health technology assessment as it incorporates new evidence when such information becomes available and is recognised by some funding and decision making bodies such as NICE in the UK (5,6,10). This also, in overall, supports a process of gathering information and reducing uncertainty in order to improve decision making. The iterative approach to economic evaluation provides a framework in which evidence from a range of sources can be synthesised, and the information is continually updated using Bayesian process. The framework is based on a stepwise approach. In other words, each stage of the research process feeds information into the next stage in order to reduce uncertainty and aid decision making throughout. This involves various stages to improve information

regarding the important parameters of interest, for example, treatment effect, the comparator in the model, and uncertainty surrounding the cost-effectiveness results. Given the iterative nature of the framework, the use of a single one-off trial is inadequate as a sole input for economic appraisal. The iterative process evolves alongside all stages of healthcare research (as illustrated in Figure 3-1) instead using one-off analysis by providing a structure to answer a given decision problem and improves decision making by reducing uncertainty. The main objective of such a process is to answer the cost-effectiveness decision problem (6).

The use of an early stage probabilistic decision analytic model can help set search priorities and inform if additional research is required (6). If additional research such as an RCT is undertaken, this will provide information on costs, effects and other important parameters. This updated information is then used to update the model. By re-running the model and performing VoI, this process allows to explore if there is any scope to acquire further information to reduce uncertainty. If there is potential for additional research, the decision model can again help to inform the design of the future research. For example, if the VoI analysis suggested that it would be of most value to gather further information on the quality of life or cost, an RCT is not the optimal research design. Instead, observational studies would be more appropriate to collect such information than conducting a large-scale RCT.

The iterative framework supports healthcare research bodies to prioritise between several competing and possibly cost-effective alternatives. The iterative approach allows decision making bodies such as NICE in the UK to assess the potential cost-effectiveness of alternative interventions and helps to identify evidence gaps and set research priorities. This will enable efficient allocation of limited resources.

Though the iterative framework improves the overall decision making as mentioned above, it has practical and methodological limitations. First, such a process requires time and is resource intensive. The VoI results assist decision makers in research prioritisation decisions, and they are described as a best practice for handling decision uncertainty (39). However, VoI analysis can be time and resource intensive to develop a de novo decision model and conduct literature searches for model inputs. Even though researchers have good knowledge and access to a programming language as well as familiarity with the VoI methodology and process, it requires considerable time to develop a decision model, undertake probabilistic analysis followed by EVPI analysis and finally undertaking EVSI calculation for a wide range of sample sizes (6). Calculation for EVPPI and EVSI for non-linear models requires sophisticated computations along with advanced expertise in economic evaluation and simulation techniques (73). The use of two-level Monte Carlo

simulation although seems straightforward, particularly in models that require individual-level simulations, this approach is computationally expensive (10). Nonetheless, in recent years, there have been advances in VoI methodology and computing tools to reduce computational challenges (165-167).

The most recent approaches offer computationally efficient procedures for estimating EVPPI and EVSI. For example, Strong et al. (168) provide an efficient method for estimating EVPPI. Their nonparametric regression-based method requires only the probabilistic sensitivity analysis sample rather than estimating EVPPI via a two-level Monte Carlo procedure. In their applied example, Tuffaha et al. (165) used the nonparametric regression approach to estimate EVPPI and EVSI calculations. They reported that the nonparametric regression method estimated EVPPI and EVSI values in less than a minute. In contrast, the Monte-Carlo simulation took around 4 hours for every EVPPI estimate and around 8 hours for every EVSI value for a given sample size. Recently Heath et al. (169) proposed a novel approximation method for the EVSI calculation using the moment matching methodology.

Second, the VoI analysis not only uses current information but also requires future patient population estimates over an 'appropriate' time horizon. A future population that could be benefitted from the information is calculated as the sum of the discounted incidence of disease. It may be appropriate to estimate future incidence and prevalence of the disease depending on the nature of disease and treatment, but it is very difficult to define an appropriate time horizon, and VoI is extremely sensitive to the time horizon selected (170,171). In addition, it is hard to estimate the effective lifetime of an intervention or a health technology given dynamic and complex nature of innovation of new therapy or technology. Ideally, the time horizon should reflect the time over which the decision question remains relevant as when new technologies and treatments become available the current decision question becomes irrelevant. A systematic assessment of the potential impact of new and emerging technologies in the early stage of technology development provides a means to estimate appropriate time horizon (172).

Third, the validity of the VoI approach within the iterative framework in economic evaluations rests on the assumption that the model structure on which the analysis is based on is correct and that uncertainty in model input parameters is appropriately characterised. Structural uncertainty arises because of uncertainty about the true structural relationship between model outputs and a set of quantities which form the model output (173). The assessment of the structural uncertainty is usually limited to running a range of scenario analyses (68) and model averaging is an alternative approach (174).

Model averaging involves averaging all the possible combinations of predictors when inferences are made about quantities of interest (175).

Following the iterative framework with earlier modelling at stage 2 of the iterative framework could reduce the cost related to the subsequent evaluation of health technology or intervention and further research. Conducting RCTs is often infeasible particularly for less prevalent diseases and can be an arduous process. For example, in rare diseases, international research projects could be desirable. Over the years, there have been international networks that support research into the rare disease which may enable more informative registries. However, many authorities require local information which could not be easily available such as resource use or quality of life (QoL) (176).

Quality of life is a ubiquitous concept that encompasses a number of different dimensions and has different philosophical, political and health-related definitions (177). The dimensions generally cover physical, psychological, social and spiritual wellbeing (178). The subjective perception one has about different aspects of life depends significantly on individuals' priorities and needs. Health-related QoL (HR-QoL) is a patient-reported outcome which is usually measured with validated instruments such as questionnaires and semi-structured interview schedules. It includes the physical, functional, social and emotional well-being of an individual. The measurement of QoL is basically done using three approaches (179): using generic instruments that provide a summary HRQoL (e.g. health profiles), specific instruments (e.g. disease specific, population specific, function specific) and preference-based measures such as health state utility. Preferences for the same health state (for example type 2 diabetes, being physically active) could be quite different in different countries. Such variation in preferences can vary, among others, by cultural belief, availability of health care and social institutions (20). Likewise, differences in methods may obscure true differences in values between countries (180). These differences can have a significant impact on the valuation of health states and the resulting cost-effectiveness of interventions (181,182).

3.5 A review on the use of iterative framework in decision making

As discussed in Chapter 1 and earlier sections of this chapter, economic evaluations are helpful in informing decision making process as they adopt a systematic approach to compare alternative options (health interventions) in terms of costs and associated health benefits. Several decision making and funding bodies such as NICE in the UK, Pharmaceutical Benefits Advisory Committee in Australia (57) use methods of economic evaluation in particular decision analytic models to inform reimbursement, and allocate

finite and constrained health care resource. Decision analytic models have become an integral part of such process (183) as it allows synthesis of all available evidence in order to identify the incremental costs and health benefits of new intervention/technology compared with current practice (section 1.4). An essential component of such model-based economic evaluation includes adequately characterising uncertainty associated with the model structure, identification of model inputs and choices or assumptions made within the analysis (38,68,183). The typical method of quantifying the level of confidence in the output of the cost-effectiveness analysis in relation to uncertainty in the model inputs is PSA (37,63). PSA have become the norm in many health economic evaluations and is recommended by HTA bodies such as NICE in the UK (63). VoI was proposed to characterise uncertainty in cost-effectiveness analyses (85) and is the notion that information is valuable because it reduces the uncertainty surrounding decisions. The analysis of VoI is an increasingly popular method to conduct PSA in health economic evaluations (5,66,164).

VoI methods have been proposed as a systematic decision analytic approach to understanding the need for further research, appropriate research design and set research priorities (82,163). In recent years, there have been methodological development and application of VoI methods in several healthcare fields. Recent systematic reviews of VoI methods in health technology assessment provided insight on evolving methods and application (73,166), how the VoI statistics interpreted (184) and used in research prioritisation (85,185). These reviews also highlighted methodological and technical challenges, for example, such as high computational demand that has limited the use of VoI methods in future research prioritisation.

An iterative framework to the economic evaluation of health technologies was suggested beginning with early indicative studies and progressing towards more rigorous assessment as data become available (4,5,43). However, it is not clear how this iterative process has been applied in real life economic evaluation. Thus, a systematic review is conducted with an aim to identify literature on how VoI method is used in decision making to inform further research within an iterative process of analysis.

The sections below describe the methodology used to review the evidence and results.

3.5.1 Literature review methods

As the focus of this literature review was on the application of VoI methods within the iterative framework in decision making to inform further research, it provides synthesised information such as where such studies fit within the framework, type of decision informed

by the VoI methods. An initial scoping search was conducted on PubMed using search term (health-care decision making AND cost-effective AND (iterative approach OR value of information[ti])) which resulted in 13 hits. Then a structured search strategy was developed by elaborating the key search words in PubMed search. Search strategies used to identify relevant published economic evaluations, listed in Appendix B1, consisted of a combination of keywords and MeSH terms. Searches were conducted in MEDLINE, Embase, CINAHL, EconLit, Cochrane library, Scopus and NIHR databases to include studies published up to 31 December 2017. In addition, citation search of Claxton et al. (72), Fenwick et al. (5), and Sculpher et al. (4,43) were done as these studies described or used VoI methods in the iterative framework. Reference list of included studies was checked in order to locate any relevant publication from the same or related study.

Studies were included if they were published economic evaluations in healthcare, were in English-language and used VoI methods within the iterative framework. Studies were excluded if they were a systematic review, the VoI methods were applied in areas other than healthcare research or were concerned with methodological research as the focus of the review was on the application of VoI methods.

Following de-duplication of database search results, articles were screened by applying the inclusion criteria on titles and abstracts of each identified article. Full-text data extraction of selected studies was performed using a standardised proforma (Appendix B2) which was developed using the CHEERS checklist (129) and ISPOR-SMDM guidance on good practice for economic modelling in health care (57).

3.5.2 Results

The search of electronic databases identified 2,078 potentially relevant articles including 389 articles identified through other sources and cross-referencing. Following de-duplication and abstract screening, 184 articles were selected for full-text screening. Of those, 89 studies met the inclusion criteria and included in this review. The remaining 95 were excluded because either they reported methodological studies (n=46), reported systematic review or were editorial or conference abstracts (n=24), did not report VoI results (n=22) or were study protocol or published as a part of full HTA report (n=3). Figure 3-2 summarises the study selection process.

On the basis of this literature, the remainder of this chapter describes the characteristics of included studies, maps with the iterative framework and discusses the main aspects of processes and approaches used in evidence gathering and or priority setting for research.

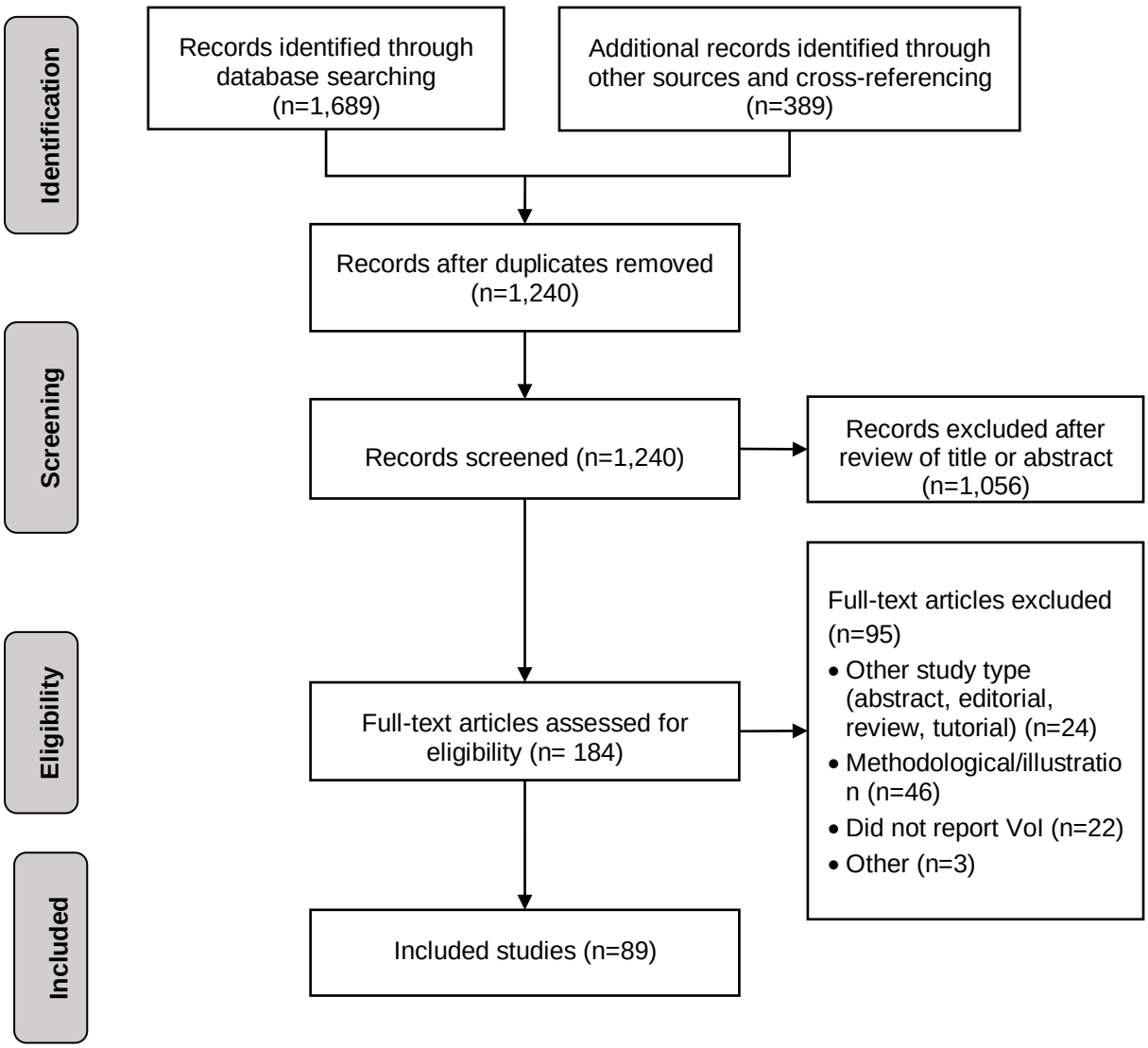

Figure 3-2: PRISMA flow diagram of study selection

3.5.2.1 Characteristics of included studies

Almost half (n=45) studies were conducted in the UK (Table 3-1.) Remaining studies were conducted in Europe (n=20), North America (n=20), Australia (n=3) or Thailand (n=1). Included studies evaluated medicines, health interventions, diagnostics and medical devices for a range of different conditions and study populations. The type of decision models used were either decision trees (n=19) (5,76,78,80,84,186-199), Markov models (n=45) (75,200-243), a combination of a decision tree and Markov models (n=12) (81,244-254), or individual patient data / discrete event simulation / microsimulation (n=4) (77,255-257), or simple linear regression (n=2) (258,259). Seven studies did not report model type, or the description was not clear (260-266). In terms of the type of VoI analysis, 82 of the included articles (92%) reported EVPI estimation, 48 (54%) reported EVPPI, 15 (17%) reported EVSI, 7 (8%) reported ENBS, and one (1%) reported ENG. These studies used

VoI to inform decisions (i.e. whether additional research was worthwhile), inform research focus and/or trial design by determining optimal sample size, or inform research priorities.

3.5.2.2 Mapping with the iterative framework

The included studies are mapped (Figure 3-3) with the 'five steps' of the iterative framework as described in section 3.3. Majority of the studies (n=72, 81%) started with evidence synthesis and decision analytical modelling whereas the remaining 17 studies started with conducting the economic evaluation (prospectively or retrospectively) alongside the clinical trial. Thirty-one studies reported funding from the NIHR or UK Medical Research Council and 27 of which reported only mapped with the first 3 steps of the iterative framework. Of these 31 studies, only two (230,267) studies did not recommend additional data collection. These studies are summarised below according to which steps in the iterative framework they pertained to:

Stages: I–III (N=68)

Sixty-eight (76%) studies described the first 3 steps of the iterative framework, i.e. identified decision problem, synthesised available evidence and populated the decision model, and performed VoI analysis for research priority setting. Usually, a single publication reported the results from the economic model and VoI analysis. However, in some cases, for example, Jutkowitz et al. study (243,268) they initially performed cost-effectiveness analysis to evaluate the cost-effectiveness of urate-lowering treatment strategies (allopurinol and febuxostat) for the management of gout (268). In a subsequent publication, Jutkowitz et al. (243) used the same Markov model and incorporated VoI analysis to quantify decision uncertainty regarding the cost-effectiveness of allopurinol and febuxostat in the management of gout, and concluded that there is value in conducting additional research on the effectiveness of allopurinol dose escalation and febuxostat dose escalation.

Stages: I–V (n=2)

Two studies (206,269) sequentially followed all the five steps. Oostenbrink et al. (269) first developed a Markov model to assess the cost-effectiveness of bronchodilator therapy in chronic obstructive pulmonary disease (COPD). Their VoI analysis showed that the utility parameter had the highest EVPPI, i.e. contributed most to the overall uncertainty as to which bronchiolitis treatment to adopt given the current information. Then additional utility research was performed in a sample of 1,234 COPD patients who completed the EQ-5D questionnaire at baseline.

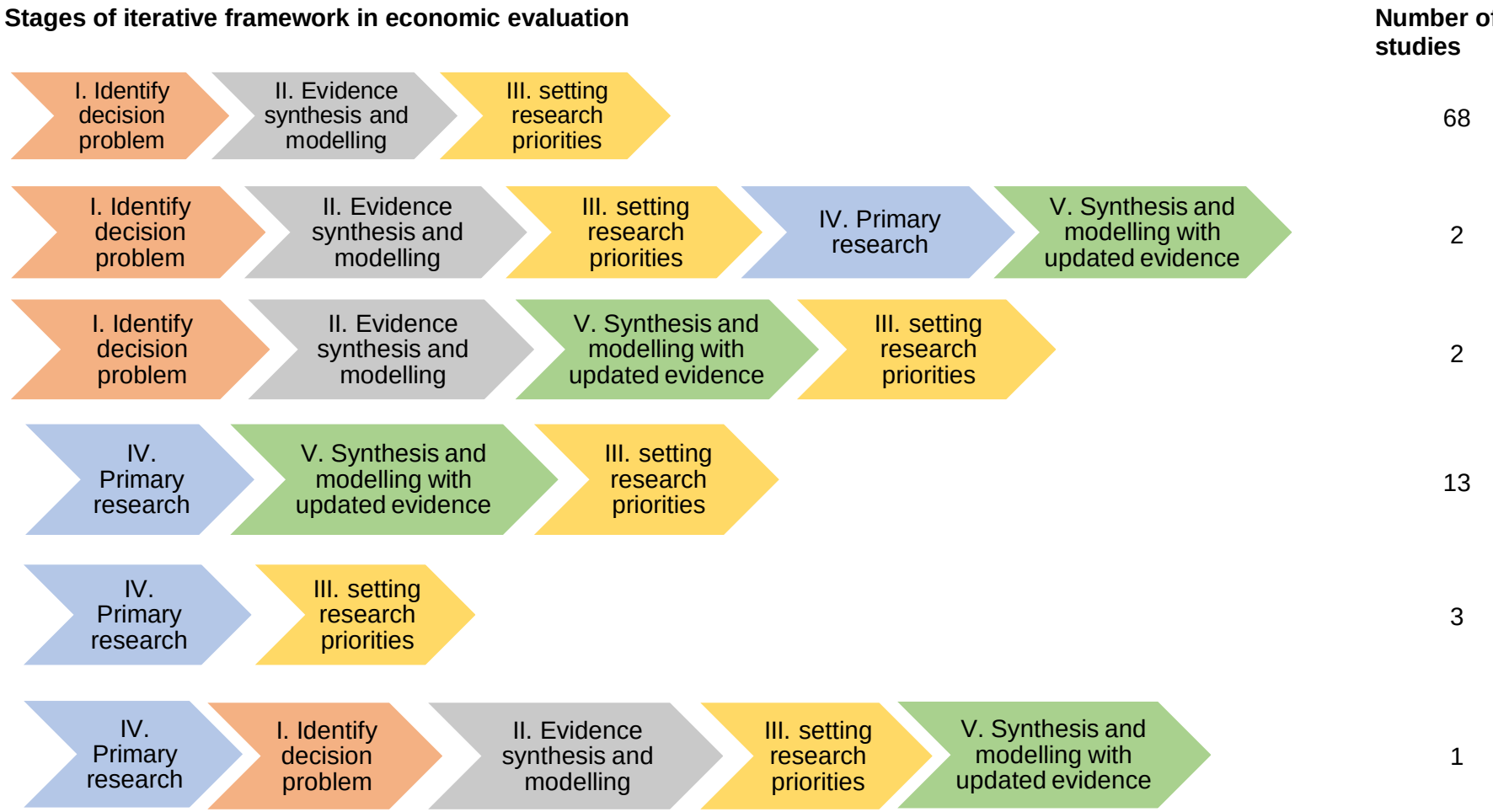

Figure 3-3: Mapping studies within the iterative framework

The newly collected information on utility was combined with the prior information (222) and the total EVPI per patient for the updated model was substantially reduce (from €1985 to €1037). Burr et al. (267) in their glaucoma screening study first evaluated the cost-effectiveness of glaucoma screening. The analysis suggested a feasibility study to improve detection, refinement of model parameters and an RCT of an intervention to improve uptake of glaucoma testing. They used a mixed method approach to inform the optimal design for a trial using a Delphi survey (270) and views of NHS providers (271). Their updated model (206) was informed by feasibility study suggested that glaucoma screening trial in the UK is unlikely to be the best use of research resource.

Stages: I, II & V, III (n=2)

Two studies (211,215) first used a decision model to estimate the cost-effectiveness of health technology. Favato et al. first developed a model (272) to evaluate the cost-effectiveness of a vaccination strategy to prevent HPV related diseases. Later they extended their model to include herd immunity, made it a dynamic model and assessed the cost-effectiveness of a quadrivalent-based HPV vaccination strategy within a Bayesian framework. Hall et al. (215) first developed a decision model to assess the cost-effectiveness of trastuzumab for HER2-positive overexpressing early breast cancer. They re-evaluated the cost-effectiveness of trastuzumab using data from a clinical trial with longer follow-up. Their VoI analysis placed the highest value on research into the duration of treatment benefit.

Stages: IV, V, III (n=13)

Thirteen studies (5,80,191,199,200,202,203,216,223,228,240,251,262) first performed economic analysis alongside the trial then updated the evidence, developed a model to assess long-term cost-effectiveness including VoI analysis. For example, in their study Boyd et al. (203) first undertook economic evaluation alongside a clinical trial, then used a model to synthesise evidence from the trial and published sources. EVPI results suggested that additional research is potentially worthwhile.

Stages: IV, III (n=3)

Only three studies (258,259,265) first performed economic evaluation alongside the clinical trial then VoI analysis in order to quantify decision uncertainty.

Table 3-1: Summary of systematic review findings

Author, year	Country	Disease or condition	Study population	Model type	VoI analysis type	Stage of iterative evaluation included*	Source of funding
Abrahamyan 2014 (260)	USA and Canada	Haemophilia A	children with severe haemophilia A	not reported	EVSI, ENG	I, II, III	Canadian Blood Services, Bayer HealthCare Pharmaceuticals, Canada
Albers-Heitner 2012 (265)	the Netherlands	Urinary incontinence (UI)	Adult patients with stress, urgency or mixed UI	not reported	EVPI	IV, III	The Netherlands Organisation for Health Research and Development
Ashby 2014 (200)	UK	venous leg ulcer	Adults aged ≥18 years with a venous leg ulcer	Markov	EVPI	IV, V, III	NIHR HTA programme
Bansback 2009 (201)	USA	CHD	Female patients with Rheumatoid arthritis	Markov	EVPPI	I, II, III	None
Bartha 2013 (202)	Sweden	hip-fracture	Patients aged >70 years, weight ≥40 kg scheduled for hip-fracture surgery during operating hours	Markov	EVPI	IV, V, III	The Stockholm County Council, Sweden
Barton 2009 (259)	UK	psychosis	People with a current diagnosis of affective or non-affective psychosis	Simple linear regression	EVPI	IV, III	Medical Research Council (MRC) trial platform grant
Boyd 2016 (203)	UK	Smoking cessation	Pregnant smoker (women) in Glasgow	Markov	EVPI	IV, V, III	Chief Scientist Office, Scottish Government
Brown 2006 (204)	UK	Breast cancer screening	Women registered with a GP practice	Markov	EVPI	I, II, III	MRC UK
Bruce 2015 (186)	UK	Otitis media with effusion (OME)	Children with cleft palate under the age of 12 years	Decision tree	EVPI, EVPPI	I, II, III	NIHR HTA programme, and Healing Foundation
Brush 2011 (205)	UK	Primary rectal cancer	Patients aged ≥50 years, undergoing pre-operative staging prior to curative surgery	Markov	EVPI	I, II, III	NIHR HTA programme
Burr 2011 (206)	UK	Open acute glaucoma	A cohort of 40-year old males	Markov	EVPI, EVPPI	I, II, III, IV, V	MRC UK

Table 3-1 (continued)

Author, year	Country	Disease or condition	Study population	Model type	VoI analysis type	Stage of iterative evaluation included*	Source of funding
Campbell 2014 (207)	UK	Ischaemic cardiomyopathy	A cohort of patients with ischemic cardiomyopathy	Markov	EVPI	I, II, III	NIHR HTA programme
Carlton 2008 (208)	UK	Amblyopia	Children aged up to 7 years	Markov	EVPI	I, II, III	NIHR HTA programme
Castelnuovo 2006 (244)	UK	Hepatitis C infection	Former injecting drug users aged 37 years old at inception	Decision tree; Markov	EVPI, EVPPI	I, II, III	NIHR HTA programme
Claxton 2001 (209)	USA	Alzheimer's disease	People with mild to moderate Alzheimer's disease	Markov	EVPI, EVPPI	I, II, III	Commonwealth Fund
Colbourn 2007 (187)	UK	Group B Streptococcal and bacterial infection	Women giving birth	Decision tree	EVPI	I, II, III	NIHR HTA programme
Collins 2007 (210)	UK	Prostate cancer	Men with metastatic hormone-refractory prostate cancer (mHRPC).	Markov	EVPI	I, II, III	NIHR HTA programme
Favato 2012 (211)	Italy	Human Papilloma Virus (HPV)	Girls aged 12-25 years	Markov	EVPI	I, II, III & V	Sanofi Pasteur MSD, Italy and UK NIHR
Fenwick 2006 (5)	UK	Elective procedure	High-risk patients undergoing major elective surgery	Decision tree	EVPI, EVPPI	IV, V, III	Bayesian Initiative
Fox 2007 (212)	UK	Heart failure	People with HF due to LV systolic dysfunction	Markov	EVPI, EVPPI	I, II, III	NIHR HTA programme
Gajic-Veljanoski 2012 (255)	Canada	Fractures	50-year old postmenopausal women without osteoporosis	Microsimulation	EVPI	I, II, III	Canadian Institutes of Health Research (CIHR)
Galani 2008 (213)	Switzerland	Obesity	Obese and overweight people	Markov	EVPI, EVPPI	I, II, III	Swiss Federal Office of Health

Table 3-1 (continued)

Author, year	Country	Disease or condition	Study population	Model type	VoI analysis type	Stage of iterative evaluation included*	Source of funding
Genders 2009 (245)	the Netherlands	Coronary artery disease (CAD)	Patients with chest pain	Decision tree, Markov	EVPI	I, II, III	Netherlands Organisation for Health Research and Development, and the Erasmus University Medical Centre
Ginnelly 2005 (214)	UK	recurrent UTI	Children	Markov	EVPI	I, II, III	NIHR HTA programme
Gurusamy 2012 (188)	UK	Gallbladder	Patients with gallbladder and common bile duct stones	Decision Tree	EVPI, EVPPI	I, II, III	No funding received
Guzauskas 2017 (246)	USA	Ischemic stroke	Patients with mild stroke	Decision tree, Markov	EVSI	IV, V	Genentech, Inc.
Hall 2011 (215)	UK	Breast cancer	Women with HER2-positive early breast cancer	Markov	EVPI, EVPPI	I-II, V	NIHR HTA Programme
Hall 2017 (216); Stein 2016 (273)	UK	Breast cancer	Women with surgically treated breast cancer	Markov	EVPI, EVPPI and EVSI	IV, V	NIHR HTA Programme
Hassan 2009 (217)	USA	Colorectal cancer	Adults aged 50-year olds in the US	Markov	EVPI, EVPPI	I, II, III	Not reported
Hassan 2010 (189)	USA	Colorectal cancer	Adults aged 60 years following complete endoscopic resection of an LR malignant polyp	Decision tree	EVPI, EVPPI	I, II, III	Not reported
Haukaas 2017 (247)	Norway	Latent tuberculosis	Immigrants <35 years of age from countries with a high incidence of TB	Decision tree; Markov	EVPI, EVPPI	I, II, III	No funding received
Havrilesky 2013 (248)	USA	Endometrial cancer	Women with grade 3 or grades 2-3 endometrial cancer	Decision tree; Markov	EVPI, EVPPI	I, II, III	No funding received

Table 3-1 (continued)

Author, year	Country	Disease or condition	Study population	Model type	VoI analysis type	Stage of iterative evaluation included*	Source of funding
Henriksson 2006 (218)	Sweden	Abdominal aortic aneurysm (AAA)	Men aged 65 years	Markov	EVPI, EVPPI	I, II, III	Health Council of Ostergotland, Sweden, and the National Pharmacy Corporation's fund for research and studies in health economics and social pharmacy, Sweden
Hewitt 2009 (190)	UK	Postnatal depression	Depressed women identified as depressed	Decision tree	EVPI, EVPPI	I, II, III	NIHR
Iglesias 2006 (219)	UK	Venous leg ulcers	Individuals aged 66 years	Markov	EVPI, EVPPI	I, II, III	pump priming research grant from the University of York
Jansen 2010 (220)	UK	Ankylosing Spondylitis	AS patients requiring daily or routine (≥25 days per month) NSAID intake	Markov	EVPI	I, II, III	Merck & Co., Inc
Jutkowitz 2017 (243); Jutkowitz 2014 (268)	USA	Gout	Hypothetical gout patient	Markov	EVPI, EVPPI, EVSI, ENBS	I-II & II-III	No funding received
Koerkamp 2008 (262)	the Netherlands	Acute Knee Trauma	Patients with acute knee trauma	not clear	EVPI, EVPPI, EVSI, ENBS	IV, V	Not reported
Koerkamp 2010 (258)	USA	Intermittent Claudication	Patients with intermittent claudication	Simple linear regression	EVPI, EVSI	IV and III	The Netherlands organization for health research and development
Kovic 2015 (231)	USA	Glioblastoma Multiforme (GBM)	Adult patients with newly diagnosed GBM	Markov	EVPI	I, II, III	Not reported
Latimer 2013 (228); Palmer 2012 (274)	UK	Aphasia	Patients with aphasia	Markov	EVPI, EVPPI	IV & V	NIHR RfPB, CLAHRC
Leaviss 2014 (235)	UK	Smoking cessation	adult smokers	Markov	EVPI, EVPPI	I, II, III	NIHR HTA programme

Table 3-1 (continued)

Author, year	Country	Disease or condition	Study population	Model type	VoI analysis type	Stage of iterative evaluation included*	Source of funding
Leelahavarong 2011 (232)	Thailand	HIV	general population aged 18 to 30 years old, FSW, IDU, MSM, and military conscripts	Markov	EVPI, EVPPI	I, II, III	Health System Research Institute (HSRI)
Lewis 2016 (191)	UK	Chronic pelvic pain	women aged 18-50 years who suffered from pelvic pain for >6 months	Decision tree	EVPI, EVPPI	IV, V	Chief Scientist Office, Scottish Government
Loon 2010 (234)	The Netherlands	Non-small cell lung cancer	Hypothetical cohort of NSCLC patients	Markov	EVPI	I, II, III	Not reported
Martikainen 2005 (233)	Finland	Glioblastoma multiforme	Patients with glioblastoma multiforme	Markov	EVPI	I, II, III	Schering-Plough, Finland Oy
McCullagh 2012 (252)	Ireland	Total hip replacement	Patients undergoing major orthopaedic surgery	Decision tree, Markov	EVPI, EVPPI	I, II, III	No funding received
McKenna 2009 (221)	UK	Angina	adults with chronic stable angina	Markov	EVPI, EVPPI, EVSI, ENBS	I, II, III	NIHR HTA Programme
McKenna 2010 (230)	UK	Post-MI heart failure	patients with post-MI HF	Markov	EVPI, EVPPI	I, II, III	NIHR HTA Programme
Micieli 2014 (256)	Canada	Atrial fibrillation	Patients with AF at risk of stroke	Microsimulation	EVPI, EVPPI	I, II, III	Heart & Stroke Foundation of Canada & University of Toronto
Miners 2014 (236)	UK	Hepatitis C infection	Migrants from the Indian subcontinent	Markov	EVPI, EVPPI	I, II, III	NICE
Miquel-Cases 2016 (238)	the Netherlands	Breast Cancer	Cohort of 40-year old women with triple-negative breast cancer	Markov	EVPI, EVPPI	I, II, III	Center of Translational Molecular Medicine
Mohseninejad 2013 (198)	the Netherlands	Coeliac disease	Patients with irritable bowel syndrome (IBS)	Decision tree	EVPI	I, II, III	Not reported
Mohseninejad, 2013(229); Van Den Berg, 2011(275)	the Netherlands	Depression	Patients with minor depression	Markov	EVPI, EVPPI	I, II & II, III	Dutch Ministry of Health, RIVM

Table 3-1 (continued)

Author, year	Country	Disease or condition	Study population	Model type	VoI analysis type	Stage of iterative evaluation included*	Source of funding
Morliere, 2015(239)	France	Complete Spinal cord injury	Patients with a complete spinal cord lesion and a neurogenic bladder	Markov	EVPI, EVPPI	I, II, III	Not clear
Ney, 2014(264); Chi, 2014(276)	USA	Primary molar sealant	children under age 12 months	Not clear	EVPI	I, II & II, III	National Institute of Dental and Craniofacial Research (NIDCR)
Oostenbrink, 2008(222); Oostenbrink, 2005(269)	the Netherlands	COPD	patients with moderate to very severe COPD	Markov	EVPI, EVPPI	I, II & II, III & IV & V	Boehringer Ingelheim International and Pfizer Global Pharmaceuticals
Palmer, 2016(240)	UK	Joint hypermobility syndrome	People with JHS	Markov	EVPI	IV, V	NIHR HTA Programme
Pandor 2011 (197)	UK	Minor Health Injury	Patients with MHI	Decision tree	EVPI	I, II, III	NIHR HTA Programme
Pei 2015 (237)	USA	HIV	Patients initiating ART	Markov	EVPI	I, II, III	National Institute of Allergy and Infectious Diseases of the National Institutes of Health, NIH
Petrou 2015 (227)	Cyprus	Renal Cell Carcinoma (RCC)	People with RCC who have been previously treated with Sunitinib or cytokines	Markov	EVPI	I, II, III	Not mentioned
Philips 2006 (249)	UK	NSTEACS	Patients at high risk of NSTEACS	Decision tree; Markov	EVPI, EVPPI	I, II, III & III	NIHR HTA Programme
Purmonen 2011 (223)	Finland	Breast cancer	HER2 positive patients aged 50 years	Markov	EVPI, EVPPI	IV, V, III	Yrjö Jahnsson Foundation and Pharma Industry
Rao 2009 (192)	UK	Oesophageal cancer	patients diagnosed with oesophageal cancer	Decision tree	EVPI	I, II, III	Elision Health Ltd.

Table 3-1 (continued)

Author, year	Country	Disease or condition	Study population	Model type	VoI analysis type	Stage of iterative evaluation included*	Source of funding
Retel 2011 (224)	The Netherlands	Head and neck cancer	Patients with advanced head and neck cancer	Markov	EVPI	I, II, III	No funding received
Robinson 2005 (250)	UK	NSTEACS	patients with non-ST elevation ACS over a period of 50 years	Decision tree, Markov	EVPI	I, II, III	NIHR HTA Programme
Rodgers 2008 (253)	UK	AF refractory	Adults with AF refractory	Decision tree, Markov	EVPI, EVPPI	I, II, III	NIHR HTA Programme
Rogowski 2009 (254)	UK	NSTEACS	Patients with NSTEACS	Decision tree, Markov	EVPI	I, II, III	NIHR HTA Programme
Simpson 2014 (77)	UK	Peripheral arterial occlusive disease (PAD)	Patients with symptomatic PAD suitable for endovascular treatment for disease distal to the inguinal ligament.	Discrete event simulation	EVPI	I, II, III	NIHR HTA programme
Singh 2008 (84)	Canada	Chest pain	Patients presenting to emergency departments with chest discomfort.	Decision tree	EVPI	I, II, III	Funding not received
Soares 2012 (81)	UK	Severe sepsis	Adult patients severely ill with sepsis in the UK	Decision tree; Markov	EVPI	I, II, III	NIHR HTA Programme
Soeteman 2017 (242)	USA	Stroke	Patients suffering from stroke aged ≥45 years	Markov	EVPI, EVPPI, EVSI, ENBS	I, II & II, III	American Heart Association
Speight 2006 (241)	UK	Oral cancer	hypothetical population over the age of 40 years	Markov	EVPI, EVPPI	I, II, III	NIHR HTA Programme
Stevenson 2009 (257); Stevenson 2011 (277)	UK	Fractures	Cohort of osteoporotic women	Individual patient model	EVSI, ENBS	I, II, III	HTA programme, on behalf of NICE

Table 3-1 (continued)

Author, year	Country	Disease or condition	Study population	Model type	VoI analysis type	Stage of iterative evaluation included*	Source of funding
Stevenson 2009 (263)	UK	Osteoporosis	Osteoporotic women	Not clear	EVSI	I, II, III	the UK National Coordinating Centre for Health Technology Assessment (NCCHTA)
Stevenson 2010 (266); Stevenson 2010 (278)	UK	Postnatal depression	Women with postnatal depression	Not clear	EVPI, EVPPI	I, II, III	NIHR
Tappenden 2004 (75)	UK	Multiple Sclerosis (MS)	Patients with MS	Markov	EVPI	I, II, III	HTA programme
Thariani 2013 (261)	USA	Breast cancer	Women undergoing surveillance after completion of primary breast cancer therapy for early-stage breast cancer	Not clear	EVSI	I, II, III	Centre for Comparative Effectiveness Research in Cancer Genomics, NIH
Ting 2015 (225)	USA	Non-small cell lung cancer	Patients with advanced EGFR mutation-positive NSCLC	Markov	EVPI, EVPPI	I, II, III	No funding received
Tuffaha 2014 (80)	Australia	Peripheral arterial catheter	Adult surgical patients admitted to post-operatively to the ICU who had a peripheral arterial catheter inserted	Decision tree	EVPI, EVSI, ENBS	IV, V	National Health and Medical Research Council, Australia
Tuffaha 2015 (193)	Australia	Elective caesarean section	Obese women undergoing caesarean section	Decision tree	EVPI, EVPPI, EVSI	I, II, III	National Health and Medical Research Council, Australia
Tuffaha 2015 (78)	Australia	pressure ulcers	Hospitalised patients who are at risk of pressure ulcer and malnutrition, aged 70 years	Decision tree	EVPI, EVPPI, EVSI, ENBS	I, II, III	National Health and Medical Research Council, Australia
Ulph 2017 (194)	UK	Newborn screening	Mothers of newborn babies in England	Decision tree	EVPI	I, II, III	HTA Programme
van den Berg 2010 (195)	the Netherlands	Pregnancy	Women with 33 weeks gestation	Decision tree	EVPI	I, II, III	Dutch Association for Acupuncture

Table 3-1 (continued)

Author, year	Country	Disease or condition	Study population	Model type	VoI analysis type	Stage of iterative evaluation included*	Source of funding
Wailoo 2008 (196)	UK	Influenza	Healthy patients with influenza	Decision Tree	EVPI, EVPPI	I, II, III	NICE and the NHS HTA Programme
Wallner 2016 (226)	Canada	Type 1 diabetes	Cohort of T1DM patients who met the transplantation criteria	Markov	EVPI, EVPPI	I, II, III	Stem Cell Network grant, a Collaborative Research and Innovation Opportunities grant by Alberta Innovates Health Solutions and salary support: Capital Health Endowed Chair in Emergency Medicine Research and the Faculty of Medicine & Dentistry from the University of Alberta (CM).
Wilson 2010 (76)	UK	Acute cholecystitis	Patients undergoing laparoscopic cholecystectomy	Decision Tree	EVPI, EVPPI	I, II, III	Not reported
Wilson 2013 (251)	UK	Pigmented skin lesions	45-year-old patient with one potentially suspicious lesion	Decision tree; Markov	EVPI, EVPPI	IV, V, III	NIHR School of Primary care Research
Wong 2012 (199)	USA	Breast cancer	Women with lymph node positive hormone-receptor-positive breast cancer	Decision tree	EVSI	IV, V, III	Centre for Comparative Effectiveness Research in Cancer Genomics (CANCERGEN)

Note:

* I: Identify decision problems; II: Synthesis and modelling; III: Setting research priorities; IV: Primary research; V: Synthesis and modelling

3.5.3 Discussion

The majority of studies identified in this review reported VoI as a measure of quantifying decision uncertainty and to inform future research priorities or design an optimal trial. The most common types of VoI methods used were EVPI and EVPPI (n=74) and only 15 (17%) studies used EVSI. When mapped within the five steps of the iterative framework in economic evaluation, only two studies followed all the five steps in sequential order. From the analysis, it still appears that the wide adoption and application of VoI approach in healthcare is still limited as most of the studies do not proceed further after identifying future research priorities. More than half of the included studies (n=46) used VoI to inform future research focus by using EVPPI.

For those studies (n=68) that reported the first 3 steps of the iterative framework (i.e. pre-trial economic model) and set research priorities, the citation search was not able to capture follow-up studies. It may be possible that these studies received further funding to carry out primary research, but the results are not published yet. For example, Lewis et al. (191) performed an economic evaluation alongside a pilot trial evaluating gabapentin in chronic pelvic pain management (GaPP1). They used a decision tree to combine trial data with evidence from published sources and performed VoI analysis. The VoI suggested the feasibility of a future large multicentre RCT to determine the efficacy of gabapentin in the management of chronic pelvic pain in women. Subsequently, the investigators secured funding to perform a large multicentre, double-blind RCT, but the results are not available yet (279). For other studies, it could be that they were not successful in securing funds because such funding and research prioritisation decision, in general, are often based on the opinions, judgements and consensus of experts on research panels evaluating the scientific merit and relevance of research proposals (85,280).

The 15 studies that reported EVSI were published after 2007 with the majority (n=10, 66%) published after 2011 reflects the advances in computing and VoI methods in recent years (281). Most of the studies started with early indicative studies (pre-trial economic model) and suggested that there is value in collecting additional data to reduce decision uncertainty. However, it was difficult to locate follow-up publications because such studies may result in more than one publications. It is possible that not all VoI analyses were identified because of restrictions in search criteria, i.e. published, full-text, English-language articles. Although reference list of included studies was scanned to identify prior study and citation search was done to identify any follow-up studies especially when the study recommended future research, it was not easy to locate such studies. Web of

Science citation report was used to identify follow-up publications, but the database has its own limitation as it doesn't include all records and often excludes papers that are published online ahead of print. Furthermore, this review did not attempt to assess the quality of included studies as there are not any validated tools to value studies of research prioritisation methods (185).

This review tried to fill the research gap in verifying how the research priorities identified using VoI analysis are being implemented within the iterative framework of economic evaluation. Although the iterative framework supports a process of information gathering and reducing uncertainty in decision making, from the reviewed studies, it seems that the use of this approach in healthcare, in general, is still limited.

3.6 Chapter summary

This chapter introduced the iterative framework in the context of economic appraisal. This framework incorporates decision analytical modelling, probabilistic and VoI analyses to inform the adoption and research priority setting decision on an iterative basis. The review on the use of VoI methods within the iterative framework provided an insight on how the method has been used in real life economic evaluations. The remainder of the thesis presents an application of the proposed iterative framework for the case study considering the cost-effectiveness of BIs to promote physical activity. Chapter 4 presents the decision analytic model and evidence synthesis and estimates the cost-effectiveness and VoI analysis of BIs given current information. Chapter 5 considers the designing of the VBI study following an iterative approach, reconsiders the cost-effectiveness of VBIs as the evidence base evolves following the publication of the first trial data. Chapter 6 presents a reflection relating to the application of iterative framework and concludes by discussing the challenges faced, and lessons learnt.

Chapter 4 Estimating the cost-effectiveness of brief physical activity interventions

4.1 Introduction

The purpose of this chapter is to outline the modelling approach to establish a link between physical activity (PA), health consequences/effectiveness, and cost-effectiveness of brief interventions in PA promotion. This chapter corresponds with stages 2 and 3 of the iterative approach (as described in Chapter 3, section 3.3) in economic evaluation, involving the development of a decision analytic model-based on existing evidence to undertake an economic evaluation of (very) brief physical activity interventions. This will determine whether the very brief interventions in PA promotion are cost-effective, or whether further research is needed to make a more informed decision. It builds on the systematic review of existing evidence on effectiveness and cost-effectiveness of brief PA interventions presented in Chapter 2 and aims to estimate the cost-effectiveness of VBIs in PA promotion using a modelling approach based on the best available evidence.

The first section describes the decision problem followed by several sections describing the methodological development of the model. This includes decisions regarding specific model structure, modelling techniques, type of model inputs including baseline population. This is followed by the methods used to calibrate the decision model and finally presents the results from the first iteration of the model. This chapter provides the theoretical framework for the remaining chapters of this thesis.

4.2 The decision problem

Physical inactivity is the fourth leading cause of mortality worldwide (282). It leads to an increased risk of developing over twenty health conditions including coronary heart disease (CHD), cancer, stroke and type 2 diabetes (87,89,90,283,284). Physical inactivity is also associated with a considerable economic burden, which accounts for 1.5% to 3% of total direct healthcare costs in developed countries (92). In 2006-07, the direct cost to the UK National Health Service (NHS) for treating the consequences of physical inactivity was estimated at £0.9 billion (285). When other costs such as the value of morbidity/premature mortality-related lost productivity are included, the annual cost of physical inactivity in England is estimated at £8.2 billion, with an additional £2.5 billion for the contribution of physical inactivity to obesity (87).

Physical activity interventions delivered in a primary care setting are effective in increasing activity levels (94,101) and are considered cost-effective (97,98). A recent systematic review of evidence on the effectiveness of brief advice in PA indicated that such interventions are effective in improving PA participation compared with usual care (100). Although brief interventions are considered highly cost-effective in other domains of public health, such as smoking cessation and alcohol misuse (107-109), little economic evidence exists about their cost-effectiveness in physical activity (121,149).

The NHS health check (114) provides an ideal opportunity to deliver brief advice or other brief interventions to a larger proportion of the population. Very brief interventions to increase physical activity are likely to be beneficial for all adults aged 40-74, the target age group for the NHS health check in England (115,119). The latest Health Survey for England (118) indicated that the majority of 40-74 year olds do not meet the new guidelines for aerobic activity (at least 150 minutes per week of moderate PA, 75 minutes per week of vigorous PA or an equivalent combination of the two, in bouts of 10 minutes or more). Moreover, the proportion of people meeting these guidelines decreases with age. Compared with more complex PA interventions, VBIs could be easily integrated into the routine health check and are inexpensive to implement on a large scale. While (very) brief interventions may have a small effect, over a large population, this could translate into a significant public health benefit.

This study aims to investigate whether there is evidence for cost-effectiveness for VBIs in PA promotion in the primary care in the UK.

4.2.1 Interventions and comparators

The three classes of BIs were identified from the review of effectiveness evidence (Chapter 2). They are:

a) *Use of pedometers*: Pedometer as a motivational tool, goal setting (e.g. walking 10,000 steps/day for five times a week), in some cases participants received individual exercise feedback (walking plus feedback)

b) *Advice or counselling*: Brief advice or counselling on PA delivered by health professionals, face to face or by phone or both

c) *Action planning interventions*: Participants formulate their action plan in the format of what, when and where (time, place and number of minutes), record their intention on PA in the logbook or calendar

All three interventions were compared against usual care, i.e. no additional intervention. These BIs aim to increase individual's activity level by increased participation in PA.

4.2.2 Population

The study population included the NHS health check population, i.e. all people aged between 40 and 74 years in England, who have not been previously diagnosed with diabetes, hypertension, chronic heart or kidney disease (114).

4.2.3 Perspective

The costs and benefits (quality-adjusted life-years gained) of each VBI were assessed from the perspective of the UK NHS. The NHS and Personal Social Services (PSS) perspective was chosen because the study was conducted in the NHS context (primary care setting) and the NICE recommends in adopting a healthcare perspective (2).

4.3 Use of modelling techniques in the economic evaluation

Physical activity interventions have a range of both short (e.g. improvements in the mood) and long-term health benefits (51). It may be difficult to measure long-term benefits of PA from a single study (i.e. prospective study). To make an informed decision to adopt a given very brief PA intervention, a long-term assessment of costs and health effects must be made to capture all relevant differences in costs and health effects. RCTs usually have too short follow-up to measure this, and this often requires a modelling component to estimate the overall change in health-related quality and quantity of life as a result of a change in activity level.

Decision analytic models synthesise relevant data available from a variety of sources and facilitate in evaluating complex processes associated with the implementation of health interventions (286). They are useful to extrapolate primary data beyond the short-term endpoint of a trial (46), inform research planning and design, characterising and presenting decision uncertainty given existing information (287). Decision analytic models in cost-effectiveness analysis establish the most cost-effective interventions in the context of uncertainty about the future states of the world (59). It provides an analytical framework that represents a decision problem explicitly, combines evidence from a range of sources and facilitates the extrapolation of cost and health effects over time and between patient groups and clinical settings (288). The process of developing a decision model is more of

an iterative process which starts with developing a conceptual model, followed by synthesis of available evidence to populate the model then revision of the model.

4.4 Model design and development

The two sections above described the decision problem and the use of modelling techniques in the economic evaluation of brief PA interventions. This section describes the review of existing evidence to inform and structure the model, selection of diseases (model boundary) and the type of model used.

4.4.1 Informing and structuring the decision model

4.4.1.1 Review of evidence concerning physical activity and health

A literature search was carried out in order to synthesise the evidence available concerning PA and health. A search on PubMed was carried out using keywords and MeSH terms covering the literature published up to January 2015. The search combined physical activity with chronic conditions namely cardiovascular, cancers, mental health as well as with musculoskeletal conditions. These disease conditions included in this search were identified from the model-based economic evaluations (Chapter 2) that modelled the impact of PA on chronic conditions, and the Department of Health report examining the impact of PA and its relationship with health (87). The search results were limited to English language publications. The search identified existing systematic reviews, and only reviews were included using the review filter under ‘Article types’. These were systematic reviews and meta-analyses of both prospective and controlled studies examining the effects of PA on health. Once the systematic reviews and meta-analysis examining the link between PA and many chronic conditions were identified, another literature search was performed using the same method to investigate the association between PA and risk factors. For this, keywords related to chronic conditions were replaced by risk factors namely cholesterol level, blood pressure, and glycated haemoglobin. In particular, the interest was on the, if PA influences risk factor values, how the intensity, duration and energy expenditure of exercise may or may not influence these risk factors (biomarkers).

The pooled evidence from meta-analyses of well-designed RCTs as well as prospective studies is summarised in Table 4-1.

Table 4-1: Health benefits of PA in adults

Measures	Study details	Physical activity	Impact of PA on measures	Source
All-cause mortality	Systematic review and meta-analysis of 80 cohort studies with 1,338,143 participants (118,121 deaths) examining the association of domain-specific PA with all-cause mortality	Higher vs lower activity level	RR of 0.74 for leisure activity, RR for 1-hr increment per week for vigorous and moderate activity were 0.91 and 0.96 respectively	Samitz et al. (289)
Total cholesterol	Meta-analysis of studies examining the effect of exercise on lipids and lipoproteins in adults aged ≥50 years, mean age 63 years,	Aerobic exercise (walking, jogging)	Decrease in total cholesterol by 3.3 (-6.5 to -0.02) mg/dL i.e.	Kelly et al. (290)
HDL cholesterol	Meta-analysis of 25 RCTs examining the effect of PA on HDL-C level, mean aged varied between 23 and 75 years	Aerobic exercise	Mean net change (increase) by 2.53 (1.36–3.7) mg/dL	Kodama et al. (291)
HbA1c	Systematic review and meta-analysis of 47 RCTs assessing PA on HbA1c in diabetic patients	Structured exercise (≥150 min/wk) vs no exercise (usual care)	Decline in HbA1c level by 0.67% (-1.26% to -0.51%)	Umpierre et al. (292)
Cardiovascular				
Blood pressure and hypertension	Meta-analysis of 54 RCTs with 2,419 participants, mean age between 21 and 79 years, the sample included both normotensive and hypertensive patients	Aerobic exercise	Decrease in SBP by 3.84 (-4.97 to -2.72) mmHg; -4.94 and -4.04 mmHg in hypertensive and normotensive samples respectively	Whelton et al. (293)
CHD	Meta-analysis, nine prospective cohort studies had quantitative estimates and included in the dose-response analysis, average age ranged from 43 to 67 years	150 min/week of moderate-intensity PA vs no PA	14% lower risk (RR of 0.86, 0.77 to 0.96)	Sattellmaier et al. (294)

Table 4-1 (continued)

Measures	Study details	Physical activity	Impact of PA on measures	Source
Stroke	Meta-analysis of 23 prospective studies examining the association between PA and stroke incidence or mortality	High activity vs low activity or sedentary	27% lower risk of stroke incidence or mortality (RR of 0.73 (0.67 to 0.79)	Lee et al. (295)
Type 2 diabetes	Meta-analysis of 9 prospective cohort studies, average age ranged from 35 to 75	Moderate intensity PA (~11 MET h/week) vs no PA	17% lower risk (RR: 0.83, 0.76 to 0.90)	Jeon et al. (296)
Cancers				
Breast cancer (female)	Meta-analysis of prospective cohort studies with average follow-up of 5 to 20 years, participant aged ≥30 years	Most active vs least active	13-17% lower risk; 3% decrease in breast cancer risk for every 10 MET-h/week increment; 6% lower risk for each additional hour of PA	Monninkhof et al. (297), Wu et al. (298)
Colon cancer	Meta-analysis of 28 cohort studies, 30-50 year olds	Most active vs least active	RR of 0.83 (0.78 to 0.88)	Wolin et al. (299)
Lung cancer	Meta-analysis of prospective cohort studies	Moderate PA vs sedentary or no activity	18% (13 to 23%) lower risk	Buffart et al. (300)
Renal cancer	Meta-analysis of 14 cohort studies,	Moderate to vigorous PA vs no or sedentary activity	RR of 0.87 (0.76 to 0.99)	Behrens et al. (301)

Table 4-1 (continued)

Measures	Study details	Physical activity	Impact of PA on measures	Source
Mental health				
Dementia	Systematic review and meta-analysis of 11 cohort studies, ≥30 years	Highest PA category vs lowest category	RR of 0.72 (0.60 to 0.86)	Hamer & Chida (302)
Depression	A meta-analysis that converted the overall effect sizes of 3 meta-analyses (37 studies) on the effect of PA on depression to binomial effect size	Running and walking or other aerobic activity	Increased success rate to 67-74% reduction in depressive symptoms	Craft & Perna (303)
Musculoskeletal				
Osteoporosis	Meta-analysis of 13 prospective cohort studies	Moderate to vigorous PA	Hip fracture reduction of 45% (31-56%) and 38% (31-44%) in men and women respectively	Moayyeri (304)
Osteoarthritis	Meta-analysis of 13 RCTs examining the efficacy of aerobic walking and home based quadriceps strengthening exercise in patients with knee arthritis, mean age ranged between 61.9 to 73.7 years	Aerobic walking, strengthening exercises	Pooled effect (mean difference of score) sizes for pain were between 0.39 to 0.52, and self-reported disability ranged from 0.32 to 0.46	Roddy et al. (305)
Rheumatoid arthritis	Systematic review and meta-analysis of 14 RCTs including 1,040 patients, mean age ranged between 44 to 68 years,	Aerobic exercise vs usual care	Improved function: SMD of 0.24 (assessed by the health assessment questionnaire) and SMD for pain on VAS was 0.31	Baillet et al. (306)
Falls prevention	Meta-analysis of 13 RCTs examining the effect of exercise on fall prevention in older adults aged ≥60 years	Exercise (walking, cycling or other endurance exercises)	Beneficial effect on the risk of falling, adjusted RR of 0.86 (0.75–0.99), the number needed to treat 16	Chang et al. (307)
Chronic low back pain	Meta-analysis of RCTs evaluating exercise therapy in a population with chronic (>12 weeks duration) low back pain	Exercise therapy	Improved pain and function, measured on a scale of 100 points, were 5.4 and 0.7 respectively	Hayden et al. (308)

Note: RR: relative risk, SMD: standardised mean difference, VAS: visual analogue scale

The current evidence suggests a significant beneficial effect of PA on different measures on cardiovascular, metabolic, mental illness, cancer and musculoskeletal system diseases. Also, these meta-analyses provide dose-response evidence between PA and risk factors namely systolic blood pressure, total and HDL cholesterol, and HbA1c. Based on the available evidence, a schematic diagram showing the relationship between PA, risk factors and chronic diseases was developed. The diagram below (Figure 4-1) depicts the relationship between different factors. For example, increased physical inactivity increases systolic blood pressure that will result in an increased risk of cardiovascular disease. An increase in CVD events leads to an increase in costs and a decrease in quality of life.

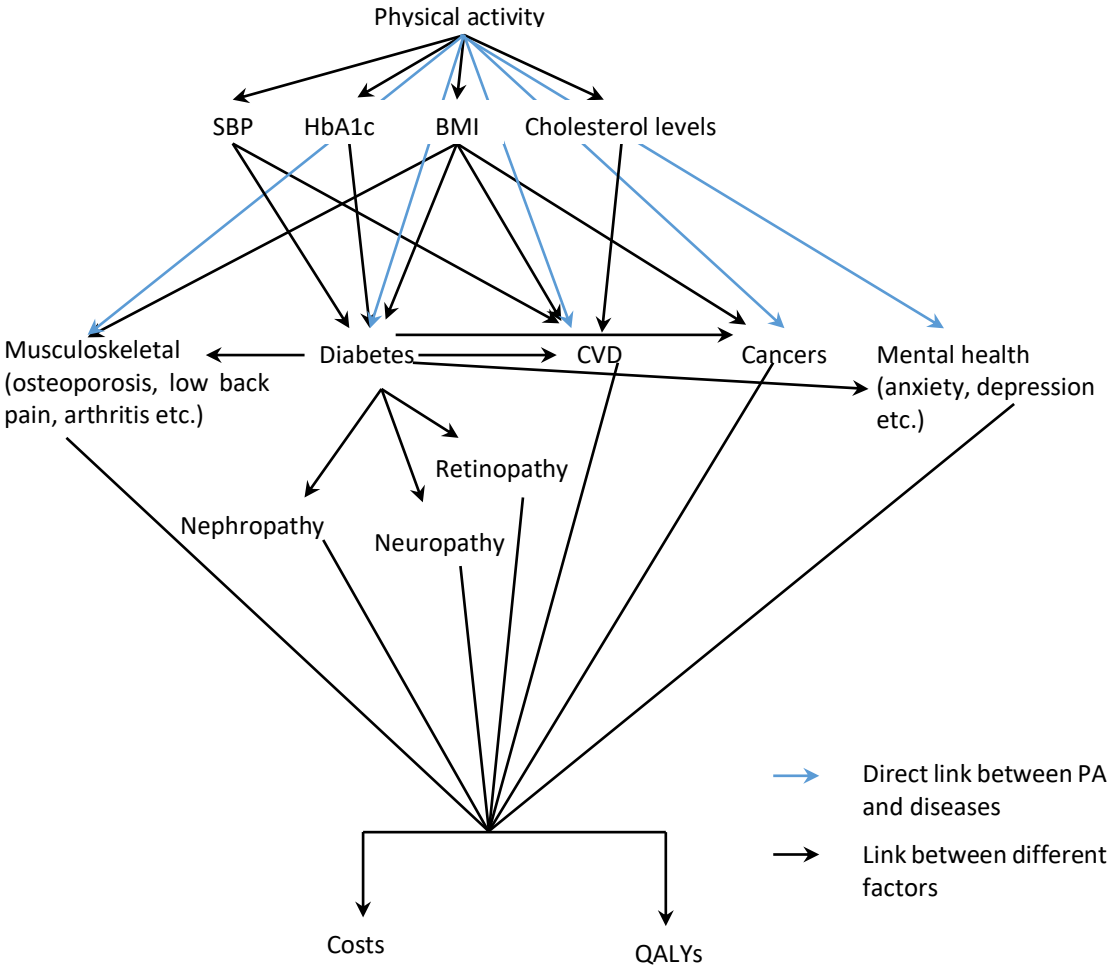

Figure 4-1: Schematic diagram showing the relationship between different factors

4.4.1.2 Selection of co-morbidities

Previous section and Table 4-1 summarised systematic reviews and meta-analyses of epidemiological studies of PA which suggested a reduced risk of cardiovascular disease (including hypertension, coronary heart disease and stroke), type 2 diabetes, some form of cancers, osteoporosis, obesity, falls and fractures, and some mental health problems (51,283,284,309). Some of these disease conditions were also included in the model-based economic evaluation of brief PA interventions as described in Chapter 2. Furthermore, Guh et al. (310) provided an estimate of the incidence of each co-morbidity related to obesity and being overweight. Their systematic review and meta-analysis included prospective cohort studies of the general population in Western countries.

These studies provided a list of chronic conditions and comorbidities attributable to physical inactivity. Regular PA could prevent the occurrences of these chronic conditions, i.e. has a beneficial effect. Risk factors such as blood pressure were the key component of the causal diagram (Figure 4-1) linking the physical activity and chronic conditions. These casual pathways were not available for all the conditions, for example, mental health. In addition, how the intensity, duration and energy expenditure of exercise may or may not influence these.

In the ideal, all diseases that are attributable to physical inactivity would be incorporated into the model. Including all diseases in a single model requires far greater time to develop and evaluate the model. In addition, there need to be a lot of structural assumptions and increasing complexity that makes the model unmanageable. From the review of existing evidence of physical activity on health, diseases attributable to physical inactivity namely coronary heart disease, stroke, type 2 diabetes, and cancers (colorectal, breast, lung and kidney) are selected (Table 4-2).

Table 4-2: The model boundary selection

Factor	Include/ Exclude	Reason for inclusion/exclusion
Risk factors	Include	A key component of the casual diagram
Mental health (anxiety, depression)	exclude	The current evidence suggests a beneficial effect of PA on mental illness (observational studies). However, the relationship between PA and mental illness is complex, and the current data are insufficient to provide dose-response relationship
CVD (hypertension, ischaemic heart disease, myocardial infarction, stroke, congestive heart failure)	Include	There is a clear dose-response link between physical activity, risk factors and CVD events. Also, it has a substantial impact on the costs and effects.
Type II diabetes	Include	Has substantial impact upon the cost and effects
Neuropathy	Include	Key outcomes associated with type II diabetes
Retinopathy	Include	Key outcomes associated with type II diabetes
Nephropathy	Include	Key outcomes associated with type II diabetes
Cancers (colorectal, breast, lung and kidney)	Include	There are clear links showing the beneficial effect of PA on cancers. However, the dose-response relationship is not clear for all cancers. Other risk factors such as BMI have also impact upon the model outcomes, e.g. higher risk of colorectal cancer in obese participants.
Musculoskeletal (osteoarthritis, osteoporosis, low back pain, rheumatoid arthritis, fall prevention)	Exclude	Not possible to quantify dose-response relation

The selection of diseases was based on the data available from previous systematic reviews and meta-analyses including the dose-response evidence between PA and risk factors (Table 4-3). The incidence of chronic diseases attributable to physical inactivity in the UK was also considered. For example, 10.5% of CHD, 13% of type 2 diabetes, 17.9% of breast cancer and 18.7% of colon cancer cases are attributable to physical inactivity in the UK (284). In addition, the selected chronic diseases had the greatest impact on health and well-being (311) and economic cost.

Table 4-3: Dose-response functions

	Study, year	Evidence (RCTs, cohort studies)	Population	Outcome	Net change/RR (95% CI) and corresponding exposure
Systolic blood pressure (SBP)	Whelton 2002 (293)	53 RCTs (2,419 participants)	Men/women, mean age range 21-79 years. Included both hypertensive and normotensive participants	Change in SBP	-3.84 mmHg (-4.97 to -2.72); 18 MET-hours per week
HbA1c	Umpierre 2011 (292)	23 RCTs (933 patients)	Men/women, type 2 diabetes patients with or without comorbidities, aged ≥18 years	Change in HbA1c	-0.67% (-0.84 to -0.49); 6.4 MET-hours per week
Total cholesterol	Kelley 2005 (290)	21 RCTs, (1,427 participants)	Men/women, sedentary but healthy, mean age ≥50 years	Change in TC level	-3.3 mg/dl (-6.5 to -0.02); 23 MET-hours per week
HDL-cholesterol	Kodama 2007 (291)	25 RCTs (1,404 participants)	Men/Women, mean age range 23-75 years	Change in HDL-C level	2.53 mg/dl (1.36 to 3.7); 15 MET-hours per week
Breast cancer	Wu 2013 (298)	7 cohort studies (19,882 cases)	Women, aged ≥20 years	Incidence breast cancer	0.97 (0.95 to 0.99); 10 MET-hours per week
Colorectal cancer	Parkin 2011 (312)	4 cohort studies (3,386 cases)	Men/women aged ≥ 30 years	Incidence colon cancer	0.994; 1 MET-hour per week
Lung cancer	Tardon 2005 (313)	11 prospective studies (5,685 cases)	Men/women, mean age ≥20 years	Incidence lung cancer	0.87 (0.76 to 0.95); 14 MET-hours per week
Type 2 diabetes	Jeon 2007 (296)	10 cohort studies (9,367 cases)	Sedentary men/women aged ≥30 years	Incidence type 2 diabetes	0.83 (0.76 to 0.90); 11 MET-hours per week

Note: CI: Confidence Interval, HDL-C: High-density Lipoprotein Cholesterol, RCTs: Randomised Controlled Trials, RR: Relative Risk, METs: Metabolic equivalent of task, TC: Total Cholesterol.

4.4.1.3 Review of existing cost-effectiveness models

A review of existing epidemiological and cost-effectiveness models related to physical activity and obesity was undertaken to help inform the model structure. This provided a list of disease conditions that had an established dose-response link with PA. The primary objective of the review was to evaluate published decision-analytic models in the area of physical activity and/or obesity to identify structural assumptions and data sources (inputs to the model) potentially relevant to this study. It is also expected that the review would highlight key areas of uncertainty and potential data gaps, and identify key input parameters requiring additional systematic reviews and/or analysis of primary data.

Reviewing methods

A systematic literature search was conducted to identify economic or epidemiologic studies or models on comorbidities related to physical activity and obesity. The search was performed in Medline (OvidSP), CENTRAL and NHS EED (Cochrane library) covering the period until January 2015. In addition, a free text search was performed using Google scholar. Web of Knowledge was used for a cross-reference search. The retrieved articles were limited to the English language.

Table 4-4: Inclusion criteria for the systematic review

Criteria	Inclusion criteria
Type of study	Modelling with an economic evaluation/pharmaco-economic component, or epidemiological models of chronic diseases that have established link to physical (in)activity
Population	Adults with or without chronic diseases and conditions (type 2 diabetes, heart disease, stroke, breast cancer, colorectal cancer, lung cancer and kidney cancer)
Intervention	Any physical activity or other interventions for chronic disease
Outcome of interest	All information on the model structure, data inputs, key economic evaluation methodology and results, any reported strengths and limitations of models used

The search terms for economic evaluation were adopted from the NHS Economic Evaluation Database Handbook (314) and modified to include epidemiological models as well. Search terms for diseases were adopted from the specialised register (electronic searches) of respective Cochrane group, where available. Details of search terms are available in Appendix C1.

Review results

In total, 2298 title and abstract records were identified. After screening titles and abstracts, 38 published papers relating to economic and/or epidemiological models on physical activity and obesity co-morbidities were included in the review (Figure 4-2). Table 4-5 summarises the chronic diseases and complications covered in the models. A summary table of the study description, modelling method used, population and setting, type of intervention, complications modelled, time horizon and primary outcome measure is presented in Appendix C3.

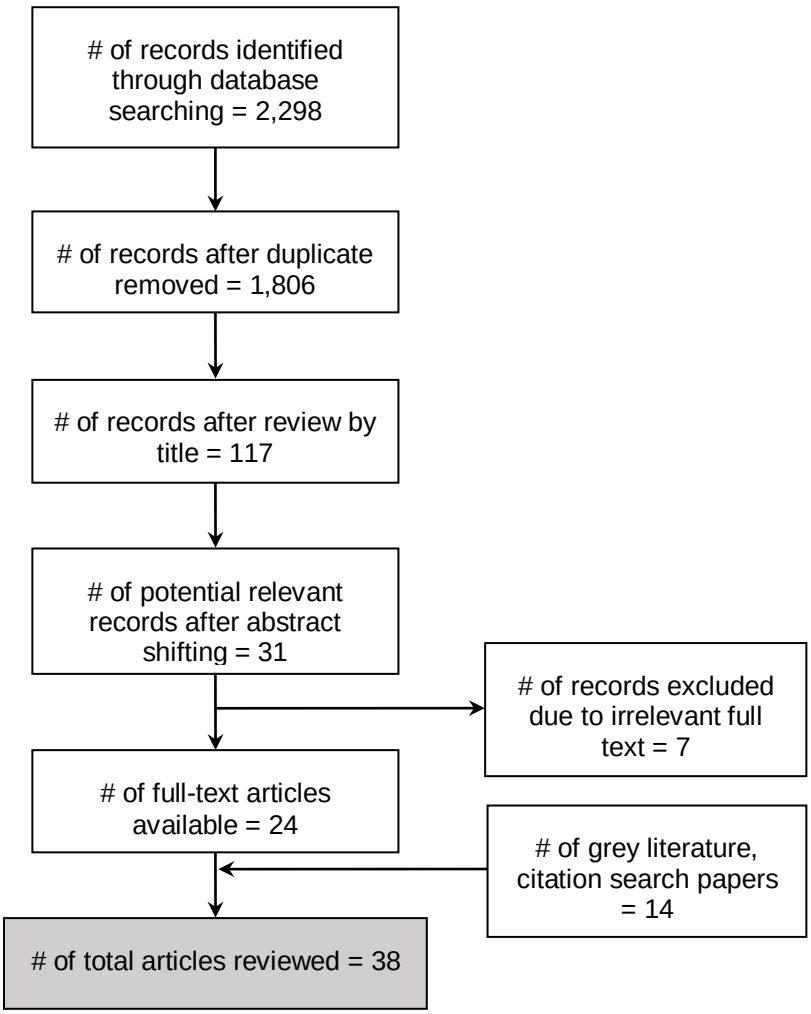

Figure 4-2: Electronic database search results

Of 38 modelling studies included, 16 were related to type 2 diabetes progression and complications (315-330), six circulatory disease (331-336), five PA or lifestyle interventions (141,337-340), five breast cancer (341-345), three colorectal cancer (346-348), two lung cancer (349,350), and one kidney cancer (351). The main data source used in these micro-simulation (141,316,318,319,321,324,325,328,329,339), Markov (315,317,320,322,323,326,327,330,337,340) and decision tree (338,352) models were from the UK Prospective Diabetes Study (UKPDS) (315-319,321,323,325-328), the

Surveillance, Epidemiology, and End Results (SEER) (341-345,349,350), Framingham Heart Study (316,327,329), WESDR (320,325,330), CORE-2 (315,323), Finnish Diabetes Prevalence study (337,340), cross-sectional surveys in Australia (141), Canadian population health survey (339), Health Survey for England (338), KORA study in Germany (352), and West of Scotland Coronary Prevention study (WOSCOPS) (321). A summary of the main data sources used is presented in Table 4-6.

Of six circulatory disease models, three were economic models (331-333), two models predicted future morbidity, mortality and cost (334,336), and the remaining one (335), an epidemiological model investigated the routine use of low dose aspirin. Breast cancer cost-effectiveness (341,342) or epidemiological models (343-345) used data from SEER programme to either develop or validate their model. Chien et al. (351) reported an epidemiological model to estimate chronic kidney disease risk in Chinese population. This model, a clinical point base, uses clinical variables and biochemical measures to predict the incidence of the disease. Colorectal cancer models enrolled patients over 40 years of age. Allen et al. (346) compared four screening strategies, Ladabaum et al. (347) compared three, and Loeve et al. (348) compared two screening strategies for colorectal cancer. In addition to the 38 modelling studies identified from the database and cross-referencing search, there were two reviews on economic models in type 2 diabetes(353) and simulation models of obesity (354). The commonly reported health and economic outcome were life expectancy, long-term costs and QALYs gained, and the incidence of chronic conditions.

The type II diabetes complication models mainly use three complication pathways for micro-vascular complications namely retinopathy, neuropathy and nephropathy. The structure of the CDC/RTI type II diabetes complication model (317) was based on previous models namely UKPDS and the Eastman model (320). Another model used by Chen et al. (318) has the same basic structure as the CDC model.

In these models, the risk of cardiovascular events in the general population is predicted using the risk prediction equations based on the Framingham Heart Study. Whereas the prediction of cardiovascular events in patients with type 2 diabetes was mainly based on the UKPDS risk equations (319). Among the reviewed models of colorectal cancer, Frazier's model (355) appeared to be comprehensive and robust regarding the model structure and natural history of disease progression. The breast cancer model by Johnston (356) provided a detailed structure of the breast cancer model including transitional probabilities of different stages of breast cancer. The data used in this model was based on a database from the Professorial Unit of Surgery at the City Hospital, Nottingham, UK (357).

Table 4-5: Summary of chronic diseases and complications covered

Study, year	Macrovascular complications	Heart disease	MI	CHF	Stroke	PVD/ PAD	Micro-vascular complications
Cobiac 2009 (141)		x			x		
Galani 2007 (337)		x			x		
Matrix 2006 (338)		x			x		
Nadeau 2011 (339), Zucchelli 2010 (358)		x				x	
Avenell 2004 (340)	x	x					
Bagust 2001 (315)	x	x	x				
Brown 2000 (316)	x	x	x	x	x	x	x
CDC /RTI Model (317)	x	x	x	x			x
Chen 2008 (318)	x	x	x	x	x		x
Clarke 2004 (319)	x	x	x	x	x		x
Eastman 1997 (320,359)	x	x					x
Eddy 2003 (321,360)		x	x			x	
Habacher 2007 (322)							
Lamotte 2002 (323)	x	x	x		x		x
McPherson 2007 (324)	x	x			x		
Muller 2006 (325)	x	x	x	x	x	x	x
Ortegon 2004 (326)							
Palmer 2004 (327)	x	x	x	x	x	x	x
Waugh 2007 (328)	x	x	x		x		x
Wilson 2005 (329)		x	x		x	x	
Zhou 2005 (330)		x			x		x
Icks 2007 (352)							
Barton 2011 (331)		x					
Clegg 2005 (332)	x			x			
Hayashino 2007 (333)	x	x	x		x		
Jacobs-van der Bruggen 2007 (334)		x		x			
Nelson 2005 (335)		x			x		
Weinstein 1987 (336)		x	x				
Anderson et al. 2006(341)							
Chen 2010 (342)							
Fryback 2006 (343)							
Hanin 2006 (344)							
Noah-Vanhouck 2011 (345)							
Chien 2010 (351)	x				x		
Das 2006 (349)							
Marshall 2001 (350)							
Allen 2005 (346)							
Ladabaum 2010 (347)							
Loeve 2000 (348)							

Table 4-5 (continued)

Study, year	Cataract/ blindness	Retino-pathy	Foot ulcer	Amputation	Nephro-pathy	Neuro-pathy	Cerebrovascular disease
Cobiac 2009 (141)							
Galani 2007 (337)							
Matrix 2006 (338)							
Nadeau 2011 (339), Zucchelli 2010 (358)							
Avenell 2004 (340)							
Bagust 2001 (315)	x	x	x	x	x	x	
Brown 2000 (316)	x	x		x	x	x	
CDC /RTI Model (317)	x	x			x	x	
Chen 2008 (318)	x			x	x		
Clarke 2004 (319)	x	x	x	x	x	x	
Eastman 1997 (320,359)	x	x		x	x	x	
Eddy 2003 (321,360)		x			x		
Habacher 2007 (322)			x				
Lamotte 2002 (323)							
McPherson 2007 (324)							
Muller 2006 (325)	x	x	x		x	x	
Ortegon 2004 (326)			x	x		x	
Palmer 2004 (327)	x	x	x	x	x	x	
Waugh 2007 (328)		x					
Wilson 2005 (329)							
Zhou 2005 (330)		x			x	x	
Icks 2007 (352)							
Barton 2011 (331)							
Clegg 2005 (332)							
Hayashino 2007 (333)							
Jacobs-van der Bruggen 2007 (334)							x
Nelson 2005 (335)							
Weinstein 1987 (336)							
Anderson et al. 2006(341)							
Chen 2010 (342)							
Fryback 2006 (343)							
Hanin 2006 (344)							
Noah-Vanhouck 2011 (345)							
Chien 2010 (351)							
Das 2006 (349)							
Marshall 2001 (350)							
Allen 2005 (346)							
Ladabaum 2010 (347)							
Loeve 2000 (348)							

Table 4-5 (continued)

Study, year	Cancers	Breast cancer	Rectal cancer	Kidney cancer	Cervical cancer	Lung cancer	Type 2 diabetes
Cobiac 2009 (141)	x	x				x	x
Galani 2007 (337)						x	
Matrix 2006 (338)		x				x	
Nadeau 2011 (339), Zucchelli 2010 (358)	x	x				x	x
Avenell 2004 (340)						x	
Bagust 2001 (315)						x	
Brown 2000 (316)						x	
CDC /RTI Model (317)						x	
Chen 2008 (318)							
Clarke 2004 (319)						x	
Eastman 1997 (320,359)							
Eddy 2003 (321,360)							
Habacher 2007 (322)							
Lamotte 2002 (323)						x	
McPherson 2007 (324)	x	x	x			x	x
Muller 2006 (325)						x	
Ortegon 2004 (326)							
Palmer 2004 (327)						x	
Waugh 2007 (328)						x	
Wilson 2005 (329)							x
Zhou 2005 (330)							
Icks 2007 (352)						x	
Barton 2011 (331)							
Clegg 2005 (332)						x	
Hayashino 2007 (333)						x	
Jacobs-van der Bruggen 2007 (334)	x	x	x	x		x	x
Nelson 2005 (335)							
Weinstein 1987 (336)							
Anderson et al. 2006(341)	x						x
Chen 2010 (342)	x						x
Fryback 2006 (343)	x						x
Hanin 2006 (344)	x						x
Noah-Vanhouck 2011 (345)	x						x
Chien 2010 (351)			x			x	
Das 2006 (349)					x		
Marshall 2001 (350)					x		
Allen 2005 (346)		x					
Ladabaum 2010 (347)		x					
Loeve 2000 (348)		x					

Table 4-5 (continued)

Study, year	Mortality	CHD-related mortality	Diabetes or diabetes complication-related mortality	Non-specific mortality/ all-cause mortality	Treatment related AE
Cobiac 2009 (141)		x	x	x	
Galani 2007 (337)		x			
Matrix 2006 (338)		x	x	x	
Nadeau 2011 (339), Zucchelli 2010 (358)	x	x	x		
Avenell 2004 (340)	x	x	x		
Bagust 2001 (315)	x	x	x	x	x
Brown 2000 (316)	x	x	x		
CDC /RTI Model (317)	x	x	x	x	x
Chen 2008 (318)			x	x	
Clarke 2004 (319)	x		x	x	
Eastman 1997 (320,359)	x		x	x	x
Eddy 2003 (321,360)		x	x	x	x
Habacher 2007 (322)				x	x
Lamotte 2002 (323)		x	x		x
McPherson 2007 (324)		x	x	x	
Muller 2006 (325)	x	x	x	x	x
Ortegon 2004 (326)				x	x
Palmer 2004 (327)	x	x	x	x	x
Waugh 2007 (328)					
Wilson 2005 (329)	x	x	x		
Zhou 2005 (330)	x	x	x	x	x
Icks 2007 (352)					
Barton 2011 (331)		x			
Clegg 2005 (332)	x				x
Hayashino 2007 (333)	x	x	x		
Jacobs-van der Bruggen 2007 (334)	x	x	x	x	
Nelson 2005 (335)	x	x		x	x
Weinstein 1987 (336)	x	x		x	
Anderson et al. 2006(341)	x				x
Chen 2010 (342)	x			x	
Fryback 2006 (343)	x			x	x
Hanin 2006 (344)	x				x
Noah-Vanhouck 2011 (345)	x			x	x
Chien 2010 (351)	x				
Das 2006 (349)	x				
Marshall 2001 (350)	x				
Allen 2005 (346)	x				
Ladabaum 2010 (347)	x				
Loeve 2000 (348)	x				

Table 4-6: Summary of main data sources used (available) in the models

Data	Population	Follow up	Outputs	Source
Cost of diabetes Type II in Europe (CODE 2 study)	More than 7000 peoples with type 2 diabetes in 8 European countries, mean age 65.9 years,	6 months cross-sectional	Total medical cost of T2DM	(323,340)
Diabetes Control and Complications Trial (DCCT)	1441 Insulin Dependent Diabetes Miletus (IDDM) patients recruited at 29 centres from 1983 to 1993, age 13-39 years	Average follow up of 6.5 years	Retinopathy, nephropathy, neuropathy, macrovascular disease	(325)
Early Diabetes Intervention Programme (EDIP)	A 5-year prospective double-blinded RCT, 215 patients from two sites	5 years	Development of diabetes, development and/or progression of diabetes-associated micro- and macro-vascular complications	(328)
Health Survey for England (HSE)	Cross-sectional survey (annual) to measure health and health-related behaviours in adults and children in England	-	Cardiovascular disease, physical activity, accidents, lung function measurement and certain blood analytes	(324,329)
Finnish Diabetes Prevention Study (FDPS)	Finnish participants aged 40-65 years, BMI 25 or higher; Intensive lifestyle intervention	1993-2013	Type 2 diabetes and cardiovascular risk	(340)
Framingham cohort study	Original cohort of 5,209 respondents of a random sample of 2/3 of the adult population of Framingham, Massachusetts, 30-62 years of age in 1948	10 years risk	Risk engines for various cardiovascular disease outcomes in different time horizons as score sheets and risk functions	(315,321,327, 329,331,333, 336,337)
Helsinki Heart Study	Middle-aged men (40-55 years) with primary dyslipidaemia, 2030 and 2051 (placebo versus Gemfiborzil)	5 years	MI	(321,323)

Table 4-6 (continued)

Data	Population	Follow up	Outputs	Source
Hoorn study The Netherlands	Initiated in 1989 to study the prevalence and determinants of T2DM in general population in the Netherlands. Original cohort of 2484 subjects aged 50-75 years old. New Hoorn study began in 2006 with 2700 men and women aged 40-65 years old – younger than the original cohort.	10 year follow up; new follow up underway	Prevalence and risk factors of diabetes and cardiovascular disease and other diabetes complications	(328)
KORA	4 large studies investigating cardiovascular disease since 1984, first 3 were part of the MONICA project, since 1996 the research is continued under the name of KORA. Longitudinal and cross-sectional study; inhabitants of Augsburg and surrounding counties, age 25-74 (n = 400,000).	7 years follow up	Prevalence of risk factors for cardiovascular and other chronic diseases	(328,352)
Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study	9,014 post-MI or unstable angina patients, the primary endpoint of CHD, randomised to pravastatin 40mg or placebo, 31-75 years old	Mean follow up 6.1 years	CHD death, fatal or non-fatal MI, Ischemic stroke	(321)
PROCAM (Prospective Cardiovascular Munster Heart Study)	More than 30,000 participants aged between 16-65 years in Munster and the northern Ruhr area, Germany	Fixed follow-up periods of 8 years; multicentre	Coronary events (non-fatal cerebrovascular events and fatal stroke), mortality of non-coronary or cerebrovascular origin	
Surveillance, Epidemiology and End Results (SEER) Programme	A database that collects complete and accurate data on all cancers diagnosed among residents of geographic areas covered by SEER cancer registries in the US. Data collection began in 1973. Requires SEER*Stat software to retrieve/analyse data from the registry	Regularly updated	All Cancers	(341-346,348-350)

Table 4-6 (continued)

Data	Population	Follow up	Outputs	Source
UKPDS	Hypertensive patients with type 2 diabetes, 758 / 390 (studied vs. control)	8.4 years (median) Multicentre	Stroke, MI, microvascular events, retinopathy, vision loss, mortality (MI, stroke, renal and diabetes related)	(315-319,321,323, 325-328)
West of Scotland Coronary Prevention Study (WOSCOPS)	Men aged 45-64 yr. with no history of MI and with raised plasma cholesterol levels; 3302/ 3293 (studied versus control)	4.9 years, multicentre	Coronary events (CHD death, MI)	(321)
WHO Multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA) project	Established to determine how trends in events for CHD and optionally stroke were related to trends in classic coronary risk factors. Risk factors monitored across 38 populations from 21 countries. Total of 69,251 men and 69,187 females aged 35-64 years	10 years (1979-1996), multicentre	CHD risk factors – smoking status, SBP, TC, BMI	(335,337)
Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)	Younger-onset T1D (996 people) and older-onset persons mostly with T2DM (1370 people) who were first examined from 1980 to 1982 in southern Wisconsin	5 follow up examination of cohort in 1984-86, 1990-92, 1995-96, 2000-01, 2006-07	Complications associated with diabetes. Eye complications – diabetic retinopathy and visual loss, kidney complications – diabetic retinopathy and amputations	(315,320,325, 330)
Wisconsin Cancer Reporting System (WCRS)	Cancer incidence and mortality in Wisconsin	1995-2008	Cancers	(343)
WHO (CHOosing Interventions that are Cost-Effective) CHOICE	Reports the costs and effects of a wide range of health interventions in the 14 epidemiological sub-regions	1998-	A wide variety of health interventions	(141)

The reviewed models differed according to the extent and type of interventions they evaluated, co-morbidities included and adverse events captured. Most had the same fundamental structure, used similar micro-simulation techniques and were based on key data sources. Some of the studies included in this review lack transparency around assumptions, equations and algorithms used to predict disease incidence, data used to calibrate or estimate model parameters, the goodness of fit measures used to calibrate data and validate results. Similar types of problems were also reported in other reviews (354).

4.4.1.4 Selection of the type of decision analytic model

Different types of models can be used in economic evaluation to combine information already available and to assess the policy implications for decision making. The availability of data plays a greater role in determining a model's structure (55,56). Brennan et al. (56) suggested that in addition to the availability of data, the background skill of the researcher and the type of software available also have a considerable role in determining the model structure. There are several guidelines for good research practices in modelling (55,57-61), and these guidelines focus mainly on transparent structure, appropriate and systematic use of evidence, and handling uncertainty.

The selection of the particular type of model structure and complexity is always a trade-off between descriptive realism and computational burden and data requirement (63). The economic models use two common approaches – aggregate or 'cohort' models and individual-level models also called patient-level simulation or microsimulation – to estimate the expected costs and outcomes (56,58). Microsimulation models use mathematical equations to simulate the behaviour of an individual taking into account the heterogeneous composition of the target population without focusing on a representative or average individual. In other words, the cost and health outcomes are modelled for individual patients.

While in a cohort-level simulation, decision trees or Markov models are frequently used (described in section 1.4.3), and the health and cost outcomes are modelled for the cohort as a whole. Decision trees are although simpler and useful for short-term analyses; they lack an explicit time variable. As the time horizon of the analysis increases, they have limited use for modelling complicated disease conditions involving a longer time period (61). Markov model overcome with this issue and can deal with the pattern of recurring disease over time. They involve a transition between various health states and outcomes over time (53). The main limitation with this approach is that they do not account for the

history of progression in the model. Markov models could be extended to include the history of disease progression, but this requires a load of tunnel states. Furthermore, this does not consider the outcomes for individual patients within that cohort. The patient-level simulation accounts for variability in all included parameters which can be characterised with empirical distribution. The models often used in the economic evaluation are the former cohort models.

From the review of existing chronic disease epidemiological and PA cost-effectiveness models, it appeared that a microsimulation approach is feasible and can be considered to model the effect of VBIs. The models need to incorporate longer-term consequences of VBIs which could be unmanageable in a decision tree. Although cohort Markov model would require less computation power, it would not have been possible to include a large number of health states and capture individual variability. The advantage of using a microsimulation approach is that it facilitates modelling of the behaviour of individuals in a complex system (36) and allows individual characteristics to be modelled as continuous variables. Although this approach requires significant computational power, this can be easily addressed using the R programming language. R is a free and powerful software environment for statistical computing and graphics (361). It is known for efficiency in coding and memory management that allows flexibility and complex models to be coded. In addition, 'R' supports parallel computing and the models coded in 'R' are more transparent because it is script based.

4.4.2 The model structure

This section builds on the review of the evidence as outlined in previous sections (4.4.1). The identification of the decision problem and the conceptualisation of the decision analytic model were informed by reviewing the relationship between PA and health (Table 4-1). The initial starting point of this process was the review of the obesity cost-effectiveness model developed by Wilson & Fordham (329). This model simulates a cohort of 2,500 patients and estimates the health impact and cost of obesity in Norfolk, England over a ten year period and was developed in Microsoft Excel. The effect of a (hypothetical) intervention was mediated through the effect on BMI levels. After a review of this model, other modelling approaches including a selection of co-morbidities were considered because this model considered the effect of intervention only on BMI levels and excluded other relevant measures.

Figure 4-1 outlines the conceptual structure of the model. The simplified schematic of the model is depicted in Figure 4-3. As mentioned in the earlier section, a probabilistic model using a simulation approach is adopted to model the effect of VBIs in PA promotion. The

current model incorporates health benefits of increased physical activity by changes in risk factors values. The change in activity level due to VBIs modifies the risk factor values such as reduced blood pressure, total cholesterol and HbA1c. Changes in these risk factors have implications for diseases and comorbidities. For example, increased physical activity lowers systolic blood pressure that will result in a reduced risk of cardiovascular disease.

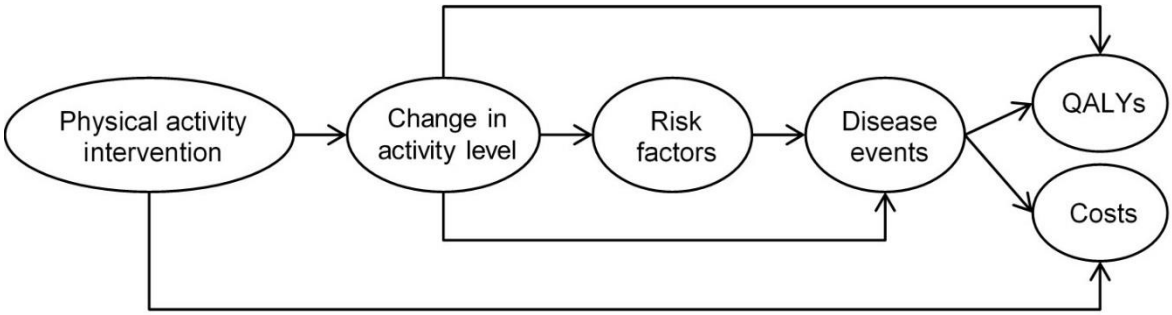

Figure 4-3: A schematic of the physical activity cost-effectiveness model

In the initial cycle, the model generates a cohort of 10,000 individuals, loads in patient cohort, intervention effect (MET-hour increase in PA) and cost of the intervention. The simulation estimates yearly changes in metabolic risk factors based on the individual's baseline characteristics and MET-hour increase in PA. Within each annual cycle, participants included in the model may develop one of the disease states of interest (Figure 4-4). Baseline characteristics and risk factors determine the individual's probability of disease events including cardiovascular disease, type II diabetes, colorectal cancer, breast cancer, lung cancer or kidney cancer. For cardiovascular and diabetes, the dose response-link between risk factors and disease event is clear (quantifiable). However, it was not clear for cancers thus the RR estimates for developing cancers are adjusted for the increase in PA (MET-hour). For example, the risk of breast cancer is reduced by 3% for every 10 MET-hour increments in PA (298).

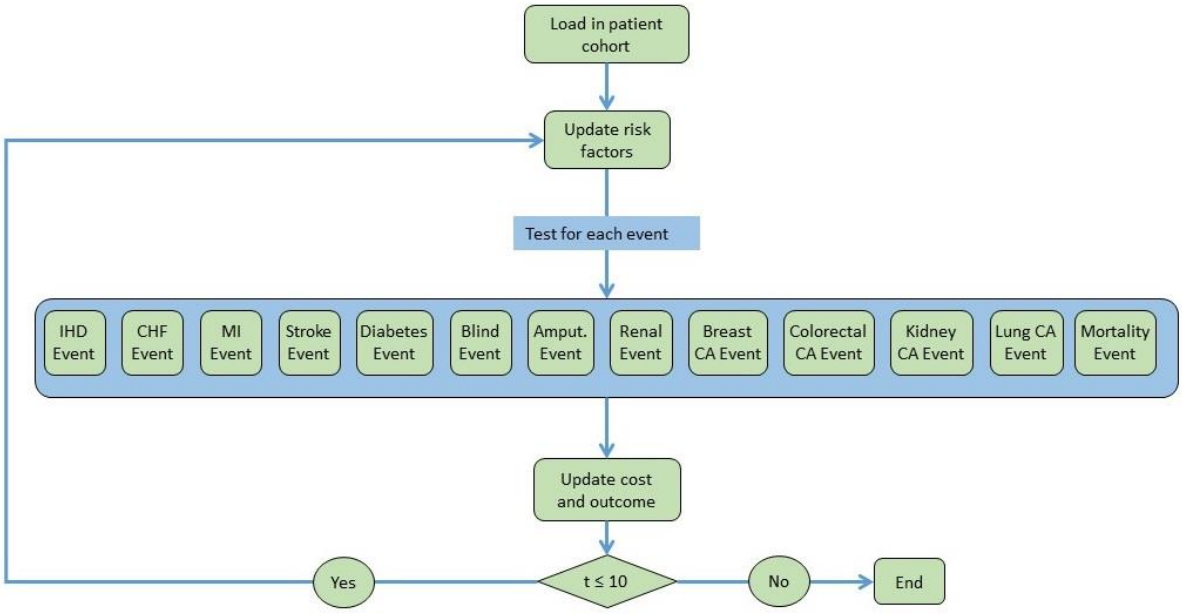

Figure 4-4: The simulation process

In subsequent cycles, the risk factor values were updated based on the values of the previous year (t-1), and the future outcomes (morbidity, mortality) including costs and QALYs are estimated.

Table 4-7 compares the VBI model with selected obesity and physical activity models that are relevant or applicable to the current decision problem. The VBI model is comprehensive in terms of the inclusion of known risk factors and comorbidities related to physical inactivity. Previous models (141,150,362,363) used physical activity categories (inactive, moderately active, and active) to model the effect of interventions. The current model measures PA changes in intensity, duration and frequency, i.e. the metabolic equivalent of task (MET). One MET represents the metabolic rate equivalent to consuming 3.5 millilitres of oxygen per kilogram of body weight per minute and is equivalent to a resting metabolic rate (364). For example, moderate intensity activity such as brisk walking elicits an intensity of 3 – 6 METs depending on how brisk the walk is. The model incorporates METs using a dose-response function as detailed in Table 4-3. The model is designed in a modular framework using 'R' (361) such that the model can be easily updated (e.g. addition of new disease condition) as the new evidence is available.

Table 4-7: Comparison of the model with existing models

	Wilson 2005 (329)	NICE 2006 (338)	McPherson 2007 (324)	Jacobs-van der Bruggen 2007 (334)	Cobiac 2009 (141)	Cecchini/Sassi 2010 (365)	Nadeau 2011 (339)	Jarrett 2012 (362)	The VBI Model
Pathway	BMI	PA	BMI	BMI, PA	PA	BMI, PA	PA	PA	BMI, PA
Software used	Excel	Not mentioned	C++	Not mentioned	Excel @RISK	Modgen	Modgen	Excel	R
Risk factors	HBP, cholesterol, HbA1C	-	-	HBP, cholesterol, blood sugar	-	HBP, cholesterol, glycaemia	-	-	HBP, cholesterol, HbA1c, smoking
Technique used	Micro-simulation	Decision tree	Micro-simulation	Micro-simulation	Cohort simulation	Micro-simulation	Micro-simulation	Cohort simulation	Micro-simulation
Co-morbidities	CHD, stroke, T2DM	CHD, stroke, T2DM, colon cancer	CHD, stroke, T2DM, arthritis, cancers	CVD, T2DM, cancers, MSD	IHD, stroke, T2DM, cancers (breast, colon)	IHD, Stroke, Cancer	Heart disease, diabetes, hypertension, cancers	IHD, stroke, T2DM, dementia, cancers (breast and colorectal), depression, Injuries	IHD, CHF, T2DM, stroke, MI, diabetic complications (retinopathy, neuropathy, nephropathy), cancers (breast, colorectal, lung, kidney)
Key data source	HSE, ONS, epidemiol-ogical studies	BHF, ONS, YHPHO, epidemiol-ogical studies	HSE, epidemiol-ogical studies	Dutch population statistics, global burden of disease study, epidemiological studies	Australian burden of disease, DISMOD, epidemiol-ogical studies	Health surveys, database from WHO/UN, epidemiological studies	Canadian community health survey, Canadian National Population Health Survey, epidemiological studies	BHF, ONS, UKPDS, FHS, STATS19, TfL, epidemiol-ogical studies	HSE, ONS, UKPDS, FHS, CRUK, WESDR, epidemiological studies

Note:

BMI: body mass index; PA: physical activity; HBP: high blood pressure, CHD: coronary heart disease; T2DM: type 2 diabetes mellitus; CVD: cardiovascular disease; IHD: ischemic heart disease; MSD: musculosketal disorder; CHF: congestive heart failure; MI: myocardial infraction; HSE: health survey for England; ONS: office for National Statistics UK; BHF: British Heart Foundation; YHPHO: Yorkshire and Humber Public Health Observatory; UKPDS: UK perspective diabetes study; FHS: Framingham heart study; TfL: transport for London; CRUK: cancer research UK; WESDR: Wisconsin epidemiologic study of diabetic retinopathy; SEER: Surveillance, epidemiologic and end results

4.4.2.1 Model parametrisation

The model requires a cohort of patients to be modelled through the cycles and a set of data inputs such as transitional probabilities between health states, morbidity and mortality rates, disease costs and utility weights for the health states. The following section describes the process used to generate a hypothetical cohort of patients followed by the data sources used to estimate disease incidence, mortality, costs and health states utility weights.

Cohort generation

A cohort of 10,000 patients was generated at random using the UK population distribution of parameters (366,367). Firstly, the demographic characteristics of individual participants (age, gender, ethnicity) were estimated using data from the Office of National Statistic figures for 2011 (366,367). The risk factor profile (systolic blood pressure, total cholesterol, HDL cholesterol, BMI, HbA1c and smoking status) and prevalence of type 2 diabetes and cardiovascular events (IHD, MI, stroke and HF) for individual participants in the cohort was generated using data from the Health Survey for England 2011 (368). The data sources used in initial cohort generation and covariates and sources for annual progression or risk equation are presented in Table 4-8.

Table 4-8: Cohort variables

Parameter	Description	Source for initial cohort generation	Covariates & sources for annual progression / risk equation
Age, gender and ethnicity	Patient age, gender and ethnicity	ONS (366,367)	n/a
SBP	Systolic blood pressure	HSE (368)	Age, gender, BMI, smoking, T2DM, TC, SBP, MI history, physical activity (293,319,369)
BMI	Body mass index	HSE (368)	Age, gender, BMI (368)
TC	Total cholesterol	HSE (368)	Age, gender, TC, physical activity (290,368)
HDL-C	High-density lipoprotein cholesterol	HSE (368)	Age, gender, HDL-C, physical activity (291,368)
TCHDL	TC/HDL ratio	HSE (368)	TC, HDL,TCHDL, T2DM (319)
HbA1c	Glycated haemoglobin A1c	HSE (368)	Gender, HbA1c, T2DM, physical activity (292,319)
Smoking	Smoking status	HSE (368)	Age, gender, T2DM,Smoking, duration of T2DM (319)
Antihypertensive	Antihypertensive drug treatment	HSE (368)	Age, gender, SBP
AF	Atrial fibrillation	Majeed et al (370) & NICE (371)	Age, gender, BMI, SBP, Antihypertensive, HF (372)
IHD	Ischaemic heart disease	HSE (368)	Age, gender, HbA1c, TCHDL, SBP, T2DM, duration of T2DM (319)
MI	Myocardial infarction	HSE (368)	Age, gender, ethnicity, SBP, TCHDL, HbA1c, smoking, IHD, T2DM, duration of T2DM (319,373)
Stroke	Stroke	HSE (368)	Age, gender, SBP, Antihypertensive, T2DM, smoking, AF, HF, MI, TCHDL, HbA1c, duration of T2DM (319,374)
HF	Congestive heart failure	HSE (368)	Age, gender, BMI, HbA1c, SBP, T2DM, duration of T2DM (319,375)
T2DM	Type 2 diabetes	HSE (368)	BMI, age, gender, physical activity (296,329,376,377)
Retinopathy	Diabetic retinopathy	WESDR (320)	T2DM, duration of diabetes (320)
Neuropathy	Diabetic neuropathy	WESDR (320)	T2DM, duration of diabetes (320)
Nephropathy	Diabetic nephropathy	UKPDS	T2DM, duration of diabetes (378)
Colorectal cancer	Colorectal cancer	CRUK (379)	Age, polyp size, physical activity (312,355,380)
Breast cancer	Female breast cancer	Maddams et al. (381)	Age, gender, prognostic groups, physical activity (298,356)
Lung cancer	Lung cancer	CRUK (379)	Age, gender, smoking, physical activity (313,382,383)
Kidney cancer	Kidney cancer	CRUK (379)	Age, gender, T2DM, physical activity (296,379,384)

Note:
CRUK, Cancer Research UK; HbA1c, glycated haemoglobin A1c; HDL-C, high density lipoprotein cholesterol; HSE, Health Survey for England; IHD, ischaemic heart disease; MI, myocardial infarction; ONS, office for national statistics; SBP, systolic blood pressure; T2DM, type 2 diabetes; TC, total cholesterol; UKPDS, the UK prospective diabetes study; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Source: Adapted from Gc *et al*. (385)

One of the limitations of the baseline cohort is that individual parameter values are determined mostly by age and gender that means it does not allow interdependencies. For example, obese and older people are more likely to have raised systolic blood pressure which the current cohort does not take into account. It would have been more appropriate to use data from cohort or cross-sectional studies that would allow interdependencies, i.e. considering individual dynamics while generating the starting population. An attempt was made to get patient-level data from the EPIC Norfolk study investigators so that the data would allow us to generate a baseline cohort taking into account the correlation between input parameters. However, the request was not successful thus as an alternative source, the HSE data tables, are used to generate the baseline cohort. Sensitivity analysis and cross tabulation are done to check if the cohort characteristics match with HSE data, and the values appeared to be within the range.

The following section deals with the data sources used to estimate longitudinal trajectories of metabolic risk factors, the probability of disease event and mortality rates.

Risk factors progression

Six risk factors – systolic blood pressure, total cholesterol, HDL-cholesterol, BMI (obesity), blood glucose (HbA1c) and smoking status are modelled. These risk factors were chosen due to their role of being an important cause of chronic conditions of interest. The progression of risk factor values in diabetic patients were updated using UKPDS risk factor equations (319). Systolic blood pressure values for individuals without a diagnosis of type 2 diabetes was updated using the regression equation from the Baltimore Longitudinal Study of Ageing (369). The annual proportional change in the mean values of the remaining risk factors was estimated using HSE data from 2000 to 2011.

Systolic blood pressure

A linear-mixed effects model from the Baltimore Longitudinal Study on Ageing (369) was used to estimate the changes in SBP in the non-diabetic population whereas the UKPDS SBP progression equation was used for the diabetic population. Table 4-9 provides the coefficient estiamtes from the BLSA.

Table 4-9: Coefficient estimates for systolic blood pressure from BLSA

	Parameter description	Mean	Standard error
β1	Constant or average	121.000	0.8599
β2	Age at first examination	0.398	0.0320
β3	(age at first examination)^2	0.005	0.0016
β4	Time	0.228	0.0561
β5	Time^2	0.021	0.0053
β6	Binary variable for CHD event	6.578	1.1290
β7	Binary variable for BMI (<20)	2.268	1.6510
β8	Binary variable for BMI (25-29.9)	2.559	0.5785
β9	Binary variable for BMI (≥30)	0.037	1.2803
β10	Binary variable for current smoking	-0.263	0.6701
β11	Binary variable for cholesterol (200-239.9 mg/dL)	1.647	0.5024
β12	Binary variable for cholesterol (≥240 mg/dL)	4.511	0.8058
β13	Age at first examination × time	0.022	0.0033
β14	(cholesterol ≥240) × time	0.376	0.1053
β15	(cholesterol >240) × time^2	-0.029	0.0120

The function form of the SBP prediction equation used in non-diabetic population is:

$$SBP_{blsa} = \beta_1 + \beta_2 Time + \beta_3 Time^2 + \beta_4 FAge + \beta_5 FAge^2 + \beta_6 CHD + \beta_7 BMI_{<20} + \beta_8 BMI_{25-29.9} + \beta_9 BMI_{\geq 30} + \beta_{10} smoke + \beta_{11} TC_{200-239.9} + \beta_{12} TC_{\geq 240} + (\beta_{13} FAge + \beta_{14} TC_{>240}) Time + \beta_{15} TC_{>240} \times Time^2$$

The coefficients used in UKPDS outcome model (319) to predict the changes in SBP values in a diabetic population is presented below in Table 4-10.

Table 4-10: Coefficient estimates for SBP estimated from UKPDS data (319)

	Parameter description	Mean	Standard error
β16	Intercept	0.03	0.014
β17	Log transformation of year since diagnosis	0.039	0.008
β18	SBP score in last period	0.717	0.004
β19	SBP score at diagnosis	0.127	0.004

$$SBP_{ukpds} = SBP_{t-1} + \beta_{16} + \beta_{17} \log(diab\ year) + \beta_{18} \frac{(SBP_{t-1} - 135.09)}{10} + \beta_{19} \frac{(SBP_{diab\ dx} - 135.09)}{10}$$

Glycated haemoglobin levels (HbA1c)

The annual change in HbA1c in the model is estimated using data from HSE. The UKPDS HbA1c progression equation (319) was used for the diabetic population (Table 4-11).

Table 4-11: Coefficient estimates for HbA1c from UKPDS data

	Parameter description	Mean	Standard error
β23	Intercept	-0.024	0.017
β24	Log transformation of year since diagnosis	0.144	0.009
β25	Binary variable for year after diagnosis	-0.333	0.05
β26	HbA1c score in last period	0.759	0.004
β27	HbA1c score at diagnosis	0.085	0.004

$$HbA1c_{ukpds} = HbA1c_{t-1} + \beta_{23} + \beta_{24}\log(diab\ year) + \beta_{25} duration_{year=2} + \beta_{26}(HbA1c_{t-1} - 7.09) + \beta_{27}(HbA1c_{at\ dx} - 7.09)$$

$$HbA1c_t = if\ diabetic\ \left(HbA1c_{ukpds}\right)\ else\ (HbA1c_{hse})$$

Smoking

The coefficient estimates for smoking status were estimated from the UKPDS data (319).

Table 4-12: Coefficient estimates for smoking estimated from UKPDS data

	Parameter description	Mean	Standard error
β28	Intercept	-4.02	0.236
β29	year since diagnosis	-0.203	0.024
β30	Age	-0.027	0.008
β31	Binary variable for female	-0.489	0.154
β32	Binary variable for smoking in last year	1.878	0.211
β33	Binary variable for smoking at diagnosis	4.879	0.494

$$Smoke_t = \beta_{28} + \beta_{29} \times duration + \beta_{30}(age - 52.59) + \beta_{31} \times female + \beta_{32} \times smoke_{t-1} + \beta 33 \times smoke_{at\ dx}$$

Cardiovascular events

The Framingham risk equations were used to predict the cardiovascular events in the general population (373-375,386). These risk predictions are based on longitudinal follow-up of CVD events in the US population. There is a CVD risk prediction equation specifically

developed for the UK population (the QRISK2) (117) however the QRISK model includes patient variables that were not available for the current cohort such as rheumatic arthritis, chronic kidney disease and deprivation score.

Risk factors included in the equations from the Framingham Heart Study such as PR interval, prevalence of heart murmur, valve disease and congenital heart disease were not simulated in this model; therefore they could not be included in the model to predict AF and HF risk. Baseline odds of AF was adjusted to reflect the expected prevalence of these risk factors in a UK population. In line with the results from the Whitehall II cohort study, PR interval was assumed to be 170ms (387). Based on HSE data, prevalence of heart murmur was assumed to be 3.3% (388). The prevalence of valve disease was estimated from a population based study in England (389). The prevalence of congenital heart disease was estimated from BHF 2003 report (390). Predicted probability of AF was calculated using Cox proportional hazards regression coefficients reported in Table 4-13.

Table 4-13: Regression coefficients for the AF risk equation

Parameter description	Mean	Standard error
Age	0.15052	0.05767
Age²	-0.00038	0.00041
Male sex	1.99406	0.39326
Body-mass index	0.0193	0.01111
Systolic blood pressure	0.00615	0.00225
Treatment for hypertension	0.4241	0.10104
Heart failure	9.42833	2.26981
10-year baseline survival	0.96337	

The probability of type 2 diabetes was estimated as a function of age and BMI using a regression equation based on the Health Survey for England data (329). The macrovascular complications of diabetes namely ischaemic heart disease (IHD), stroke, myocardial infarction (MI) and heart failure (HF) were modelled using the UKPDS risk equations (319). Details of the risk equation used within the IHD, stroke, MI, heart failure and type 2 diabetes risk equations are presented below in Table 4-14.

Table 4-14: Risk equations coefficients used to estimate the risk of cardiovascular events in the general population

Disease condition	Risk equation
IHD (386)	L_chol = β1*Age + β2*TC1+ β3*TC2 + β4*TC3 + β5*TC4 + β6*TC5 + β7*HDL1 + β8*HDL2 +β9*HDL3 + β10*HDL4 + β11*HDL5 + β12*SBP1 + β13*SBP2 + β14*SBP3 + β15*SBP4 + β16*SBP5 + β17*DIAB + β18*SMOK A = L_chol – (3.00069 for men; 9.9914136 for women) B = e^A *IHD risk* = 1 – [s(t)]^B where s(t) = 0.90015 for men; 0.96246 for women
Stroke (374)	L= β1*Age + β2*SBP+ β3*NEWHRXSBP + β4*MIHx + β5*LVH + β6*SMOKE + β7*AF + β8*DIAB A = L – (5.6770 for male; 7.6074 for female) B = e^A Stroke risk = 1 –[S(t)]^B
MI (373)	mu.hat = 11.4712 +10.5109*female - 0.7965*log(age) – 5.4216 *log(age)*female + 0.7101*log(age)^2*female – 0.6623*log(SBP) – 0.2675 * smoke – 0.4277 *log(TC/HDL) – 0.1534*diab – 0.1165*diab*female – 0.1588 *LVH*male sigma.hat = e^(3.4064 – 0.8584 * mu.hat) v.hat = e^((log(1) - mu.hat)/sigma.hat) Mi risk = 1 – e^(-v.hat)
Heart failure (375)	x = α + β1*Age/10 + β2*SBP/20 + β3*Diabetes +β4*BMI heart failure risk = 1/ (1 + exp(-x))

Table 4-15 presents the parameter coefficients used in IHD risk equation (386).

Table 4-15: Covariates used in IHD risk equation

Abbvr	Parameter	Variable	Men	Women
AGE	β1	Age, y	0.04826	0.33766
		TC, mg/dL		
TC1	β2	<160	-0.65945	-0.26138
TC2	β3	160-199	Ref	Ref
TC3	β4	200-239	0.17692	0.20771
TC4	β5	240-279	0.50539	0.24385
TC5	β6	≥280	0.65713	0.53513
		HDL-C, mg/dL		
HDL1	β7	<35	0.49744	0.84312
HDL2	β8	35-44	0.2431	0.37796
HDL3	β9	45-49	Ref	0.19785
HDL4	β10	50-59	-0.05107	Ref

Table 4-15 (continued)

Abbvr	Parameter	Variable	Men	Women
HDL5	β11	≥60	-0.4866	-0.42951
		Blood pressure		
SBP1	β12	Optimal	-0.00226	-0.53363
SBP2	β13	Normal	Ref	Ref
SBP3	β14	High normal	0.2832	-0.06773
SBP4	β15	Stage I hypertension	0.52168	0.26288
SBP5	β16	Stage II-IV hypertension	0.61859	0.46573
	β17	Diabetes	0.42839	0.59626
	β18	Smoker	0.52337	0.29246
		Baseline survival [s(10)]	0.90015	0.96246

Table 4-16 reports the coefficient estimates for risk of stroke from Framingham Heart Study (374). The probability of an event was calculated from the survival function at one year raised to the power of *B* where *B* is the exponential of sum product of coefficients (Table 4-16) multiplied by the individuals' characteristics. One year survival probability [S(t)] for male and female are 0.9948 and 0.9977 and mean values (M) for men and women are 5.6770 and 7.6074 respectively.

The equation for the probability of stroke event in year t is calculated as $p = 1 - S(t)^B$, $B = \sum \beta X$

Table 4-16: Coefficient estimates for risk of stroke by gender

Parameter description	Mean (Male)	Standard error (Male)	Mean (female)	Standard error (female)
Age	0.0488	0.0103	0.0699	0.0089
Systolic blood pressure	0.0152	0.0031	0.0161	0.0024
newHRxSBP	0.00019	0.0001	0.00026	0.00007
Prev diagnosed CHD, CF or intermittent claudication	0.546	0.0151	0.4404	0.1462
Binary variable for left ventricular hypertrophy	0.7864	0.2846	0.8055	0.2429
Binary variable for cigarette smoking	0.5224	0.1429	0.5419	0.1453
Binary variable for atrial fibrillation	0.5998	0.3011	1.1173	0.2302
Binary variable for diabetes mellitus	0.3429	0.1894	0.5604	0.1706

newHRxSBP = HRx (dummy variable defined as one if the individual is on antihypertensive medication and 0 if not) × (SBP – 100) × (SBP – 200).

The risk of heart failure in the general population was calculated using regression coefficients reported in Table 4-17 as $p = 1/(1 + \exp(-Xbeta))$ where Xbeta is the sum of intercept and sum product of regression coefficients reported in Table 4-17 multiplied by the individual's characteristics (i.e. value of risk factor).

Table 4-17: Regression coefficients estimates for HF risk prediction in general population

Parameter description	Men Mean (SE)	Women Mean (SE)
Intercept	-9.07269629	-10.6277
Age	0.0412 (0.072)	0.0503 (0.078)
Systolic blood pressure	0.00804 (0.061)	0.00337 (0.057)
Diabetes	0.2244 (0.0174)	1.3857 (0.185)
BMI		0.0578 (0.014)

Table 4-18 lists the risk equations used along with coefficients used to estimate the risk of type 2 diabetes and complications mainly IHD, MI CHF and stroke.

Table 4-18: Risk equations coefficients used to estimate the risk of type 2 diabetes and risk and cardiovascular events in the diabetic patient

Disease	Risk equation
Diabetes (329)	Risk of type 2 diabetes = (-853.08 + 1.415 * age + 36.616 * bmi)/100,000 for male; (-997.312 + 0.279 * age + 43.868 * bmi)/100,000 for female
IHD (319)	β = -5.31 + 0.031 * (age at diagnosis - 52.59) - 0.471 * sex + 0.125 * (HbA1c$_t$ - 7.09) + 0.098 * ((SBP$_t$ - 135.09) / 10) + 1.498 * (ln (tcHDL$_t$) - ln (5.23)) *IHD risk* = e^β * year^1.150 * BMI Risk Factor * CV Risk Factor }
MI (319)	β = -4.977 + 0.055 * (age at diagnosis - 52.59) - 0.826 * sex - 1.312 * ethnicity + 0.346 * smoking + 0.118 * (HbA1c$_t$ - 7.09) + 0.101 * ((SBP$_t$ - 135.09) / 10) + 1.190 * (ln (tcHDL$_t$) - ln (5.23)) + 0.914 t t t 1.257 * IHD Event Occurred + 1.558 * CHF Event Occurred *MI risk* = e^β * year^1.257 * BMI Risk Factor * CV Risk Factor
CHF (319)	β = -8.018 + 0.093 * (age at diagnosis - 52.59) + 0.066 * (BMI$_t$ - 27.77) + 0.157 * (HbA1c$_t$ - 7.09) 0.114 * ((SBP$_t$ - 135.09) / 10) *CHF risk* = e^{β} * $year^{1.711}$ * BMI Risk Factor * CV Risk Factor
Stroke (319)	β = -7.163 + 0.085 * (age at diagnosis - 52.59) - 0.516 * sex + 0.355 * smoking + 0.128 * (HbA1c$_t$ - 7.09) + 0.276 * ((SBP$_t$ - 135.09) / 10) + 0.113 * (ln (tcHDL$_t$) - ln (5.23)) + 1.428 * AF + 1.742 * CHF Event occurred *Stroke risk* = e^{β} * $year^{1.497}$ * BMI Risk Factor * CV Risk Factor Risk

Microvascular complications of type 2 diabetes

The model structure for microvascular complications of diabetes was informed by the CDC and Eastman models (320). If diabetes is not treated, it can lead to an increased risk of developing a number of different health problems. Sustained high glucose levels are associated with damage to blood vessels, nerves and organs. These microvascular complications were chosen because they are the key outcomes of type 2 diabetes (as described in section 4.4.1.2). This section describes the three sub-modules of type 2 diabetes complications, i.e. diabetic nephropathy, retinopathy and neuropathy. Transitional probabilities and hazard rates were taken from Eastman et al. (320,391) to model the natural history of diabetic retinopathy and neuropathy.

Diabetic retinopathy

Based on the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), it is assumed that twenty per cent patients with type 2 diabetes have background retinopathy (BDR) at the time of the first diagnosis of diabetes.(392) The retinopathy model includes five health states – no retinopathy, non-proliferative retinopathy (BDR), proliferative Retinopathy (PDR), significant macular oedema (ME), and blindness.

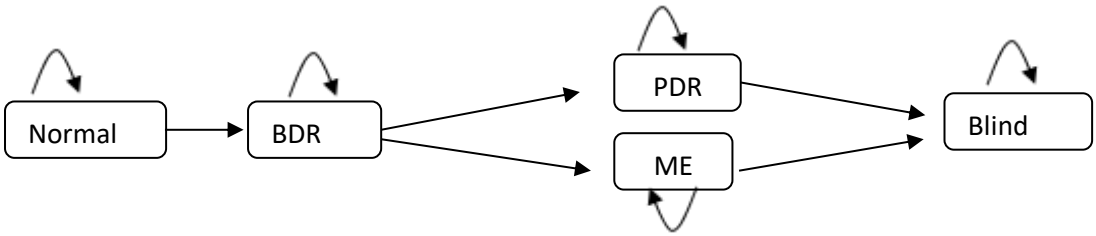

Figure 4-5: Diabetic retinopathy health states

Progression to a health state within retinopathy module is dependent on the current health state and duration of diabetes. Annual transitional rates for the different stages of retinopathy (378) were taken from the WESDR study (Table 4-19).

Diabetic neuropathy

Diabetic neuropathy is the damage to peripheral nerves in the body that is associated with sustained high blood sugar levels from diabetes. The natural history model includes normal (no neuropathy), symptomatic neuropathy, first lower-extremity amputation (LEA), and second LEA health states (Figure 4-6).

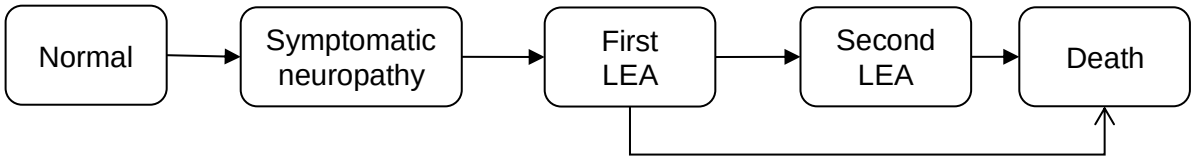

Figure 4-6: Diabetic neuropathy health states

The hazard rates of diabetic neuropathy depend on the duration of diabetes were taken from Eastman et al. (320) (Table 4-19).

Table 4-19: Annual transitional rates through the different stages of retinopathy and neuropathy

Characteristics	Duration of diabetes	Hazard rate (per year)
Background diabetic retinopathy (BDR) risk	1—4	0.073
	5—9	0.129
	10—14	0.116
	15+	0.113
Macular oedema (ME) risk	1—4	0.47
	5—9	0.095
	10—14	0.092
	15+	0.08
Proliferative diabetic retinopathy (PDR) risk	1—4	0.0025
	5—9	0.009
	10—14	0.0095
	15+	0.026
	Condition	*Hazard rate (per year)*
Progression of PDR to severe vision loss	Untreated	0.088
	Treated	0.0148
Progression of ME to blindness	Untreated	0.05
	Treated	0.033
Diabetic neuropathy		
Progression to diabetic neuropathy	All durations	0.0144
Progression to first lower-extremity amputation (LEA)	1–8	0.028
	9—13	0.0350
	14—19	0.0467
	20+	0.14
	12—20	0.0385
	21+	0.074
Second LEA subsequent to the first LEA	All durations	0.1386

Diabetic nephropathy

The prevalence data for diabetic nephropathy, i.e. development of microalbuminuria were based on the UKPDS data (Table 4-20) and include pre-specified renal outcomes in newly diagnosed diabetes (378).

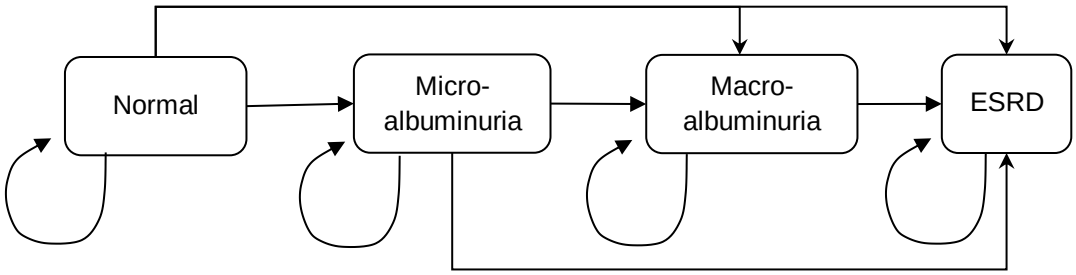

Figure 4-7: States and transition probabilities in diabetic nephropathy

The health states modelled for diabetic neuropathy include micro-albuminuria, macro-albuminuria, and end-stage renal disease (ESRD). The values presented in Table 4-20 are annual transition rates and 95% CI levels.

Table 4-20: Annual transition rates through the stages of nephropathy to death from any cause

	No nephropathy	Micro-albuminuria	Macro-albuminuria	ESRD	Death
No nephropathy	0.964 (0.0962-0.966)	0.02 (0.019-0.022)	0.001 (0.001-0.002)	0.001 (0.001 – 0.002)	0.014 (0.013-0.015)
Micro-albuminuria	-	0.938 (0.933-0.944)	0.028 (0.025-0.032)	0.003 (0.001-0.004)	0.03 (0.026-0.034)
Macro-albuminuria	-	-	0.931 (0.918-0.944)	0.023 (0.015-0.03)	0.046 (0.036-0.057)
ESRD	-	-	-	0.808 (0.756-0.86)	0.192 (0.14-0.244)

Breast cancer

The breast cancer model starts by estimating the number of women aged 50 years and above. From this group, a proportion of women receive a diagnosis of breast cancer. For those with breast cancer, disease severity is classified according to the Nottingham Prognostic Index (NPI) prognostic groups – ductal carcinoma in situ (DCIS), excellent,

good, moderate and poor.(393) The annual transition probabilities by different prognostic groups and recurrences and death (Table 4-21) were adopted from Johnston (356).

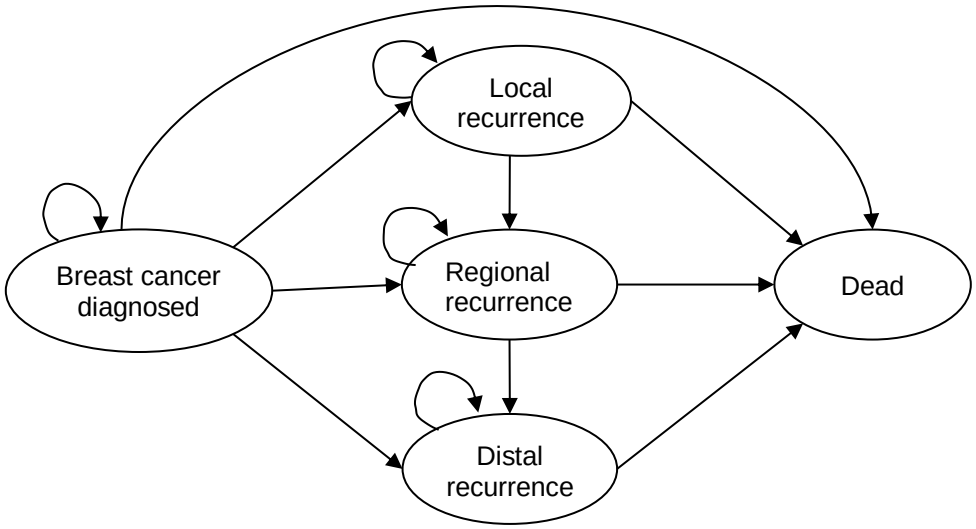

Figure 4-8: Health states for breast cancer

Table 4-21: Annual transition probabilities of breast cancer differing by prognostic group

Transition/Prognostic groups	DCIS	Excellent	Good	Moderate	Poor
Annual transition probabilities by prognostic groups					
BCD to LR	0.0044	0.0015	0.0069	0.0110	0.0279
BCD to RR	0.0054	0.0045	0.0080	0.0155	0.0257
BCD to DR	0	0	0.0074	0.0155	0.0764
BCD to dead (breast cancer) – age-specific					
50 – 59 years	0	0.0039	0.0097	0.0602	0.2770
60 – 69 years	0	0.0051	0.0100	0.0837	-
70 – 79 years	0	0.0061	0.0112		-
80 – 89 years	0	0.0069	0.0121	-	-
90 – 99 years	0	0.0073	0.0132	-	-
Annual transition probabilities for breast cancer recurrences and death					
	Local recurrence	Regional recurrence	Distal recurrence	Death	
Local recurrence	-	0.400	0.2258	0.2152	
Regional recurrence	-	-	0.2258	0.2438	
Distal recurrence	-	-	-	0.7450	

Note:

BCD, breast cancer diagnosed; LR, local recurrence; RR, regional recurrence; DR, distal recurrence; DCIS, ductal carcinoma in situ

Colorectal cancer

Colorectal cancer (CRC) is the fourth most common form of cancer in the UK, where approximately 41,700 new cases of CRC diagnosed each year, resulting in around 16,000 CRC-related deaths annually (379) and the risk depends on increasing age. The baseline parameter values were derived from Frazier et al. (355) and applied to the baseline population to generate prevalence of CRC. The model simulates the evolution of cancer from normal epithelium to adenomatous polyp to cancer. Person representative of the 50-year-old are placed into health states defined by the presence of polyp (380) or cancer (Table 4-22).

Table 4-22: Baseline parameter values and transitional probabilities for colorectal cancer

Variables	Value (range)
Baseline data	
Normal epithelium	0.78875
Prevalence of polyps at age 50 (low risk)	0.206
High-risk polyps	0.004
Colorectal cancer – localised (early)	0.001
Colorectal cancer – regional (regional)	0.0002
Colorectal cancer – distant (advanced)	0.00005
Prevalence of polyps at age 50 years, %	21 (11-42)
Proportion of polyps at age 50 years that are of high risk %	2 (1-10)
Annual transition probabilities	
Normal epithelium to low-risk polyp	
50 – 54 years	0.005
55 – 59 years	0.0065
60 – 64 years	0.008
Over 65 years	0.0095
Low-risk polyp to high risk polyp	0.02 (0.01-0.04)
High risk polyp to localised cancer	0.05 (0.2-0.10)
Localised cancer to regional cancer	0.28 (0.10-0.50)
Regional cancer to distant cancer	0.63 (0.32-0.80)
Annual CRC specific mortality rates	
Localised cancer	0.002
Regional cancer	0.032
Distal cancer	0.566

Lung cancer

Lung cancer is one of the most deadly cancers, and it is the second most common cancer diagnosed in the UK after breast cancer (379). Non-small cell lung cancer accounts for 78% of lung cancer in England and Wales (379). Age and sex specified incidence rates of developing lung cancer in the general population are based on the estimates from the Cancer Research UK data (383). The risk in non-smokers is estimated by adjusting the general population estimates using the equation from Godfrey et al. (382).The relative risk in current smokers (Male 9.87 [6.85-14.24] and Female 7.58 [5.36-10.73]) was taken from a meta-analysis of observational studies published between 1961 and 2003 (394). The probability of developing lung cancer based on age, sex and smoking status (382,394) is presented in Table 4-23.

Table 4-23: Probability of developing lung cancer by age, sex and smoking status

Age group	Men		Women	
	Non-smokers	Smokers	Non-smokers	Smokers
35–39	0.00%	0.01%	0.00%	0.01%
40–44	0.00%	0.01%	0.00%	0.02%
45–49	0.00%	0.04%	0.01%	0.04%
50–54	0.01%	0.11%	0.01%	0.09%
55–59	0.02%	0.23%	0.03%	0.19%
60–64	0.04%	0.42%	0.04%	0.32%
65–69	0.07%	0.71%	0.07%	0.52%
70–74	0.10%	0.95%	0.08%	0.64%
75–79	0.15%	1.47%	0.12%	0.93%
80–84	0.18%	1.78%	0.14%	1.03%
85+	0.17%	1.63%	0.11%	0.80%

Kidney cancer

Kidney cancer is the eighth most common cancer in the UK, accounting for 3% of all new cases. Of those new kidney cancer diagnosed in 2004, 85-90% were renal cell carcinomas (379). The major risk factors for kidney cancer include age, sex, obesity, smoking, and some genetic and medical conditions such as hypertension. Renal cell carcinoma is nearly twice as common in men as in women, and most commonly affects adults aged 50-80 years. Approximately 25% of kidney cancer patients represent with advanced and/or metastatic disease (stage III or IV). An estimated 50% of patients who

have curative resection for earlier stages will develop recurrent and/or metastatic disease. Without the treatment, median survival is only 6-12 months, and the two-year survival rate is 10-20% (395).

The age and sex-specific incidence rates for kidney cancer were obtained from the Cancer Research UK statistics for 2010 (379) and were adjusted for diabetes (384) to estimate the risk of kidney cancer.

Table 4-24: Annual probability of developing kidney cancer by age, sex and diabetes status

Age Range	Men		Women	
	Diabetic	Non-diabetic	Diabetic	Non-diabetic
15 to 19	0.000001	0.00000	0.00000	0.00000
20 to 24	0.000003	0.00000	0.00000	0.00001
25 to 29	0.000005	0.00001	0.00001	0.00001
30 to 34	0.000014	0.00001	0.00002	0.00002
35 to 39	0.000039	0.00002	0.00005	0.00004
40 to 44	0.000072	0.00004	0.00009	0.00006
45 to 49	0.000109	0.00006	0.00014	0.00009
50 to 54	0.000195	0.000107	0.000246	0.000182
55 to 59	0.000302	0.00017	0.000381	0.000289
60 to 64	0.000444	0.000229	0.000559	0.000389
65 to 69	0.000563	0.000292	0.000709	0.000496
70 to 74	0.000782	0.000396	0.000985	0.000673
75 to 79	0.000924	0.000478	0.001164	0.000813
80 to 84	0.001003	0.000505	0.001264	0.000859
85+	0.000981	0.000474	0.001236	0.000806

It would be appropriate to model different stages of lung and kidney cancers. From the epidemiological studies, only the stage-specific mortality rates were available, and transition rate information was missing. Thus, only three health states are considered for lung and kidney cancers – progression-free, progressive and dead. To capture the disease progression in cancer, it requires a more complex model structure to estimate additional parameter values, such as missing transition rate information (396).

Mortality risks

Background mortality rates were taken from life tables for the English population (397). Death rates for cardiovascular (MI and stroke) and cancers were excluded from all-cause

mortality to estimate other cause mortality rates. These rates adjust age-specific UK annual incidence of mortality. Annual transitional probabilities for breast cancer recurrence to death were taken from Johnston (356). The rates are assumed to be the same for prognostic groups. Mortality estimates for colorectal cancer by stages were based on Frazier et al. (355). These rates vary by cancer stages. Lung cancer mortality estimates were obtained from a comparative study of lung cancer survival in six developed countries (398). The mortality rate for lung cancer was calculated as one minus one-year net survival rate: 28.8% (28.3 – 29.4) in the UK. Mortality rates for kidney cancer were estimated using UK survival rates for kidney cancer (379). It was assumed that mortality rates associated with disease conditions that were not explicitly modelled remain stable at the rates recorded in the relevant population. To avoid double counting, deaths from type 2 diabetes were not modelled as adults with diabetes are more likely to die from cardiovascular conditions.

Costs

Health care resource use was estimated for each health state. The annual costs associated with each state were estimated by multiplying the healthcare utilisation associated with the state by the costs of each unit of health care and inflated to 2011 UK £ sterling using inflation indices from the Hospital and Community Health Services (HCHS) index (28). Previous economic models, HTA reports, RCTs and cost-of illness studies were searched to obtain the most recent and appropriate evidence to populate costs. The costs associated with the model and associated parameters and ranges for the probabilistic analysis are reported in Table 4-25. These costs were considered from the UK NHS perspective where possible. Gamma distributions are assumed to sample costs because costs are constrained to be either zero or positive (positively skewed) (36).

Table 4-25: Costs of health states in the cost-effectiveness model

Health state, source	Cost	Cost, year (original)	Cost (2011 prices)
Hypertension by age – male (399)			
35-54	£30.06	2009/10	£30.89
55-64	£28.76	2009/10	£29.55
65-74	£31.74	2009/10	£32.61
75+	£32.56	2009/10	£33.46
Hypertension by age – female (399)			
35-54	£29.20	2009/10	£30.00
55-64	£30.06	2009/10	£30.89
65-74	£31.20	2009/10	£32.06
75+	£33.64	2009/10	£34.57
LVH (329)	£898.21	2004	£1,067

Table 4-25 (continued)

Health state, source	Cost	Cost, year (original)	Cost (2011 prices)
Type 2 diabetes (400)	£653	2005	£724
Ischaemic heart disease (IHD) (401)	£3,880	2009	£4,010
IHD (history) (402)	£171	2004	£203
Myocardial infraction (first) (402,403)	£4,448	2004	£5,284.75
MI (subsequent) (402)	£171	2004	£203.17
MI (fatal) (404)	£1,166	2004	£1,825.96
Stroke (first) (402)	£8,046.00	2004	£9,559.60
Stroke (subsequent) (402)	£2,163.00	2004	£2,569.90
Stroke (fatal) (402)	£7,041.00	2004	£8,365.54
CHF (404)	£2,221	2004	£3,478.09
CHF (history) (404)	£631	2004	£988.15
Dilated eye examination for diabetic retinopathy (28)	£24.98	2010/11	£24.98
Cataract extraction (404)	£1,553	2004	£2,432.00
Blindness (404)	£872	2004	£1,365.55
Blindness (history) (404)	£281	2004	£440
Micro- albuminuria (405)	£104	2001	£146
Overt nephropathy (proteinuria) (405)	£6,084	2001	£8,545
End Stage Renal Disease (ESRD) (405)	£27,924	2001	£39,221
Amputation (404)	£8,459	2004	£13,247
Amputation (history) (404)	£300	2004	£470
Lung cancer initial treatment (382)	£12,902	2009	£13,336.90
Annual cost (382)	£5,611	2009	£5,800
Kidney cancer (406)	£26,653	2007/08	£28,527
Localised (407)	£10,370	2004/05	£12,352.43
Regional (407)	£19,077	2004/05	£22,723.11
Metastatic (407)	£11,946	2004/05	£14,229.00
Breast cancer – DCIS (356)	£2699	1998/99	£4,139.76
Breast cancer – Excellent (356)	£2700	1998/99	£4,141.30
Breast cancer – Good (356)	£2,935	1998/99	£4,501.74
Breast cancer – Moderate (356)	£3,156	1998/99	£4,840.72
Breast cancer – Poor (356)	£3,262	1998/99	£5,003.30
Follow-up after primary treatment (356)	£71	1998/99	£108.90
Breast cancer - local recurrence (356)	£2,502	1998/99	£3,837.60
Breast cancer - regional recurrence (356)	£3,327	1998/99	£5,103.00
Breast cancer - distal recurrence (356)	£5,249	1998/99	£8,050.99
Breast cancer - follow-up after local and regional recurrence (356)	£163	1998/99	£250.01
Breast cancer - follow-up after distal recurrence (356)	£4,336	1998/99	£6,650.62
Breast cancer - palliative care (356)	£2,750	1998/99	£4,217.99

Antihypertensive treatment

Treatment costs for hypertension were taken from National Clinical Guidelines Centre 2011 (399) that undertook an updated review of the costs for hypertension. These costs include annual check-up and cost of the hypertensive drug.

Diabetes and complications

The cost of type 2 diabetes without complications is taken from Ara & Brennan (400). This cost includes GP and nurse visits, lab tests and drug costs. Costs of diabetic retinopathy and neuropathy were taken from the UKPDS study (404). The cost of amputation in the first year of surgery and subsequent years were extracted and inflated to 2011/12 prices. Costs of diabetic nephropathy were taken from a cost of illness study by Gordois et al. (405). These costs are based on the health care cost estimation of diabetic nephropathy in the UK and include the costs of outpatient clinics, treatment and drug costs.

Cardiovascular events

Treatment costs for cardiovascular events were taken from Ward et al. (402). The cost of angina pectoris was used as a proxy for ischaemic heart disease (402). This includes the cost of GP contact plus medication costs.

Cost of non-fatal MI in the first year was taken from Palmer et al. (403) and Ward et al. (402). The cost was based on the Nottingham heart attack register study. As this cost does not include primary care costs, primary care and medication costs were assumed to be the same as angina. Cost of MI in subsequent year was based on the assumption that all the patients receive primary care support. Cost of fatal MI and CHF were taken from the UKPDS study (404). The cost of CHF was based on the UKPDS study, i.e. for diabetic patients thus costs for CHF events may be higher than the cost of CHF for the non-diabetic population.

Cost of stroke was taken from an HTA report by Ward et al. (402). The cost is based on the Nottingham Heart Attack Register (NHAR) study and includes the cost of inpatient stay, GP visits, outpatient, readmission, respite care and day hospital care (408). The estimated cost of non-fatal and subsequent stroke is based on the cost of acute events (mild, moderate and severe) weighted by the distribution of severity of stroke.

Cancers

Breast cancer treatments costs (356) include costs for primary treatment, recurrences and follow-up. The initial treatment and annual costs of lung cancer are taken from Godfrey et al. (382). These costs include lung cancer-related costs for the NHS. Costs related to kidney cancer treatment are taken from the PenTAG model (406). Kidney cancer treatment costs include GP consultations, blood tests, CT scans, drug administration (Sunitinib) and pain medication.

Health state utility values

The primary outcome of the model is expressed in terms of QALYs using estimates of survival and quality of life attributable to each health state. The utility values represent the strength of an individual's preferences for specific health-related outcomes. They are measured in an interval scale of zero reflecting states equivalent to death and one reflecting perfect health (1,409). Utility values associated with each health state depend on the presence or absence of a particular health state.

The CEA registry (410) was searched to identify utility estimates for inclusion in the model. The original source papers were scanned to extract data on disease, country, year, time horizon, perspectives used, participants, sample size, response rate, reference estimation, the method used to value, and quality score (if available). To obtain health state utilities, a choice based technique (e.g. standard gamble or time trade-off) or a generic instrument (e.g. EQ-5D) was used, where available. Table 4-26 indicates the condition-specific utility values used in the model. The beta distribution was used to sample utility values.

Most of the utility values for health states in the model were taken from Sullivan et al. (411). Sullivan and colleagues applied community-based UK preferences to EQ-5D descriptive questionnaire responses in the US-based medical expenditure panel survey. Utility values for type 2 diabetes, amputation and blindness were taken from the UKPDS study (412). Clarke et al. estimated the impact of diabetes complications on quality of life using EQ-5D questionnaires. Utility values for diabetic nephropathy and foot ulcer were from Coffey et al. (413). Their study included 2,048 patients with type 1 and type 2 diabetes and used self-administered quality of well-being index to calculate a health utility score. Utility values for background and proliferative diabetic retinopathy were taken from a prospective observational study of diabetes care in the US (414). This study included 7,327 individuals with type 2 diabetes and measured the quality of life using EQ-5D. Utility values for breast cancer recurrences were taken from Lidgren et al. (415). In their study,

Lidgren et al. included 361 breast cancer patients and estimated the impact of breast cancer on quality of life using the EQ-5D questionnaire. Utility values for health states related to colorectal cancer were taken from Ness et al. (416,417).

Table 4-26: Condition-specific utility values

Health states	Value	Standard error	Source
Healthy	1.00		
Hypertension	0.72	0.0035	(411)
IHD	0.65	0.0203	(411)
Acute MI	0.60	0.022	(411)
Stroke	0.52	0.0192	(411)
Congestive heart failure	0.49	0.0194	(411)
Left ventricular hypertrophy	0.62	0.0087	(411)
Atrial fibrillation	0.69	0.0095	(411)
Type 2 diabetes	0.785	0.0530	(412)
Diabetic retinopathy			
Background diabetic retinopathy	0.78	0.005	(414)
Proliferative retinopathy	0.76	0.008	(414)
Blindness or vision loss	0.711	0.018	(412)
Diabetic neuropathy			
Foot ulcer	0.60	0.009	(413)
Amputation	0.56	0.056	(412)
Diabetic nephropathy			
Micro/macro albuminuria	0.678	0.009	(413)
Renal failure	0.611	0.026	(413)
Lung cancer	0.56	0.0433	(411)
Breast cancer	0.76	0.0133	(411)
Local/regional recurrence	0.78	0.0373	(415)
Distal recurrence	0.69	0.0293	(415)
Colorectal cancer			
Localised cancer	0.74	0.023	(417)
Regional cancer	0.67	0.026	(417)
Distal cancer	0.25	0.028	(417)
Kidney cancer	0.66	0.0729	(411)

4.4.3 Time horizon

The National Institute for Health and Care Excellence (NICE) recommends a lifetime time horizon for chronic disease interventions (2). The effectiveness evidence of VBIs in physical activity is based on studies with up to 2 years of follow-up data. For this model, a 10-year time horizon is chosen. This is based on the estimates that the long-term effects of PA would be 55% of the effect after one year of intervention (334). The shorter time horizon may underestimate the long-term benefits of increasing physical activity, but a longer time horizon would need larger assumptions about the uptake of physical activity, study population demographics, disease incidence, mortality rates and costs. Sensitivity analyses were performed with varying decay rates between 0% (lifelong behaviour change) and 100% (behaviour change reversed after the first year post-intervention).

4.4.4 Discounting

Cost-effectiveness analysis is based on intervention in the first year, with all health outcomes and costs measured over the 10-year period. In health economic evaluations, it is the standard practice to adjust costs and health outcomes for differential timing by applying a rate of discount. This allows comparison of costs and health outcomes in terms of net present value. All future costs and health outcomes are discounted at 3.5% per annum (2) using the following formula:

$$V_0 = \frac{V_t}{(1+r)^t} \tag{4-1}$$

Where V_0 is the current value, V_t is the value at time t and r is the rate of discount.

4.4.5 Cycle length

The model uses one-year cycle length. This is based on the availability of data. Previous models of PA (141,337,339) used a similar approach in terms of cycle length. Use of a monthly cycle would increase the processing time because it would result in a 12-fold increase in evaluation time over a year.

4.5 Model calibration

The above section detailed the development of the model and how it was parametrised, this section now describes the model calibration. As the model included more than ten co-

morbidities and as varied sources were used to inform model parameters, it was essential to assess the accuracy of the model's predictions (418). This section describes the model calibration process including calibration endpoints and assessment of goodness-of-fit.

Model calibration is the process of identification of a set of inputs that generates model outputs that best predict observed data (418). It seeks to explicitly modify model input coefficients such that simulated values of parameters match as closely as possible to the observed. This is an essential and often under-appreciated part of the model development process and seeks to check that the model predictions are consistent with the other data sources describing the model output (419,420). The accuracy of the model predictions depends on the structural assumptions of the model and the quality of key input parameters (421).

The effect of increased physical activity in the model on disease events is mediated through the risk factors, and there exists direct evidence on the link between increased physical activity and risk of a disease event. The risk equations used to predict cardiovascular outcomes in non-diabetic patients were from the Framingham Heart Study. Cardiovascular events contribute largely in terms of healthcare costs and quality of life. To overcome with such issues, it is necessary to calibrate the model using these targets, i.e. using the direct link between physical activity and risk of disease event (relative risks) and incidence/prevalence of diseases in the UK.

4.5.1 Model calibration endpoints and model parameters

Seven endpoints were selected as calibration targets due to their likely influence on the cost-effectiveness of interventions as well as the availability of data examining the direct effect of physical activity on disease events (Table 4-27). The endpoints relate to relative risks (of all-cause mortality, stroke and CHD) with various levels of physical activity, disease incidence (MI and stroke) and prevalence (of CHD and diabetes). The evidence for these endpoints was derived from meta-analyses of observational studies, cross-sectional analysis of national statistics, and longitudinal studies (294,296,422,423).

Table 4-27: Model calibration endpoints

Calibration endpoints and source	Values (Observed)	Weight
MI incidence per year per 100,000 (424)	13.58	0.09
Prevalence of CHD (424)	5.3 %	0.07
Stroke incidence per year per 100,000 (424)	14.89	0.09
Prevalence of Diabetes (425)	5.5 %	0.07
Relative risk of CHD (0 vs 11.3 METs) (294)	0.86	0.12
Relative risk of stroke (0 vs 11.5 METs) (423)	0.89	0.18
Relative risk of all-cause mortality (0 vs 11 METs) (422)	0.81	0.37

4.5.2 Assessing the goodness-of-fit of calibration results

Goodness-of-fit metric measures the accuracy of the calibrated input in replicating the target endpoints (426). As the model has multiple endpoints, we combined the measure of goodness-of-fit across all calibration targets using the absolute weighted mean deviation (WMD). The WMD is calculated as the weighted sum across all the seven endpoints of the proportional difference between the predicted and observed values of a given parameter (Equation 4-2).

$$Weighted\ Mean\ Percentage\ Deviation = \sum_{i=1}^{n} w_i \frac{|pred_i - obs_i|}{obs_i} \quad (4\text{-}2)$$

Where n = number of endpoints, $pred_i$ = model-based estimates of the i^{th} end point, obs_i = data-based target value of the i^{th} end point, and w_i= weight of the i^{th} endpoint

Weights were assigned to each endpoint based on the relative importance of the estimates in the cost-effectiveness analysis (Table 4-27). In order of importance, from most important to least important, these were: relative risk (RR) of all-cause mortality, RR of stroke, RR of CHD, disease incidence (stroke and MI) and prevalence (CHD and diabetes). The weights were then assigned as 1/order of importance and normalised by dividing the raw weights of each endpoint over the sum of the weights for all endpoints (Equation 4-3) (427). As a result, RR of all-cause mortality had higher weights and prevalence of diabetes and CHD parameters have lower weights.

$$w_i = \frac{1/r_i}{\sum_{j=1}^{k} \left(1/r_j\right)} \quad (4\text{-}3)$$

Where $r_i$is the rank of the i^{th} end point, k is the total number of end points

4.5.3 Parameter search algorithm

Different parameter search strategies have been described in the literature to calibrate models in economic evaluation, for example, grid search, generalised reduced gradient, simulated annealing and mixed approaches (418,419,421,426,428). There is no single approach that would be suitable for all models (429). In theory, all algorithms should ultimately produce model outputs that match the specified calibration target most closely. Therefore, the choice of algorithm is ultimately a pragmatic decision based on computational efficiency, as all algorithms should converge on the optimal solution, given sufficient searches. We chose the Nelder-Mead search algorithm(430) as our preferred method, implemented using the 'neldermead' package in R (431). This method has previously been used to calibrate cost-effectiveness models and was found to be efficient (428,432,433). Others have suggested that the Nelder-Mead method performs best with a relatively smaller number of variables (434). We identified the top ten most influential coefficients in the model by performing one-way sensitivity analyses, evaluating the WMD of the model outputs with each coefficient at its lower and upper 95% confidence interval (CI) values, respectively. The ten coefficients yielding the biggest variation in WMD were selected for calibration using the Nelder-Mead function.

The Nelder-Mead algorithm converged but not a true minimum after 703 iterations, i.e. the value of the objective function (weighted mean deviation) did not reduce further. As a result, we chose the typically less efficient but widely used method in health economics, the directed random search method (429). This was done in two stages. First, 100,000 sets of all model parameter values (coefficients) were generated by sampling randomly from the mean +/- two standard errors with a uniform distribution. Second, the set yielding the lowest WMD was used as the starting point for a further 100,000 sets of sampled coefficients +/- one standard error. The set yielding the lowest WMD was chosen as the optimal set.

4.5.4 Model calibration results

Before calibration, the value of the objective function (WMD) was 43%. The best-fitting parameter set from the random search method had a WMD of 12%. Figure 4-9 shows the percentage deviation from the aggregated target for each calibration endpoint. The model predicted endpoints from the random search calibration deviated from the target endpoints by -11% to 23%.

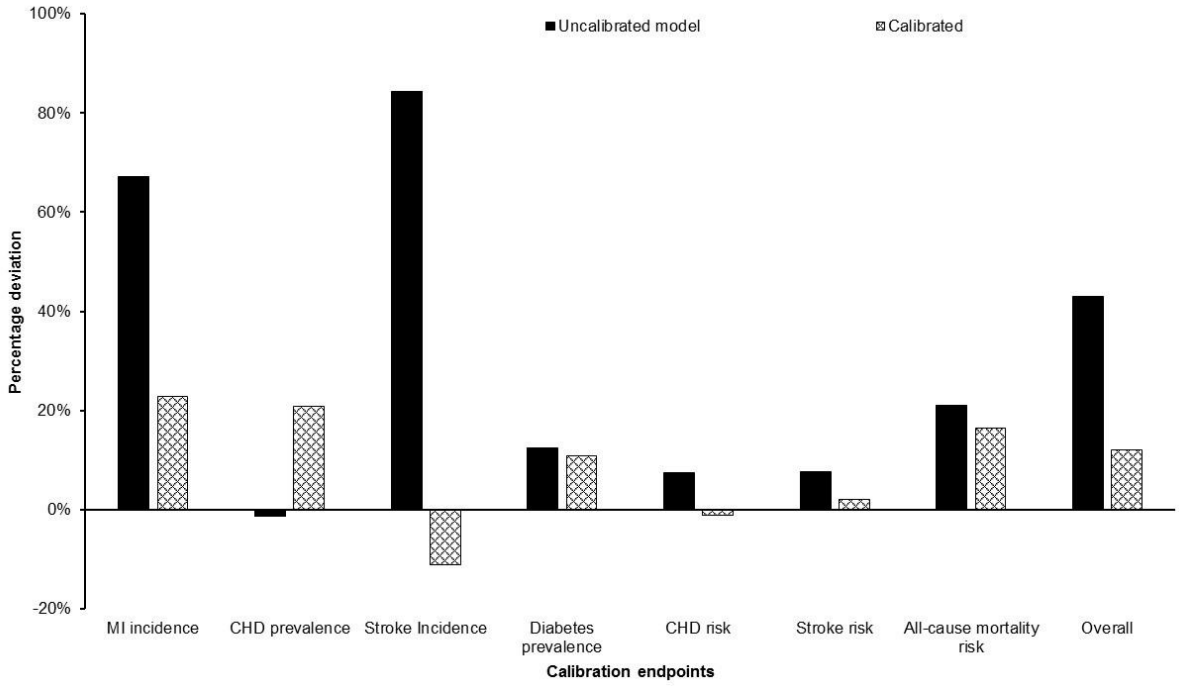

Figure 4-9: Comparison of aggregated endpoints by the calibration method

In our case, the Nelder-Mead method could not further minimise the goodness-of-fit value after 703 iterations with a weighted mean deviation of 18%. It is possible that the optimisation problem may have multiple local minima, i.e. the smallest value that a function can take in a region of its domain. The Nelder-Mead method is known to work reasonably well for problems that do not have multiple local minima (435).

Although the random search method was less efficient, it resulted in a better goodness-of-fit. Parameter values used in the random search method were restricted to a plausible range within the parameter space. This required longer processing time to search for the largest or the smallest value on the entire range of the function (global extremum), and it took approximately 80 processor-days to run 100,000 iterations. The weighted mean deviation was chosen as a measure of goodness of fit because it combines measures of goodness-of-fit across all calibration targets. However, the weights assigned for multiple endpoints remain arbitrary.

4.6 Intervention effectiveness and costs input to the model

Having described the development of the model and how the model was calibrated, this section now first details the brief interventions and reports the results for each brief intervention considered reporting incremental cost per QALY gained. This section also describes the approach used to harmonise the PA outcome measures reported in studies included in the meta-analyses and estimating cost of delivering BIs.

4.6.1 Brief interventions

A literature search was performed in PubMed and found four recent high-quality reviews (meta-analyses of RCTs) of BIs that could be delivered in primary care/community setting. They include advice or counselling on PA in primary care (101), use of pedometers as a motivational tool to promote PA (151,436) and action planning interventions (437). These meta-analyses summarised effectiveness evidence as continuous outcomes in either mean difference or standardised mean difference (SMD). Kang and colleague (436) included 32 studies in their meta-analysis of pedometer-based physical activity interventions compared to 8 studies in Bravata and colleagues (151) and reported a pooled SMD of 0.68 (95% CI: 0.55 – 0.81). They included all study designs in their meta-analysis. In contrast, Bravata and colleagues (151) included 8 RCTs and 18 observational studies in their meta-analysis. Their analysis reported estimated intervention effects separately for RCTs and observational studies, and the effect size was measured in terms of increases in steps per day which facilitates clinical interpretation. Thus, effectiveness evidence from the Bravata review was included in this analysis.

The model includes changes associated with activity level over time with varying decay rates of VBIs. The follow-up period of the studies included in the meta-analysis of BIs was short; only a few studies had >12 months follow-up. As there were no other estimates on how effects of PA interventions decay over time, Over et al. (146,334) provided estimates on a decay rate of 55%. We used this rate of decay after one year of intervention.

4.6.2 Physical activity outcome translation

Although mean difference and SMD are commonly used summary statistics for meta-analysis of continuous data (438), choosing a common exposure metric measure such as intervention changes in intensity, duration, and or frequency of physical activity (METs) allows direct comparison of results. It is possible to convert steps per day figures directly to MET hour per day using the formula for physical activity outcome translation (Table 4-28) presented by Wu et al.(439) However, it is not possible to translate SMD values directly to MET-hours of activity per day.

Table 4-28: Formula for physical activity outcome translation

Reported measure	MET-hour gained per day
kcal/kg/minute	MET-hour=(kcal/kg/minute)×(average weight)×(6/7)
kcal/minute	MET-hour=(kcal/kg/minute)×(6/7)
kcal/week	MET-hour=(kcal/week)/70/7
Steps/day on walking	MET-hour=(steps/10,000)×4.25×(1/3)×3 MET
30-minute blocks in physical activity per day	MET-hour=[(30-minute block)/4]×MET assigned
Minutes/day on physical activity	MET-hour=[(minutes/day)×MET assigned]/60
% people meeting guideline	MET-hour=(% people)×(1.5 MET-hour for adults)
MET minutes/week	MET-hour=(MET minutes/week)/60/7
Active days (at least 3 MET-hour) per week	MET-hour=(active days)×(3.0 MET-hour)/7

Source: Wu et al. (439)

For this, firstly the exposure measure (PA outcome) from individual studies included in the original meta-analysis were extracted. Then these values were converted into MET-hours of activity per day by selecting the estimate from the 2011 compendium of physical activity (364). Finally, the meta-analysis was re-run with translated values (MET-hours). Table 4-29 provides the summary of interventions included and their effectiveness.

When the activity levels were not described in terms of METs, moderate-intensity physical activity was assigned to 3.0 METs, moderate-to-vigorous physical activity 4.5 METs and vigorous physical activity 6.0 METs (309). Once the physical activity outcomes of individual studies included in these meta-analyses were translated into MET-hours, the meta-analysis was updated using the translated values (MET-hours). As in the original meta-analyses, a random-effects model was used to estimate the pooled effect, expressed as a difference in means.

4.6.3 Short-term effectiveness of BIs

Table 4-29 provides a brief description of BIs included in the meta-analyses along with the reported changes in PA (outcome) reporting both original figures reported in the meta-analyses and translated MET-hour values. Converting step counts per day into MET-hour per day was straightforward following the PA outcome translation formula (Table 4-28) because all 8 RCTs included in the meta-analysis measured PA outcome in terms of step counts per day. However, it was not possible to translate the reported outcome from some of the studies included in these meta-analyses into MET-hours. This was mainly the case for five of the nineteen RCTs included in the meta-analysis of action planning interventions

(437). These five studies either did not provide details on changes in intensity, duration and/or frequency of activity required for MET-hours translation, or the outcome was expressed in composite units (e.g. a sum of scores where responses were rated on a scale). Thus, these five studies were excluded while re-running the meta-analysis with MET-hour values.

Table 4-29: Description of brief interventions and their effectiveness

Intervention	No of studies	Intervention description	Changes in PA, original and translated values, mean (SE)
Use of pedometers (151)	8 RCTs	Pedometer as a motivational tool, goal setting (e.g. walking 10,000 steps/day for 5 times a week), in some cases participants received individual exercise feedback (walking plus feedback)	Increase in steps per day: 2491 (711) MET-hr per day = 1.06 (0.30)
Advice/counselling in primary care (101)	15 RCTs	Brief advice or counselling on PA delivered by health professionals, face to face or by phone or both	SMD = 0.25 (0.07) MET-hr per day = 0.22 (0.03)
Action planning interventions (437)	24 RCTs	Participant formulate their action plan in the format of what, when and where (time, place and number of minutes), record their intention on PA in the logbook or calendar, intervention delivery time 5-20 minutes	SMD = 0.24 MET-hr per week = 0.035 (0.01)

There were some practical issues while converting the exposure to MET hours. For example, moderate intensity activity such as walking is generally considered to be 3 to 6 METs. While converting such exposure, mid-point of moderate intensity was taken at 4.5 METs. Woodcock et al. (422) also used a similar approach for exposure translation in their meta-analysis of non-vigorous physical activity and all-cause mortality.

4.6.4 Intervention costs

As the included studies in the meta-analyses did not report the cost of the intervention, we first extracted resource use data based on the intervention description provided for individual studies in the meta-analyses. Then each intervention was costed based on the quantities of resources used multiplied by the unit cost of each resource component (Table 4-30).

Table 4-30: Unit costs of health care utilisation

Cost item	Unit cost	Source
Primary care consultation	£36 per consultation	PSSRU 2011 (28)
Physiotherapist	£34 per hour	PSSRU 2011 (28)
Exercise physiotherapist	£34 per hour	Same as physiotherapist
Practice nurse (face-to-face)	£51 per hour	PSSRU 2011 (28)
Nurse	£39 per hour	PSSRU 2011 (28)
Pedometer	£14 per unit	Shaw et al. (147)
Physical activity diary	£0.96 per unit	UEA print service (www.uea.ac.uk/print-services)
Physical activity information pack	£1.21 per unit	UEA print service (www.uea.ac.uk/print-services)
Trained facilitator*	£10.89 per hour	NHS Staff Earnings 2011 (http://goo.gl/WDpmv)
Telephone call	£0.13 per min	BT Tariff Guide (http://goo.gl/QjVvG)
Text messaging	£0.11 per SMS text	BT Tariff Guide (http://goo.gl/QjVvG)
Postal cost	£0.75 per letter	The Royal Mail Price Finder

* Median FTE total earnings for broad non-medical occupational groups

The costs of a pedometer intervention include the cost of a pedometer, intervention material and consultation time with either a GP, nurse or physiotherapist. Each RCT included in the meta-analysis was costed for each item of resource use based on the description of the intervention reported. Unit costs for nurse and physiotherapist were taken from the PSSRU unit costs (28). The cost of a pedometer was taken from a community-based pedometer study (Walking for Wellbeing in the West) (147). Costs of production and delivery of exercise diary (A4 size black and white paper) and information booklet (A4 size colour paper) were estimated from the unit cost of printing and binding on A4 size paper (The UEA print service).

Table 4-31: Intervention costs associated with implementing BIs promoting PA

Brief interventions	No. of studies	Total no of participants	Median (range) duration of follow-up	Intervention costs*
Advice/counselling in primary care (101)	9 RCTs	3,445	12 months	£71.26
Action planning interventions (437)	14 RCTs	1,864	10 (2–52) weeks	£33.21
Pedometer interventions (151)	8 RCTs	277	11 (4–24) weeks	£54.33
Current practice ('doing nothing')			-	-

Advice/counselling interventions included advice or counselling sessions given face-to-face or by phone (or both) and written materials. A counselling session with primary care clinician was assumed as a standard primary care consultation with a general practitioner lasting around 12 minutes. Unit costs for primary care consultation, general practitioner, physiotherapist and practice nurse were taken from the PSSRU unit costs (28). Costs of production and delivery of written material (information booklet) were estimated from the unit cost of printing (front-page colour, four pages black and white print) and binding on A4 size paper.

Action planning intervention included the cost of printing and developing materials (e.g. activity logbook, calendar, pamphlet), adoption of intervention material (e.g. visual education material) tailored to local context, designing and operating the web-portal for SMS texting service, staff (nurse, health worker or fitness instructor's time) for induction/training of participants; and other costs such as fitness club membership (437). In a typical action planning BI, the questionnaire prompted participants to formulate an action plan. Unit costs of administering the questionnaire (nurse admin time) were taken from the NHS staff earnings Jul-Sept 2010 (http://goo.gl/WDpmv), and health and social care costs were derived from the PSSRU unit costs for the nurse, health worker, physician or other health professional time (28). Costs of production and delivery of the physical activity questionnaire and toolkit were estimated from the unit cost of printing and binding on A4 size paper (The UEA print service; www.uea.ac.uk/print-services) and standard UK post rates (The Royal Mail Price Finder, http://www.royalmail.com/price-finder). Costs of phone calls and text messages were taken from standard BT prices (BT Tariff Guide, http://goo.gl/QjVvG). The cost of fitness club membership was estimated at £33 per month (Sportspark, http://www.sportspark.co.uk).

Finally, the cost per participant was then evaluated as a weighted average of intervention costs for each RCT in the meta-analysis. Full details on costing of each intervention are provided in Appendix C2.

4.7 Results from the first iteration of the model

The above sections defined the decision problem, detailed the development and calibration of the decision model, and estimated intervention effectiveness (in MET-hours) and costs, this section now reports the results from the first iteration of the model reporting incremental cost per QALY for all the three BIs included in this analysis. The economic evaluation of BIs was undertaken from the perspective of UK NHS reporting incremental cost per QALY.

4.7.1 Point estimates

Table 4-32 presents the mean costs, QALYs, and net benefits at a willingness to pay (WTP) of £20,000 per QALY and associated standard errors for the base-case analysis. Over a time horizon of 10 years, the point estimates for per person costs and QALYs for all interventions were similar. Pedometer BIs dominated both advice/counselling and action planning BIs, i.e. pedometer BIs were both less expensive and more effective. When compared with current practice, all three BIs were both more effective and more costly.

Table 4-32: Cost-effectiveness of brief interventions over ten years (base case costs, QALYs and NBs)

Brief intervention	Mean cost (SE)		Mean QALY (SE)		Mean NB* (SE)	
Current practice	£1,712	(583)	7.848	(0.228)	£ 155,254	(5,072)
Action planning	£1,738	(583)	7.851	(0.228)	£ 155,291	(5,079)
Advice/counselling in primary care	£1,758	(580)	7.857	(0.229)	£ 155,378	(5,084)
Pedometer interventions	£1,723	(579)	7.864	(0.229)	£ 155,549	(5,097)

*NB calculated at a WTP of £20,000 per QALY, ICER: incremental cost-effectiveness ratio

The QALY gains associated with the BIs were as expected. Pedometer interventions were more effective (in terms of MET-hours) than advice/counselling and action planning interventions. The higher costs associated with delivering advice/counselling interventions is reflected in the results, having a higher mean cost compared to other BIs.

4.7.2 Analysis of uncertainty

The model was run probabilistically, using Monte Carlo simulation (n=10,000 iterations for the whole cohort of 10,000 patients each time) to determine the expected costs, expected outcomes (QALYs gained) and expected cost-effectiveness.

Figure 4-10 plots the incremental costs versus incremental QALYs comparing each BI with current practice for the 10,000 iterations, illustrating the uncertainty surrounding the expected incremental cost and incremental QALYs for all three BIs. The plot shows the points scattered across all four quadrants of the CE plane, with the majority of the points overlapping with each other.

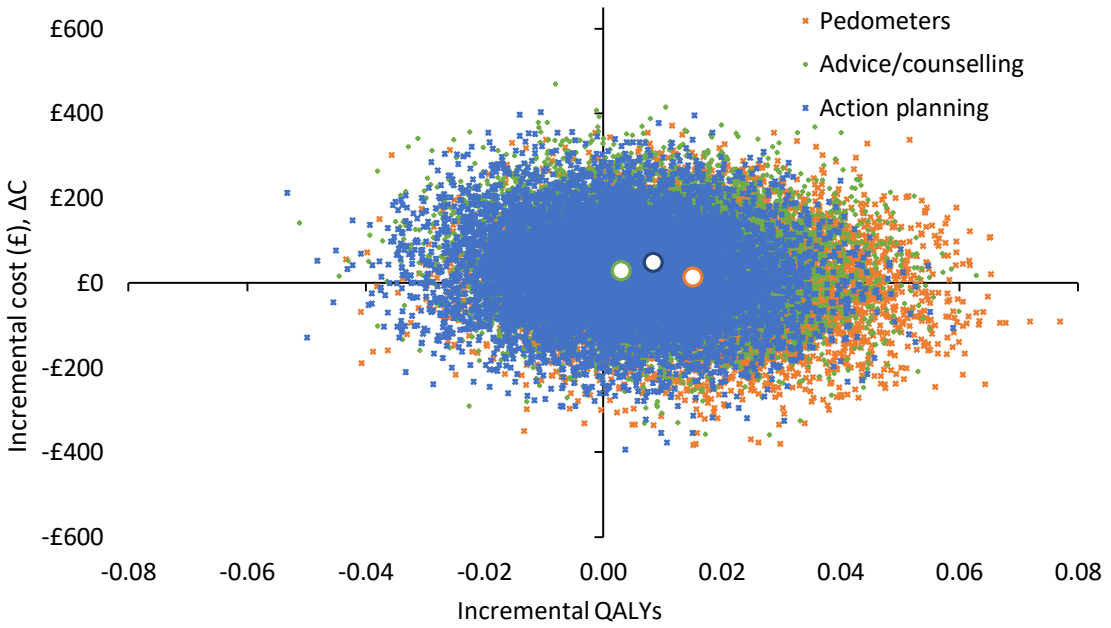

Figure 4-10: The cost-effectiveness plane for promoting PA in primary care

The joint distribution of costs and effects from the probabilistic analysis plotted in Figure 4-10 demonstrated the impact of uncertainty in model parameters on the model outcomes. The spread through the origin passing through the horizontal and vertical axes represent uncertainty in incremental costs and QALYs. The extent of the spread also indicates the extent of uncertainty.

The cost-effectiveness acceptability curve (CEAC) for BIs is illustrated in Figure 4-11. The CEAC shows the probability that BIs are cost-effective at different values for the maximum willingness to pay threshold (λ).

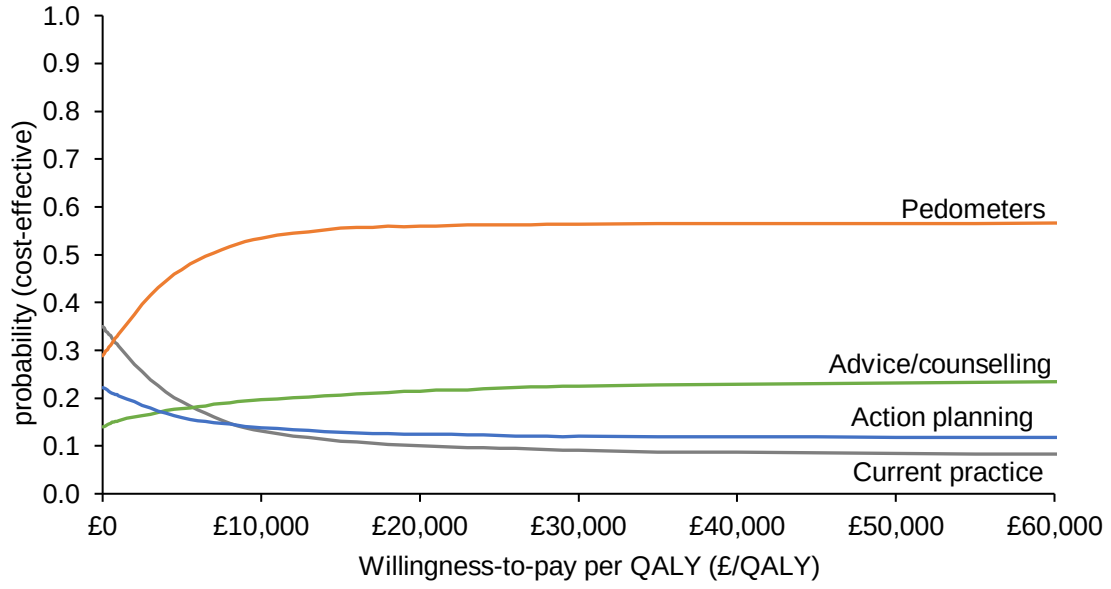

Figure 4-11: The CEAC showing the probability of BIs being optimal by the threshold value

At a WTP threshold value of £20,000 per QALY, the probability that pedometer interventions will be cost-effective is 56%. The advice/counselling intervention was optimal in 22% of the 10,000 iterations at a WTP of £20,000 per QALY. The CEAC shows that at a monetary threshold of £20,000 per QALY the probability that action planning interventions and usual care being cost-effective in comparison to pedometers and advice/counselling interventions is less than 13%.

At a monetary threshold of less than £1,000 per QALY, the no intervention 'current practice' is the most cost-effective (had a higher probability of being cost-effective) compared to other BIs.

4.7.3 Scenario analyses

In the base-case analysis, it was assumed that the effect of BIs (increases in MET-hours) decays over time at a rate of 55% per year. This assumption was based on previous modelling studies estimating the long-term effect of PA interventions. However, the true rate of decay for these behavioural interventions is unknown. The sensitivity analyses below present the impact of assumption on decay rates on the cost-effectiveness results. In these analyses, the decay rate varies between 0% (no decay in intervention effect i.e. lifelong behaviour change) and 100% (intervention effects reversed after the first year post-intervention).

Figure 4-12 shows the effect of a change in intervention decay rates to expected net benefit (Y-axis). At a higher decay rate, the expected NBs of all interventions were quite similar which ultimately dropped below that of current practice. At lower decay rates, the expected NBs were higher for pedometers ad advice/counselling interventions followed by action planning interventions. This is to be expected as the decay rates increases, the treatment effect (MET-hour change) declines towards that of current practice (zero effect).

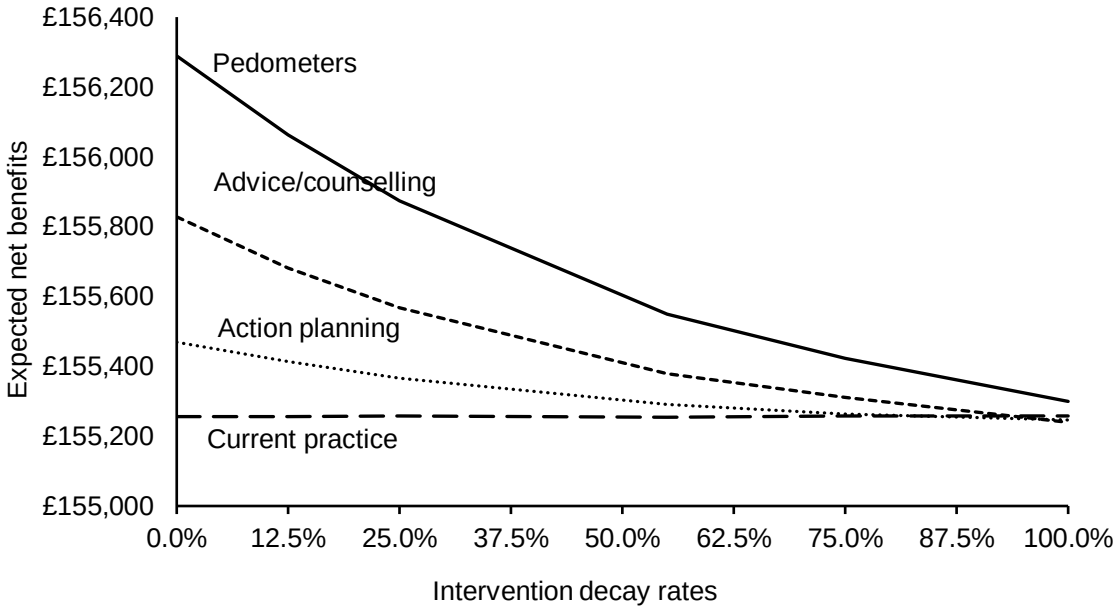

Figure 4-12: Sensitivity analysis of intervention cost-effectiveness to decay in intervention effects at a WTP of £20,000/QALY

Having examined the impact of varying decay rates on cost-effective results and results from the previous RCT with more than one-year follow-up (143), it would be difficult to maintain the level of activity after any PA intervention. Indeed Elley and colleagues (143) reported higher incremental costs associated with a change in at least moderate intensity activity per kcal/kg/day at 24 months compared to 12 months. In other words, the physical activity advice and counselling intervention in primary care was less cost-effective at 24 months than at 12 months. This was because there were fewer people who were moved from sedentary to active and maintained this at 24 months than at 12 months.

It will be difficult to maintain the same level of activity achieved due to brief interventions over time. Behaviour change interventions require personal commitment, encouragement and support over time. Thus, now it is logical to examine what would be the optimal time to repeat these interventions given the fact that NHS health check happens every five years. In order to answer this question, scenario analyses with the interventions being repeated once every 2, 5 and 10 years were performed. Figure 4-13 shows the impact of intervention repeat years on expected net benefits. While performing these analyses, the additional (discounted) cost of the intervention was added in repeat years.

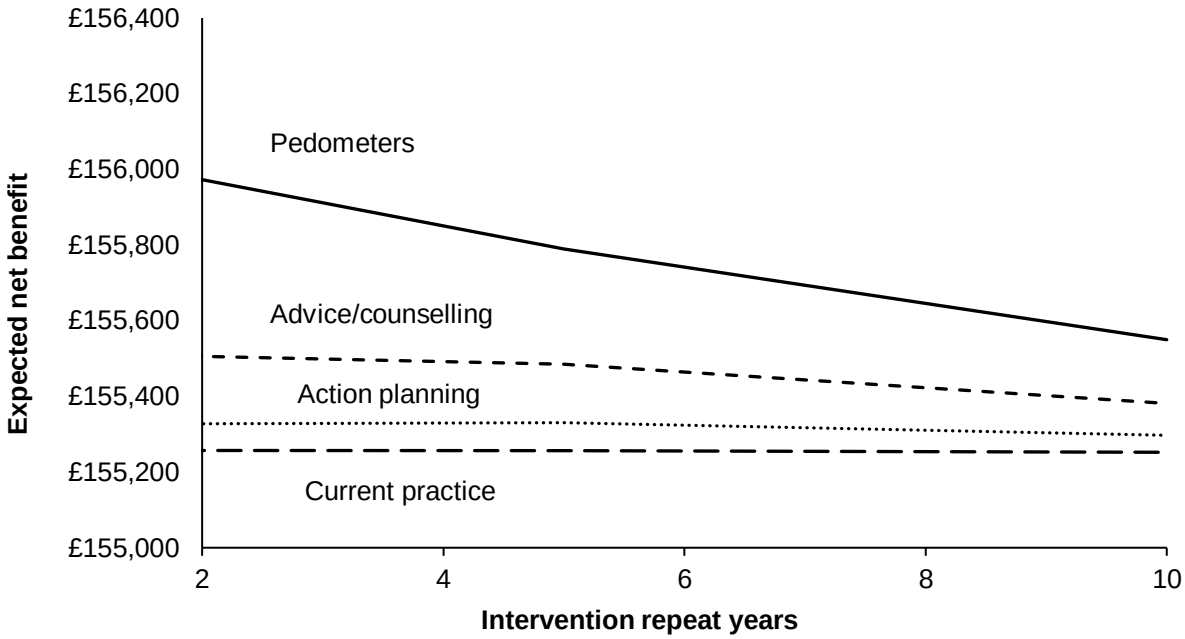

Figure 4-13: Sensitivity analysis of intervention cost-effectiveness to the intervention repeat year at a threshold value of £20,000/QALY

In all the three repeat year scenarios, pedometer BIs were found to be the optimal option. The expected NB for pedometer interventions was highest when the intervention was repeated once every 2 years. The pedometer BIs had higher MET-hour gains compared to other BIs as a result had higher expected NBs compared to other BIs.

The model included disease conditions that have established links to physical (in)activity. This might underestimate the potential impact of physical activity on other disease conditions, most notably mental health. The effect of physical activity on the prevention of depression is still a subject of debate (440) and a clear dose-response relationship between physical activity, and reduced depression is not readily apparent (441). To explore this further, a scenario analysis was performed by including a short-term effect of increased physical activity on health-related quality of life.

Only a few studies measured the short-term improvements in quality of life associated with physical activity in the general population (442,443), as most of the studies focused on older adults and those with chronic conditions (444). A pragmatic RCT evaluating the national exercise referral scheme in Wales (445) provided utility data. This 'utility gain' (0.03 ± 0.023) was added in the first year of intervention to reflect the short-term benefits of physical activity.

Table 4-33 presents the cost and QALY outcomes of including short-term health gains (utility boost) from the increased physical activity. The results were similar compared to

base-case analysis; pedometer BIs being the most cost-effective intervention. However, there was a parallel shift upwards for the three BIs. This is because of applying the same 'utility boost' for all BIs irrespective of their effect size. The probabilities of pedometer and advice/counselling BIs being cost-effective at a threshold value of £20,000 per QALY increased to 61% and 24%, respectively, up from 56% and 22% in the base case scenario.

Table 4-33: Cost-effectiveness of BIs when accounting for short-term direct health benefits of physical activity

Brief intervention	Mean cost	Mean QALY	Mean NB* (SE)	
Advice/counselling	£ 1,758	7.8869	£ 155,980	(5,105)
Action planning	£ 1,736	7.8818	£ 155,900	(5,093)
Pedometers	£ 1,721	7.8936	£ 156,152	(5,115)
Current practice	£ 1,713	7.8484	£ 155,255	(5,078)

*NB calculated at a WTP of £20,000 per QALY.

4.7.4 Value in future research: EVPI & EVPPI

The above sections presented the PSA results and explored the decision uncertainty by illustrating the probability of each BI being cost-effective at different willingness to pay thresholds. Additional scenario analyses examined the structural and parameter uncertainty. Now following the iterative process in decision making it is important to consider given the current evidence, and decision uncertainty: (i) should the intervention be adopted, and (ii) is there further value of conducting research in this area? Adoptions decision should be made on expected values, i.e. choose the intervention strategy that has a highest expected net benefit. The value of information analysis would be useful to formally evaluate whether further research is necessary to support the decision to adopt or reject the intervention.

The expected value of perfect information (EVPI) was calculated by extending the PSA, i.e. using the probabilities of each BI being cost-effective which were generated in the CEAC calculation over a range of willingness to pay threshold values. The EVPI results showed that at a WTP of £20,000 per QALY, the base-case per person EVPI associated with a decision between pedometer BIs and current practice was £97.

To understand the EVPI value, it is useful to consider the PSA results and the decision uncertainty presented in Figure 4-11. The results showed that at a threshold value above £1,000 per QALY, pedometer BIs is most likely that it will be cost-effective, but at a

threshold value of £20,000 per QALY, there is only 56% probability of cost-effectiveness. Given that there is a 44% probability that the optimal intervention strategy will be the wrong decision. The EVPI is equivalent to the opportunity loss of choosing pedometer BIs in 44% of instances that the optimal strategy would have been wrong given perfect information. At a threshold value of £20,000 per QALY, the expected value of further research is £97 per decision.

As this value is per person value, it is important to represent EVPI per decision in terms of the relevant population who would benefit from the additional information. In order to determine the effective English population, defined as those eligible for an NHS health check (40-74 year olds and without a pre-existing condition). Given that approximately 30% of the population are on a primary care disease register (446), the effective population over a 10-year time horizon equates to approximately 20 million adults (Table 4-34). The future population was discounted at 3.5% per annum.

The population EVPI results are presented in Figure 4-14. The EVPI per decision translated to a population level EVPI of £1.85 bn to the NHS Health Check population. This means that at a threshold value of £20,000 per QALY, the upper limit for research into which intervention is most cost-effective is £1.85 bn.

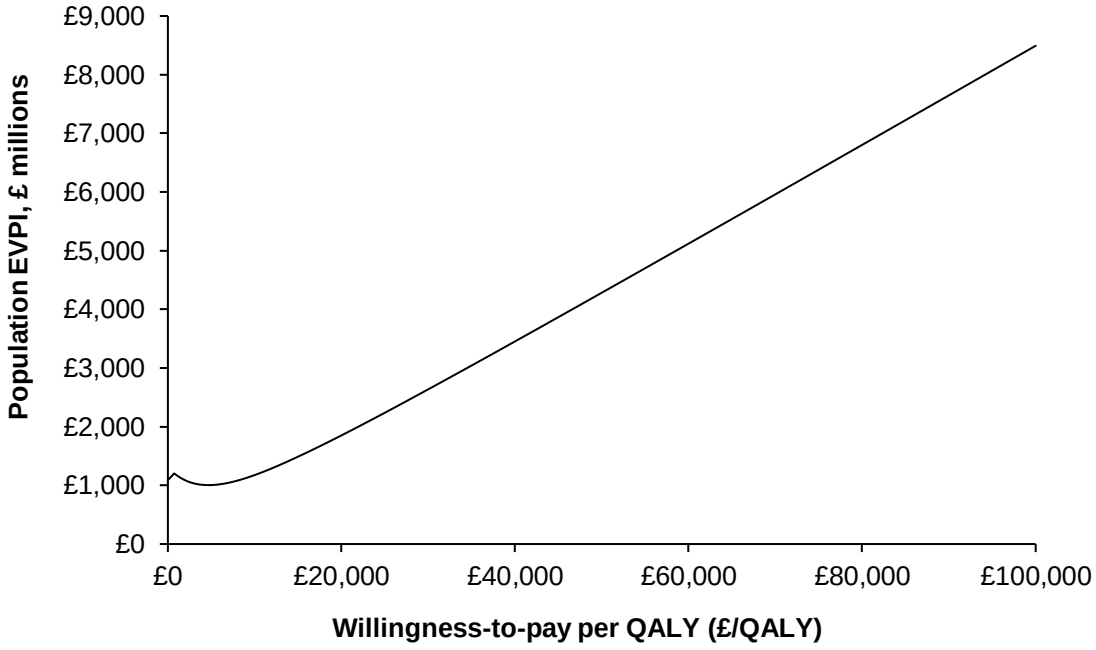

Figure 4-14: Expected value of perfect information (EVPI) against varying WTP values for cost-effectiveness – population level

Table 4-34: Effective Health Check population

	Total resident population aged 40 to 74 (447)	Estimated on the disease register (446)	Estimated eligible population aged 40-74	Total discounted population aged 40-74
	A	B	C = (A-B)	D
Prevalent population	21,88,7396	6,566,219	15,321,177	15,321,177
Incident population (year 1)	764,005	229,202	534,803	516,718
Incident population (year 2)	731,914	219,574	512,340	478,275
Incident population (year 3)	699,168	209,750	489,418	441,427
Incident population (year 4)	685,626	205,688	479,938	418,238
Incident population (year 5)	668,403	200,521	467,882	393,944
Incident population (year 6)	662,338	198,701	463,637	377,169
Incident population (year 7)	660,465	198,140	462,325	363,383
Incident population (year 8)	700,813	210,244	490,569	372,544
Incident population (year 9)	738,069	221,421	516,648	379,081
Total	**7,198,218**	**8,459,460**	**19,738,737**	**19,061,956**

Having established that further research is likely to be worthwhile, it is useful to consider what type of research is required. Further research in this decision problem does not necessarily mean that we need a large scale, RCT. Instead, the type of research depends on the different parameters that require further information. For example, utility values can be collected as a part of large RCT. However, if they are the main source of uncertainty, it would be much more efficient and cheaper to determine utility values from observational studies. Thus, to define the type of further research that is required to reduce decision uncertainty, we need to consider what is driving the uncertainty and which parameters would add the most value through further research. The expected value of perfect parameter information (EVPPI) is used to identify the parameters for which collecting additional information would be of most value.

EVPPI was undertaken to explore which groups of parameters would add most value through further research. The various model parameter inputs were considered, and model parameters were grouped into the following six sub-groups that were deemed to be of potential value in further research on intervention effects, utility values, costs, the risk of MI, the risk of stroke, and parameters used in systolic blood pressure equation.

Of these six parameter groups, the treatment effect is the only one group which would require a randomised trial to gain further information. A planned randomised trial to gather intervention effect data could also gather information on costs and quality of life for disease states without requiring additional duration for longer-term follow-up. The EVPPI was run 500 × 1,000 iterations for each of the six parameter groups, using a threshold value of £20,000 per QALY. The EVPPI analysis reports result in terms of value per decision but is important to consider this value to the relevant (effective) population who would benefit from the additional information. The population EVPPI was based on the same patient population (Table 4-34) and time horizon (10 years) specified in the EVPI calculation. The results of the EVPPI are presented in Figure 4-15.

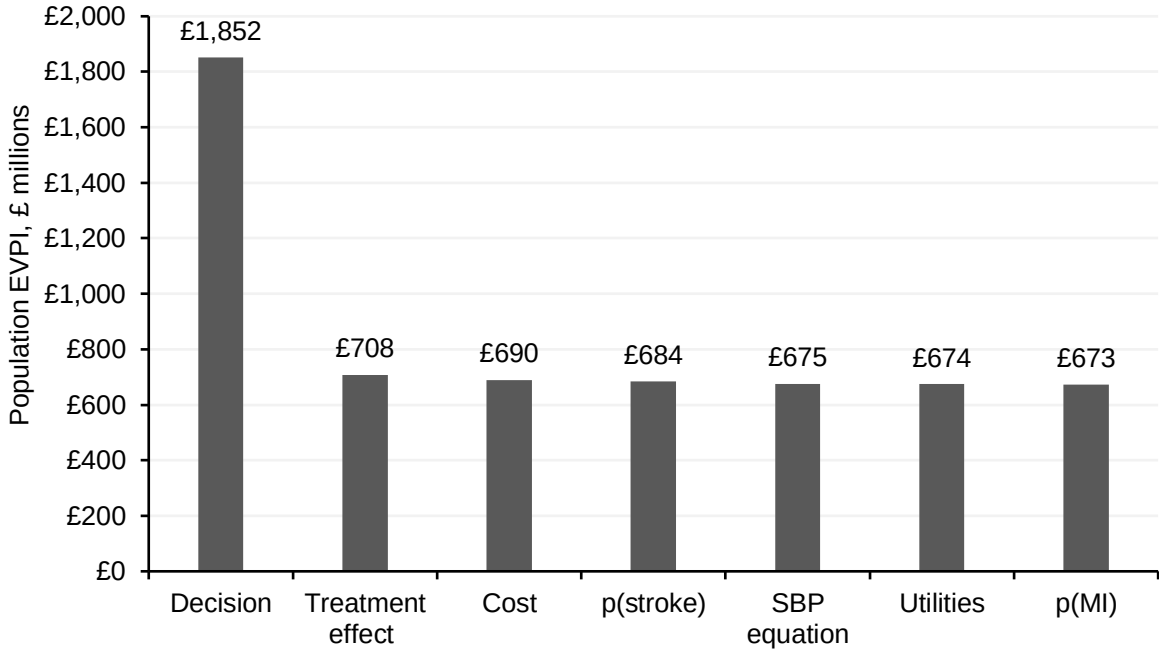

Figure 4-15: EVPPI results for the base case at a WTP value of £20,000 per QALY – population level

Among the groups of different parameters, intervention effects had the highest population EVPPI of £708 million followed by costs (£690 million) and risk of stroke (£684 million) parameters at a WTP of £20,000 per QALY. Utilities and probability of MI had an EVPPI similar to the SBP equation group. This means that at a threshold value of £20,000 per QALY, the effects of pedometer interventions accounted for most of the decision uncertainty.

4.8 Discussion

This chapter presented the development of a decision analytical model and the use of available evidence to evaluate the potential cost-effectiveness of BIs to promote physical activity in primary care. The chapter also explored uncertainty in the point estimates and demonstrated that using the value of information analysis techniques model results can be examined in terms of decision uncertainty to estimate the value of further research. This is useful information for the decision makers and funders in order to prioritise allocation of limited resources. The results will now be summarised followed by a discussion of using VoI methods.

4.8.1 Cost-effectiveness results

The model estimated the expected costs and health outcomes of BIs promoting physical activity for apparently healthy adults who are eligible for NHS health checks in primary

care. The cost-effectiveness plane showed that there was a great deal of uncertainty as to whether choosing pedometer BIs over advice/counselling or action planning interventions. All the three BIs considered in the analysis had similar expected NBs, with pedometer interventions having slightly higher expected NB than other BIs. The cost-effectiveness acceptability curve showed that the probability of pedometers BI being the optimal intervention strategy was only 56% (when all BIs were evaluated simultaneously) at a threshold value of £20,000 per QALY. This means that we can be certain in 56% of cases that the pedometer BIs is a cost-effective strategy.

The scenario analyses explored the impact of model assumptions on the degree which intervention effects are maintained over time (decay rates). The results showed, as expected, BIs become less cost-effective at higher intervention decay rates and more cost-effective at lower (or zero) decay rates. It is important to note that the three BIs considered in the analysis represent a broad class of interventions. Conceptually, a meta-analysis combines results from multiple studies, which are statistically similar and provides a summary estimate. However, not all comparators included within individual studies were usual care or current practice. While these BIs had the potential to be delivered in primary care or community settings, these three classes of BIs were somewhat heterogeneous.

Ideally, decision-makers should be making decisions on long-term expected cost-effectiveness. So, whilst we are highly uncertain, the currently 'best bet' would be to opt for pedometer BIs. The benefits of pedometer BIs are highly uncertain and probably small, but then so is the cost. This level of uncertainty leads to an EVPI of £1.85 billion for the NHS health check population in England assuming a time horizon of 10 years. The higher expected net benefit for pedometer BIs could be explained by the larger intervention effects (expressed in MET-hours) than the other BIs. Thus, there is considerable decision uncertainty, and therefore it is potentially worthwhile collecting additional information to inform the decision regarding cost-effectiveness.

Having established that further research in this area is worthwhile, it is necessary to identify which parameter or a group of parameters that contribute the most of the overall decision uncertainty and for which future research is the most promising. The EVPPI analysis found that there was potential value in understanding all six (group of) parameters, but the treatment effect parameter had the highest EVPPI value. With a population value of £708 million, it is clear that further research on this parameter would be beneficial and help reduce uncertainty in the cost-effectiveness decision. However, this is the necessary but not sufficient condition. EVSI and ENBS give a clear indication if it is beneficial to conduct further research on this parameter but it was not feasible to perform these analyses due to computational burden.

This indicated that a new study would be of most value to collect unbiased evidence on the effectiveness of pedometer BIs in primary care. If such a trial were being undertaken, it would be advantageous to collect information on cost and utility parameters as well.

4.8.2 Model conclusions

The review of economic evidence undertaken for this research found that although PA interventions are generally considered good value for money, there is limited evidence regarding the long-term cost-effectiveness of (very) brief interventions promoting physical activity in primary care. Therefore, a decision model was designed, developed, and populated based on data from the available literature or routine data sources. The model was calibrated against seven calibration targets such that simulated values of parameters match the observed parameters as closely as possible.

The model calibration achieved a weighted mean deviation of 12% using the random search method. Based on the WMD, it is difficult to conclude how small or large the WMD was compared with other risk factor or disease outcome models as there is only one study (428) that used a similar approach to calibrate cervical cancer model in the USA. Taylor et al. (428) reported a 7% goodness of fit metric (WMD) using the Nelder-Mead and 10% using the random search method. Given that the WMD of 12% in this study, the goodness of fit metric in this study was comparable with Taylor et al. study. Though their model was specific to cervical cancer whereas the current model is a multi-disease model.

The cost-effectiveness results showed that pedometer BIs to be a cost-effective way of promoting physical activity in primary care when compared to BIs such as action planning or advice/counselling in primary care. Offering the pedometer BI once every two years appeared to be the most efficient repeat interval. However, the cost-effectiveness of pedometer BI is conditional on the assumed intervention decay rate and the ability of repeat contacts to maintain physical activity. A new study will not eliminate uncertainty but is expected to reduce it. Therefore, the expected value of sample information (EVSI) of such a study (e.g. randomised trial) will be less than the EVPI.

An attempt was made to calculate the EVSI and the expected net gain of sampling, which is computed as EVSI less the total cost of a proposed study, but due to computational demands, it was not possible to generate meaningful and stable results. The EVSI analysis requires two-level expectations (Monte Carlo simulations) to be evaluated and this “nested” evaluation would lead to a further significant computational burden (161).

Chapter 5 Designing trials following an iterative approach

Although physical activity interventions in primary care are considered good value for money, there was limited evidence on the cost-effectiveness of brief PA interventions in primary care (Chapter 2). In 2013, the NICE updated 2006 guidance on four commonly used methods to increase PA (112) and produced specific guidance on brief advice for adults in primary care (448) in which three economic evaluation studies were identified for full review. The limited evidence from three studies included in the NICE guidance suggested that brief advice on PA in primary care is more cost-effective than usual care. Results from the first iteration of the model indicated that the use of pedometer brief interventions is the most cost-effective strategy to promote PA in primary care. In addition, the value of information analysis showed that there is a value in further exploring the effectiveness of pedometer brief interventions.

The next logical step following the iterative approach is to conduct a primary study. Parallel to the review of economic evidence of brief PA interventions in primary care (Chapter 2) and economic modelling (Chapter 4), the VBI study research team conducted a feasibility study to select the most promising VBIs which could be implemented during the NHS Health Check (449). Pedometer interventions were selected from the feasibility study as the most promising VBI for the trial evaluation (450). Nevertheless, these steps did not happen sequentially because of timing. At the time of selecting pedometer VBI as a candidate VBI to be tested in full-scale trial, the VoI results were not available. This limited the influence of VoI on the study design.

The first part of this chapter describes the VBI trial, i.e. the case of the VBI explanatory trial followed by within-trial economic evaluation. The within-trial economic evaluation evaluates the potential cost-effectiveness of pedometer-based VBI ('Step It Up') to increase PA in primary care compared to NHS Health Check only (usual care) over the trial period. The second part of the chapter (sections 5.4 to 5.5) describes the updating of the evidence base used in Chapter 4 with the results from the VBI trial, and then presents the results from the second iteration of the model. The results from the second iteration of the model include an assessment of the incremental costs and QALYs from pedometer-based VBI over the long term (10 years) and VoI analysis. Model results are summarised followed by a discussion of the practical realities of applying the iterative approach. This approach of updating the evidence and re-running the model is in line with the iterative framework for economic evaluations described in Chapter 3. The second iteration of the

model allows further investigation of the role of VBIs in PA promotion in primary care to inform adoption and research priority setting decisions.

5.1 The case of VBI explanatory trial and economic evaluation

The VBI study is described earlier in section 1.6 (of Chapter 1). In brief, this was a five-year research programme funded by the NIHR Programme Grant for Applied Research which aimed to develop and evaluate VBIs to increase physical activity that could be delivered in a Health Check or another primary care consultation.

The first stage was a development stage in which evidence and expertise from multiple sources were combined to develop a short-listing of promising VBIs. The generation and short-listing of VBIs was done through the review of existing evidence (113,451,452), consultation with stakeholders, and the VBI study team discussion. This exercise short-listed four promising VBIs that could be implemented during health check consultations: (a) motivational intervention; (b) action planning interventions; (c) pedometer intervention; and (d) physical activity diary intervention. The first iteration of the model (Chapter 4) included three brief interventions namely (a) exercise advice by the GP; (b) action planning interventions; and (c) pedometer interventions compared against usual care ('do nothing'). The feasibility study (449) assessed the feasibility and acceptability of the four short-listed VBIs using qualitative interviews with four practitioners and 68 patients. Considering the practicability (acceptability, feasibility and cost), and potential efficacy from the outset, the feasibility study demonstrated that all four VBIs were acceptable and feasible as part of the routine Health Check consultation (449). These criteria were considered of equal importance as cost and effectiveness and were given equal weights.

In the next phase, a pilot trial, hereafter called the VBI pilot trial was conducted to evaluate the potential efficacy, feasibility, acceptability and cost of three VBIs in primary care to select the most promising intervention for the evaluation in a subsequent large-scale RCT (450). The three VBIs evaluated as part of the usual Health Check consultations were motivational VBI, pedometer VBI and combined (motivational plus pedometers) VBI compared against Health Check consultation only.

Three hundred and ninety-four adults aged between 40-74 years from 8 GP surgeries were recruited in the pilot trial (450), and were allocated to receive one of three VBIs as part of the usual Health Check consultation (motivational: n=83, pedometer: n=74, or combined: n=80) or the Health Check consultations only (control arm; n=157) by block randomisation. This pilot trial aimed to assess the potential efficacy, feasibility,

acceptability and cost of three VBIs against the health check alone; and select the most promising VBI for evaluation in a subsequent large-scale RCT designed to provide robust estimates of effectiveness and cost-effectiveness (450). Physical activity was objectively measured by tri-axial accelerometer. Participants were asked to wear the accelerometer around their waist for 7 days during all walking hours.

Accelerometers measure bodily movements in terms of acceleration, i.e. change in velocity over time enabling intensity of PA to be quantified (453). These devices can measure human activity on the vertical axis (uniaxial) or the anteroposterior and/or lateral (biaxial or triaxial) planes. Accelerometers usually provide a count value which is frequently used to describe the intensity, frequency and duration of PA, and often also a step value, per epoch (454). Energy expenditure, which is a composite of counts from these three planes of motion, can be estimated from vector magnitude counts using a proprietary algorithm (455).

The pilot trial results (450) showed that the Motivational and Pedometer VBIs had the greatest potential to increase PA compared to the Health Check only. Combined VBI had the lowest potential efficacy (i.e. the probability of a positive difference between an intervention arm and control arm in mean PA measured by accelerometry at four weeks), and Pedometer VBI was the only VBI deliverable within 5 minutes. Practitioners felt most confident delivering the Pedometer and Combined VBIs, and the average cost of the VBIs ranged from £6.83 per participant for the Motivational VBI to £20.98 per participant for the combined VBI (2013 prices) (450). Based on the four criteria (efficacy, acceptability, feasibility and cost), Pedometer VBI was selected for evaluation in the main trial to estimate the effectiveness, cost-effectiveness and potential public health impact (456).

The section below describes the evolving evidence base on VBI promoting PA in primary care and summaries the effectiveness evidence from the VBI trial.

5.2 Evolving VBI evidence – the effect of the intervention on accelerometer assessed physical activity outcomes (The VBI trial)

Following the feasibility study (449) and pilot trial (450), the most likely to be effective and cost-effective intervention, pedometer-based VBI (VBI trial), was selected to evaluate in the large-scale trial. The trial was a pragmatic multicentre randomised controlled trial of two parallel groups (pedometer VBI versus Health Check alone) with 1:1 individual allocation. Mitchell et al. (456) set out the protocol for methods, including for the economic evaluation. In brief, the trial recruited 1,007 study participants from 23 general practices

in East of England – 12 practices in Cambridgeshire, 8 in Hertfordshire and Bedfordshire, and 3 in Norfolk. Participants were recruited through the NHS Health Check programme. The study was conducted between October 2014 and December 2015. The study was approved by the East of England – Cambridge East Research Ethics Committee (14/EE/1004) and the trial was registered with Current Controlled Trials, number ISRCTN72691150.

Study participants included those eligible for the NHS Health Check (114), i.e. aged between 40 to 74 years without pre-existing conditions. The trial excluded participants who were not able to provide written informed consent and patients whom their GP considered unsuitable for inclusion (456).

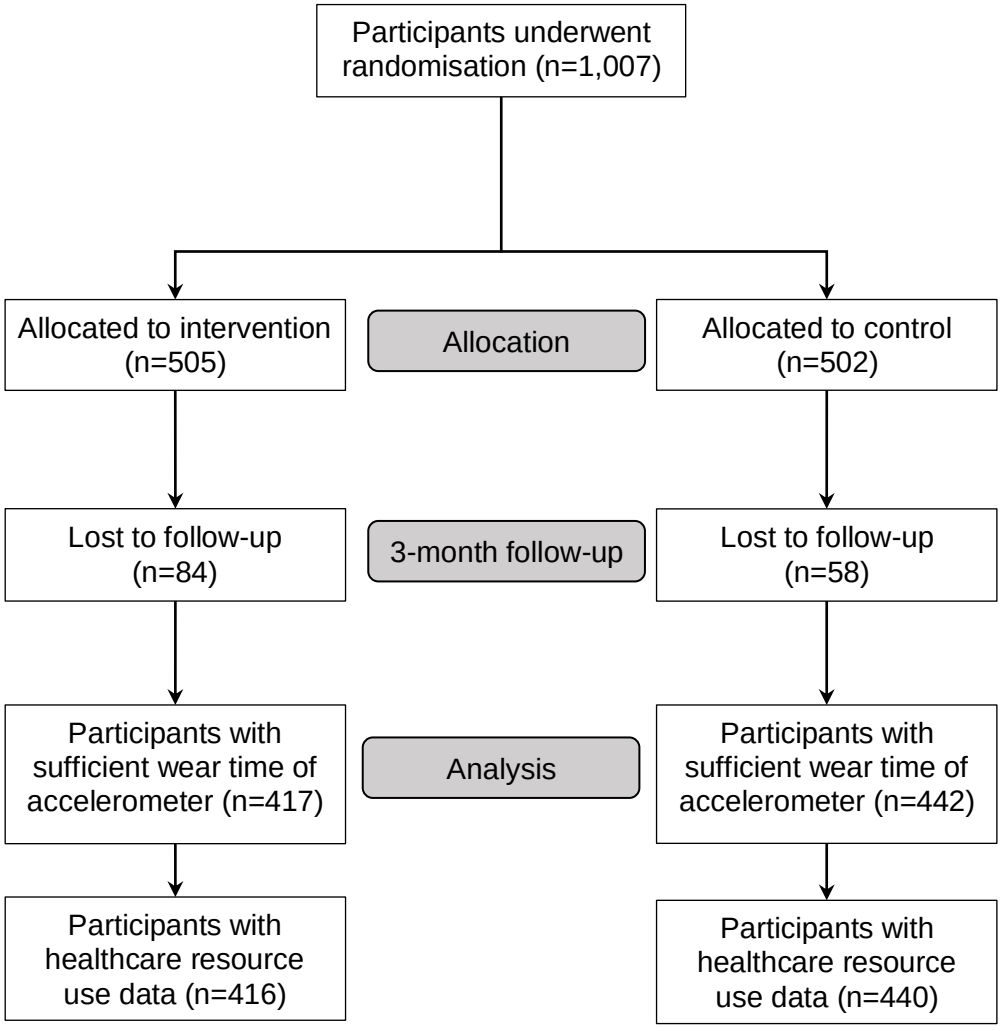

Figure 5-1: CONSORT flow diagram showing participant flow through the VBI trial

Source: Adapted from Figure 1, Hardeman et al. (457)

The control group received the usual NHS Health Check only. The health check included blood pressure measurement, calculation of BMI from measured height and weight, and taking a blood sample (116). The intervention group received the pedometer-based

intervention ('Step It Up') at the end of NHS Health Check. 'Step It Up' consisted a five minute (brief) face-to-face discussion with practice nurse or healthcare assistant, provision of a Yamax Digiwalker SW200 pedometer, a Step Chart for self-monitoring, and a 'Step It Up' Booklet (456). The 'Step It Up' booklet included (456) (a) UK government PA recommendations, (b) instructions on how to use the pedometer, (c) health benefits of becoming physically active, (d) a graph showing that small changes in PA can lead to significant health benefits, (e) tips for achieving more steps, and (f) links to other PA resources.

A total of 1,007 participants were randomised (Figure 5-1) in the trial: 505 participants were allocated to the intervention arm and 502 to the control arm of the trial. The trial outcomes were measured by accelerometer and questionnaires at three-months post-intervention. The final analysis included study participants who provided sufficient accelerometer data, i.e. at least four days of data with ≥600 minutes per day of wear time, to measure primary outcome (n=859). The primary outcome of the trial was physical activity measured by tri-axial accelerometry expressed as average vector magnitude acceleration – counts per minute (456).

5.3 Within-trial economic analysis

Table 5-1 shows the outcomes of accelerometer measured PA at 3 months follow-up. The primary outcome, i.e. counts per minute were similar between the groups with an adjusted intervention effect of 8.8 counts per minute increase (95% CI: -18.7 to 36.3) relative to control. PA outcome was adjusted for gender, five-year age group and primary care practice. Likewise, there were no significant differences between trial arms in accelerometer measured step counts per day, and time spent in moderate, moderate to vigorous and vigorous activity.

Table 5-1: Primary and secondary accelerometry outcome data at 3 months follow-up

	Intervention (n=417)	Control (n=442)	Intervention vs control	
	Mean (95% CI)	Mean (95% CI)	Effect (95% CI) ‡	p-value
Total physical activity volume (counts per minute)*	668 (648 to 689)	660 (641 to 679)	8.8 (-18.7 to 36.3)	0.53
Step counts per day	8,419 (8,110 to 8,729)	8,191 (7,911 to 8,471)	242 (-172 to 656)	0.25
Time (min/day) in moderate activity†	72.0 (68.8 to 75.2)	71.8 (68.9 to 74.8)	0.3% (-5.4% to 6.5%)	0.91
Time (min/day) in moderate to vigorous activity†	77.1 (73.7 to 80.6)	77.0 (73.8 to 80.3)	0.9% (-4.9% to 7.2%)	0.76
Time (min/day) in vigorous activity†	3.2 (2.9 to 3.6)	2.9 (2.6 to 3.2)	11.9% (-2.9% to 28.8%)	0.12

Note:

* Counts per minute are vector magnitude counts per minute

† Means are geometric means for time in activity at different intensities and compared as a percentage increase of the intervention group to the control

‡ Comparison of means is adjusted for gender, five-year age group and practice

Source: Adapted from Table 2, Hardeman et al. (457)

An economic analysis alongside the VBI trial was designed (456). The objective of the analysis was to compare the costs and cost-effectiveness of a very brief pedometer-based intervention with health check alone from the NHS and Personal Social Services perspective (NHS and PSS), and societal perspective. The predefined outcome of the within-trial economic analysis was the incremental cost per incremental MET-hour of physical activity gained estimated from accelerometer counts (456).

The VBI trial participants wore either ActiGraph GTEX+ or ActiGraph w-GT3X-BT (456) accelerometer. ActiGraph website listed 12 different MET algorithms (458) that could be used to convert accelerometer counts to MET-hour. Of these 12 algorithms, only 8 algorithms (from 6 studies) were derived from the adult population who wore an accelerometer on their waist. These eight algorithms are summarized in Table 5-2.

Table 5-2: Algorithms to convert counts per minute (cpm) to MET-hour

Study	Accelerometer brand	Physical activity	Study participants	Formula
Freedson 1988 (459)	CSA accelerometer	Treadmill exercise	50 adults (25 males, 25 females) during treadmill exercise at three different speeds (4.8, 6.4, and 9.7 km/hr)	1.439008 + (0.000795 × CPM)
Hendelman 2000 (460)	CSA accelerometer (model 7164)	Walking and other activities (accelerometer was worn on hip)	25 participants completed four bouts of overground walking at a range of self-selected speeds, played two holes of golf, and performed indoor (window washing, dusting, vacuuming) and outdoor (lawn mowing, planting shrubs) household tasks.	1.602 + (0.000638 × CPM) (walking activities) 2.922 + (0.000409 × CPM) (all activities)
Swartz 2000 (461)	CSA accelerometer (model 7164)	All activities (accelerometer was worn on hip)	70 participants completed one to six activities within the categories of yard work, housework, family care, occupation, recreation, and conditioning	2.606 + (0.0006863 × CPM) (all activities)
Leenders 2003 (462)	CSA accelerometer (model 7164)	Walking on a treadmill (accelerometer was worn on hip)	28 subjects (11 male, 17 female) walked on a motorized treadmill at 5 different treadmill velocities.	2.240 + (0.0006 × CPM)
Yngve, 2003 (463)	CSA accelerometer (model 7164)	Walking on indoor track and treadmill (accelerometer worn on hip)	28 participants (14 men, 14 women) walked at a normal pace, walked at a fast pace and jogged at a comfortable pace on an indoor track. One activity monitor was worn on the hip and one on the lower back. In a field study, 34 subjects (18 men, 16 women) each wore two monitors (hip and low back placement) for seven consecutive days	0.751 + (0.0008198 × CPM) (all activities – hip, track setting)
Brooks, 2005 (464)	CSA accelerometer (model 7164)	Walking (accelerometer worn on hip)	72 adults (35-45 year olds) walked around a level, paved quadrangle at what they perceived to be a moderate pace. Speed, heart rate, and Borg rating of perceived exertion were monitored.	2.32 + (0.000389 × CPM) 3.33 + (0.000370 × CPM) - (0.012 × BM)

Note: BM = body mass (kg), CPM = counts per minute, CSA = Computer Science and Application, Inc.

These eight algorithms listed above used an earlier version of ActiGraph accelerometer (model 7164) which are uniaxial accelerometers. In contrast, the VBI trial participants wore tri-axial ActiGraph (ActiGraph GTEX+ or ActiGraph w-GT3X-BT) accelerometer (456) which measure PA during walking with more precision than the uniaxial accelerometer (465). These studies used different domains of PA, for example, treadmill exercise, routine activities of daily living (Table 5-2:). Due to these differences and uncertainties over the algorithm to convert accelerometer counts per minute to MET-hours, the analysis below presents an incremental cost per incremental 1000 steps increase per day. The VBI trial presents data on accelerometer-measured counts per minute as well as other outcomes including step counts per day allowing calculation of other incremental cost-effectiveness ratios as desired.

5.3.1 Identification and measurement of resource use

The VBI trial prospectively collected resource-use data as an integral part of the trial. A search of the Database of Instruments for Resource Use Measurement (DIRUM) (www.DIRUM.org) was performed to identify any questionnaires that were used in primary care to collect resource usage data. Based on which a bespoke questionnaire was developed to collect resource use data at three-month follow-up. The resources monitored included health service use in primary care and secondary care, and out-of-pocket expenditure on health, sports clubs or other physical activities. The primary care consultations included all face-to-face, home visits and telephone consultations with GP, practice nurse or other healthcare professional. For patients admitted to the hospital, the length of stay and reason of admission were noted.

The effect of any health problems on the ability to work and perform regular activities (workplace productivity) was assessed using an adapted version of the validated Work Productivity and Activity Impairment (WPAI): General Health Questionnaire (466). The WPAI-general health (WPAI-GH) questionnaire consists of six questions (Appendix D1): 1=currently employed; 2=hours missed due to health problems; 3=hours missed other reasons; 4=hours actually worked; 5=degree health affected productivity while working; 6=degree health affected productivity in regular unpaid activities (466). These six WPAI questions were added at the end of the resource use data collection questionnaire resulting in 16 questions altogether.

An accelerometer and resource use questionnaire were sent to study participants at three months after their Health Check. Participants completed the questionnaire and returned by mail.

All resource use data were collected at the end of 3 months after the respondents Health Check using a self-administered questionnaire. Trial administrative/management records were used identify of intervention materials such as a pedometer, booklets. Intervention delivery time was not recorded in the trial, and it was assumed 5 minutes based on the time taken to deliver pedometer VBI in the pilot trial (450).

5.3.2 Valuation and aggregation of cost

NHS resource use was valued using national tariffs extracted from the published UK sources. All costs were expressed in 2014-15 (the study year) pounds sterling (£) and inflated to the same base year when appropriate using HCHS inflation index (467). As the study period was less than one year, costs and outcomes were not discounted. Quantities of resources (NHS and social care services) used were multiplied by unit costs and summed to generate a total cost per participant. Lost productivity was measured in terms of wages forgone by multiplying the UK national median hourly wage rate (468) and the number of hours reported as taken off work by an individual.

5.3.2.1 Estimating costs

The unit costs of GP and community services, and services from other healthcare providers were based on PSSRU estimates (Table 5-3). Unit costs for physiotherapist home visit and other allied healthcare professionals (home visit or surgery consultation) were assumed to be the same as a physiotherapist surgery consultation. Allied health professional telephone consultations were assumed to be half of the surgery consultation.

Table 5-3: Unit costs of primary care, therapy services and social care

Resource item	Unit cost	Source and basis of estimate
Primary care		
GP surgery consultation	£44.00	Derived from the cost per surgery consultation from PSSRU 2014-15 (467) p. 177 including qualification
GP home visit	£116.30	PSSRU 2012-13 (469) p. 191 per out of surgery visit inflated to 2015 prices using the HCHS index (PSSRU 2014-2015 (467) p. 242)
GP telephone consultation	£27.00	PSSRU 2014-15 (467) p. 177, per surgery consultation lasting 7.1 min incl. direct care staff costs and qualifications
Nurse surgery consultation	£14.47	PSSRU 2014-15 (467) p. 174, per hour of face-to-face contact including qualification × 15.5 min per surgery consultation

Table 5-3 (continued)

Resource item	Unit cost	Source and basis of estimate
Nurse home visit	£56.00	PSSRU 2014-15 (467) p. 174, per hour of face-to-face contact including qualification (assumes home visit takes one hr)
Nurse telephone consultation	£14.47	Assumed same as surgery consultation
Specialist nurse surgery consultation	£25.00	PSSRU 2014-15 (467) p. 175, per surgery consultation (15 mins) including qualifications
Community nurse/midwife consultation	£27.92	PSSRU 2014-15 (467) p. 169, assumed same as community nurse, 25 min consultation including qualification
Therapy services or other allied health professional costs		
Physiotherapist surgery consultation	£47.95	PSSRU 2012-13 (469) p. 175, mean cost for one-to-one contact inflated to 2015 prices using the HCHS index (PSSRU 2014-2015 (467) p. 242)
Physiotherapist home visit	£47.95	Assumed same as Physiotherapist surgery consultation
Other AHP surgery consultation	£47.95	Assumed same as Physiotherapist surgery consultation
Other AHP home visit	£47.95	Assumed same as Physiotherapist surgery consultation
Other AHP telephone consultation	£23.97	Assumed half of the surgery consultation
Chiropractor surgery consultation	£55.00	Mean cost of chiropractor consultation (470)
Chiropodist surgery consultation	£41.83	PSSRU 2012-13 (469) p. 178, mean cost for a contact in chiropody/podiatry services inflated to 2015 prices using HCHS index (PSSRU 2014-2015 (467) p. 242)
Osteopathic consultation	£41.83	Assumed same as a chiropodist
Cognitive behaviour therapy	£98	PSSRU 2014-15 (467) p. 90, per session
Social care		
Health visitor surgery consultation	£25.33	PSSRU 2014-15 (467) p. 171, per hour of patient-related work including qualification-assumed patient contact time of 20 min
Social worker office visit	£79.00	PSSRU 2014-15 (467) p. 188, per hour of client-related work including qualification
Other costs		
Travelling costs	£0.45	HMRC (471) cost of car transport per mile
Time off work (hourly wage)	£14.08	ONS Annual Survey of Hours and Earnings 2015 (468), median gross (for men and women) hourly earnings

Note:

AHP: Allied Health Professionals, HCHS: Hospital and Community Health Service, HMRC: Her Majesty's Revenue and Customs, ONS: Office for National Statistics, PSSRU: Personal Social Services Research Unit

For costs relating to outpatient, inpatient or day case procedure, a healthcare resource group (HRG) code was identified based on the description of the reasons given for outpatient visit, inpatient stay or day case procedure. If the participant did not record the reason for secondary care, i.e. hospital visit or inpatient stay, a weighted average cost extracted from the National Reference Costs 2014-15 Tariff (472) was used (Table 5-4).

Table 5-4: Secondary care costs

Resource item	Unit cost (£)	Source and basis of estimate
Outpatient appointment	114.50	Reference Costs 2014-2015 (472), weighted average of all outpatient attendance
Hospital inpatient stay	3,573.02	Reference costs 2014-2015 (472), weighted average of all elective inpatient stays
Day case procedure	720.78	Reference costs 2014-2015 (472), day cases HRG data, worksheet DC, weighted average
A&E attendance	131.92	Reference costs 2014-2015 (472), worksheet EM, a weighted average of all A&E attendance
Cost of mammogram	48.23	Robertson et al. (473), inflated to 2015 prices using the HCHS index (PSSRU 2014/2015 (467) p. 242)

Note:
A&E: Accident and Emergency, HCHS: Hospital and Community Health Service, Reference Costs: Department of Health and Social Care unit costs,

Patients' out of pocket expenditures such as road transport to a health club using their own vehicle were costed at £0.45 per mile as per HMRC guidance (471). Only 2 participants reported the use of hospital or community transport and thus this category of cost was excluded from the analysis.

5.3.3 Productivity costs

Productivity costs were defined as costs due to lost or impaired ability to work or to engage in leisure activities (466). The WPAI-GH questionnaire considered the number of hours missed from work due to any health problems, the number of hours missed from work because of other reasons (such as vacation, holidays or time off), hours worked and productivity while working. The WPAI-GH measures productivity (questions 5 and 6) using a visual analogue scale ranging from zero (health problem did not affect work) to ten (health problems completely prevented from working) (466). The scoring of WPAI instrument yields four types of scores: (a) absenteeism – work time missed, (b) presenteeism – impairment at work or reduced on the job effectiveness, (c) work productivity loss – overall work impairment, i.e. absenteeism plus presenteeism, and (d) activity impairment due to health. These scores are expressed in percentages by

multiplying the scores by 100 which was done using scoring instructions for the WPAI general health (474). Productivity loss costs were calculated by multiplying the total number of hours lost by their hourly income.

5.3.3.1 Cost of the intervention

The cost of the 'Step It Up' intervention includes time spent by the practice nurse or healthcare assistant in delivering the intervention and intervention materials. The pilot trial (450) recorded the intervention delivery time and the mean delivery time for pedometer VBI was 5 minutes. Cost per minute of face-to-face contact for practitioner was based on figures from the PSSRU 2015 unit costs (467), taking the midpoint of the relevant scales and including employer costs and appropriate overheads. The cost of a pedometer, pedometer booklet and step-chart are sourced from the trial records.

5.3.4 Measurement, valuation and aggregation of outcomes

The primary outcome of the trial was PA determined by accelerometer worn for approximately one week: total volume of body movement expressed as average vector magnitude acceleration (counts per minute) at three-month follow-up (456). Step counts (average step counts per day) and the average number of minutes per day spent in sedentary/light activity, moderate activity, vigorous activity and moderate or vigorous activity, all measured using the accelerometer, were secondary outcomes.

5.3.5 Method of analysis

5.3.5.1 Missing data

Of the 1,007 participants randomised, 859 participants provided 'adequate' wear time data on the primary outcome at three-month follow-up. Data were considered 'adequate' if there were at least four days of accelerometer data, with ≥600 minutes/day of wear time. Eight hundred and sixty-four participants returned the completed resource use questionnaire: 422 in the intervention and 442 in the control arm. Of the 859 who had valid data on primary outcome, 856 (99.6%) participants had resource use data available, i.e. only three participants did not have resource use data available (Figure 5-1). The economic analysis included complete case dataset (n=856) that is those participants who had valid data on primary outcome and completed resource use questionnaire. In the sensitivity analysis, to account for missing health care, transportation and lost productivity costs (n=859), the mean imputation technique was used (475), and the results amongst the complete case sample and full sample with imputed data were compared.

5.3.5.2 Incremental cost-effectiveness analyses

The analysis followed that specified in the within-trial health economic analysis plan in the study protocol (456). The analysis used patient-specific resource use and costs, and health outcomes. Incremental cost and incremental health effect, here, the difference in the average number of step counts per day per participant between study groups were calculated. Regression analysis was used to adjust incremental cost and health outcome estimates for baseline covariates. Predefined covariates (456) included in the model are primary care practice, gender and age group. The ICER was expressed in thousands of steps, thus representing incremental cost per 1,000 additional step counts achieved. Subgroup analyses were conducted to examine the differential mean cost between the intervention and control groups by pre-specified subgroup variables: gender, age (40-59; 60-74 years), educational qualifications, marital status, employment status, occupation and household income (<£31,000, ≥£31,000).

5.3.5.3 Sensitivity analyses

Cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) were constructed to reflect the stochastic uncertainty surrounding the mean incremental cost-effectiveness (476). A non-parametric bootstrapping analysis (477) (resampling with replacement, 10,000 iterations) was used to generate scatterplot of the increment cost and incremental health effect. The CEAC indicates the probability of the 'Step It Up' intervention being cost-effective at varying society's willingness to pay per an additional 1000 steps.

5.3.6 Results

Baseline characteristics of 1007 participants randomised were similar in each group (Table 5-5). The mean age of the participants was 56 years, and two-thirds were female. The study sample was predominantly white, and about two-thirds were in paid employment.

Table 5-5: Baseline characteristics of participants allocated to intervention and control

Characteristics	No of people randomised at baseline		No of people with sufficient wear time data	
	Control (n=502)	Intervention (n=505)	Control (n=442)	Intervention (n=417)
Mean (SD) age	56.5 (9.4)	55.7 (9.6)	56.7 (9.3)	56.5 (9.5)
Female % (number)	61 (305)	63 (316)	61 (269)	62 (260)
White ethnicity % (number)	95 (476)	96 (484)	95 (420)	96 (401)
Married or cohabiting % (number)	81 (375/465)	80 (383/480)	81 (330/411)	81 (320/398)
Have dependants % (number)	35 (164/468)	39 (186/482)	33 (137/411)	38 (153/399)
Work status	*n*=472	*n*=482	*n=411*	*n=396*
Paid work	61 (286)	62 (301)	60 (246)	60 (236)
Unemployed/homemaker	6 (29)	6 (28)	6 (24)	6 (22)
Full-time student	0 (0)	0 (1)	0 (0)	0 (1)
Retired	32 (152)	31 (148)	34 (141)	35 (137)
Other	1 (4)	1 (4)	0 (0)	0 (0)
Income	*n*=410	*n*=424	*n=358*	*n=351*
Less than £18,000	26 (105)	21 (88)	25 (90)	19 (67)
£18,000 - £30,999	22 (91)	22 (94)	23 (84)	23 (81)
£31,000 - £51,999	28 (114)	29 (124)	29 (104)	31 (108)
£52,000 - £100,000	18 (72)	20 (85)	16 (59)	20 (71)
> £100,000	7 (28)	8 (33)	6 (21)	7 (24)
Occupational group	*n*=295	*n*=314	*n=255*	*n=250*
Manual	24 (71)	27 (84)	22 (55)	25 (62)
Non-manual	68 (200)	65 (203)	70 (179)	68 (169)
Other	8 (24)	9 (27)	8 (21)	8 (19)
Highest qualification	*n*=485	*n*=494	*n=425*	*n=409*
None	9 (46)	9 (44)	8 (34)	9 (36)
GCSE	60 (290)	66 (326)	62 (264)	67 (276)

Note: Values are % (numbers) unless otherwise stated
Source: adapted from Table 1, Hardeman et al. (457)

Table 5-6 presents data on resource use by type of contact for each arm of the trial. Healthcare resource use was broadly similar between the groups.

Table 5-6: Average health and social care utilisation per participant, using complete cases, by trial arm

Resource category	*N* (control, intervention)	Control		Intervention	
		Mean	(SD)	Mean	(SD)
Primary Care Consultations					
GP surgery visit	(442, 422)	0.50	(0.85)	0.46	(0.72)
Nurse surgery visit	(442, 422)	0.28	(0.63)	0.23	(0.55)
Other HP surgery visit	(442, 422)	0.15	(0.65)	0.12	(0.52)
GP home visit	(442, 422)	0.00	(0.00)	0.01	(0.08)
Nurse home visit	(442, 422)	0.002	(0.05)	0.00	(0.00)
Other HP home visit	(442, 422)	0.01	(0.24)	0.01	(0.11)
GP phone consultation	(442, 422)	0.07	(0.53)	0.07	(0.28)
Nurse phone consultation	(442, 422)	0.03	(0.21)	0.01	(0.10)
Other HP phone consultation	(442, 422)	0.01	(0.08)	0.02	(0.21)
Hospital visits					
Outpatient visit	(442, 422)	0.28	(0.69)	0.22	(0.65)
Day case procedures	(442, 422)	0.01	(0.12)	0.02	(0.15)
Hospitalisations	(442, 422)	0.004	(0.07)	0.01	(0.08)
A&E visit	(442, 422)	0.02	(0.14)	0.01	(0.15)
Health club membership					
Health club visits	(138, 156)	2.46	(1.54)	2.55	(1.57)
Time spent on travel to health club	(139, 155)	2.00	(1.20)	1.99	(1.22)
Loss of productivity, hours					
Hours off work due to illness	(263, 244)	0.32	(2.46)	0.26	(2.12)
Hours off work due to other reasons	(254, 237)	1.97	(6.11)	2.16	(7.62)

5.3.6.1 Cost of intervention and healthcare services

Delivery of ‘Step It Up’ intervention cost £18.04 per participant. The cost of intervention included a face-to-face nurse consultation (£4.67), a pedometer (£11.25), pedometer booklet (£1.52) and step-chart (£0.60). The duration of face-to-face consultation was not recorded in the trial but based on the pilot trial (450), in which delivery of pedometer VBI was shorter than five minutes, practice nurse’s five minute time was costed.

Comparing the ‘Step It Up’ with Health Check only at three-month follow-up (Table 5-7) show that the average cost per participant was higher in the intervention group. The inclusion of ‘Step It Up’ delivery cost to NHS costs resulted in the intervention group costing £16.72 (95% CI: -31 to 64, p=0.49) more per participant than the control group. Total societal costs which included NHS costs, out of pocket expenditure and lost productivity were £54.07 (95% CI: -97 to 205, p=0.48) more per participant in the intervention group. When adjusted for covariates, at three months, the costs of the

intervention group were higher than that of the control group for both NHS and societal perspectives.

Table 5-7: Average effects and costs per participant by trial arm

	N (Intervention, control)	Intervention mean (SD)	Control mean (SD)	Unadjusted increment mean (SE)	Adjusted* increment mean (SE)
Effects					
Total PA volume (counts per minute)	(417, 442)	668 (213)	660 (202)	8 (14)	9 (14)
Step counts per day	(417, 442)	8419 (3215)	8191 (2998)	228 (212)	242 (211)
Costs					
Cost of intervention	(416, 440)	18.04 (0.00)	0.00 (0.00)	18.04 (0.00)	
Primary care	(403, 430)	32.05 (52.46)	35.20 (60.82)	-3.14 (3.95)	
Hospital costs	(402, 427)	71.32 (370.68)	68.93 (307.71)	2.39 (23.61)	
Total NHS costs	(416, 440)	118.01 (379.22)	101.29 (326.96)	16.72 (24.16)	21.55 (24.21)
Patient out-of-pocket costs	(416, 440)	110.54 (194.80)	101.12 (215.20)	9.42 (14.06)	
Lost productivity costs	(416, 440)	386.03 (1130.44)	358.10 (938.17)	27.93 (70.85)	
Total societal costs	(416, 440)	614.58 (1212.01)	560.51 (1042.17)	54.07 (77.13)	53.46 (76.97)

Note:
* Comparison of means is adjusted for gender, five-year age group and practice.

5.3.6.2 Cost-effectiveness

Based on the adjusted incremental estimates, the ICER was £96.32 per 1000 steps using the NHS costs and £238.89 per 1000 steps using the societal perspective respectively (Table 5-8). The values presented in Table 5-8 are bootstrapped mean and 95% credible intervals. The main trial reported that the intervention group increased daily step counts by 242 (95% CI: -172 to 656) compared with control group (442 control and 417 intervention) whereas the incremental step counts presented in the table are for 856 (440 control and 416 intervention) observations with complete cost and outcomes data only.

Table 5-8: Cost-effectiveness analysis from the NHS and societal perspectives

Analysis	Complete case analysis (n=856)			Adjusted with missing data imputed (n=859)		
	Inc cost (95% CI)	Inc step counts (95% CI)	ICER	Inc cost (95% CI)	Inc step counts (95% CI)	ICER
NHS perspective	21.55 (-26 to 69)	224 (-193 to 640)	£96.32	21.21 (-26 to 69)	242 (-172 to 656)	£87.60
Societal perspective	53.46 (-98 to 205)	224 (-193 to 640)	£238.89	48.65 (-102 to 199)	242 (-172 to 656)	£201.00

Note:

CI confidence interval, *ICER* incremental cost-effectiveness ratio for 1000 additional steps, *Inc* incremental. Incremental costs and step counts were adjusted for gender, five-year age group and practice.

The cost-effectiveness planes (Figure 5-2) showed that the joint distribution of incremental costs and health outcomes with the majority (69% using NHS perspective and 65% using societal perspective) falling in the Northeast quadrant, i.e. higher costs with better health outcomes.

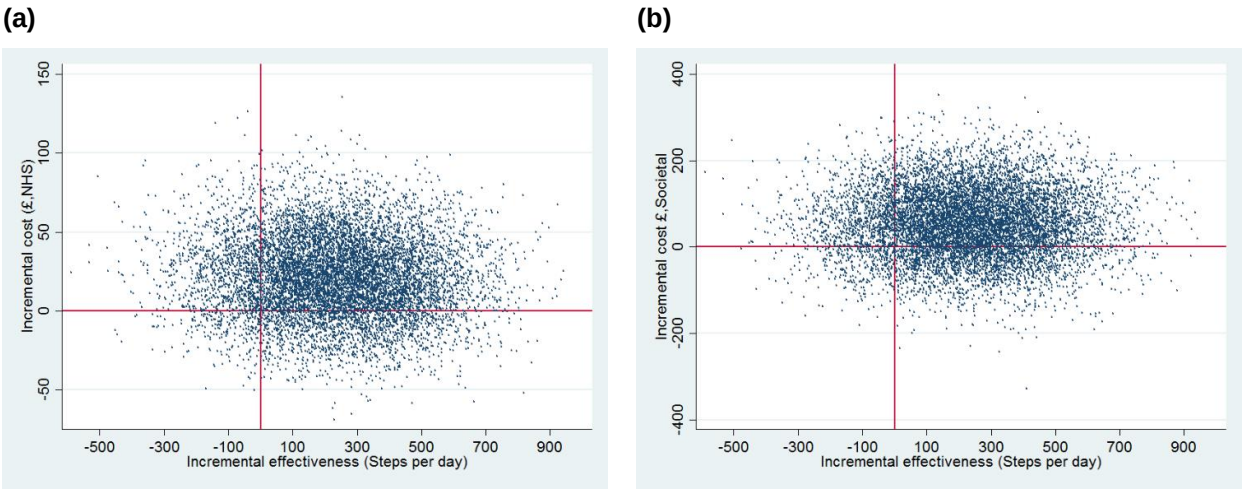

Figure 5-2: Cost-effectiveness plane for the 'Step It Up' versus the control group at three months using (a) NHS perspective, (b) societal perspective

The CEAC (Figure 5-3) showed that if the society is willing to pay a greater amount for additional steps, the likelihood that the 'Step It Up' is cost-effective rises to 53% (NHS perspective) when society's willingness to pay reaches £100 for 1000 additional steps. When considering the NHS perspective, the probability that the intervention would be cost-effective is 84% (highest probability) at a willingness to pay threshold of £1150 per 1000 additional steps. Likewise, using the societal perspective, the likelihood that the 'Step It Up' is cost-effective rises to 36% when willing to pay value reaches to £100 for

1000 additional steps, with 81% (highest probability) at a willingness to pay threshold of £1450 per 1000 additional steps.

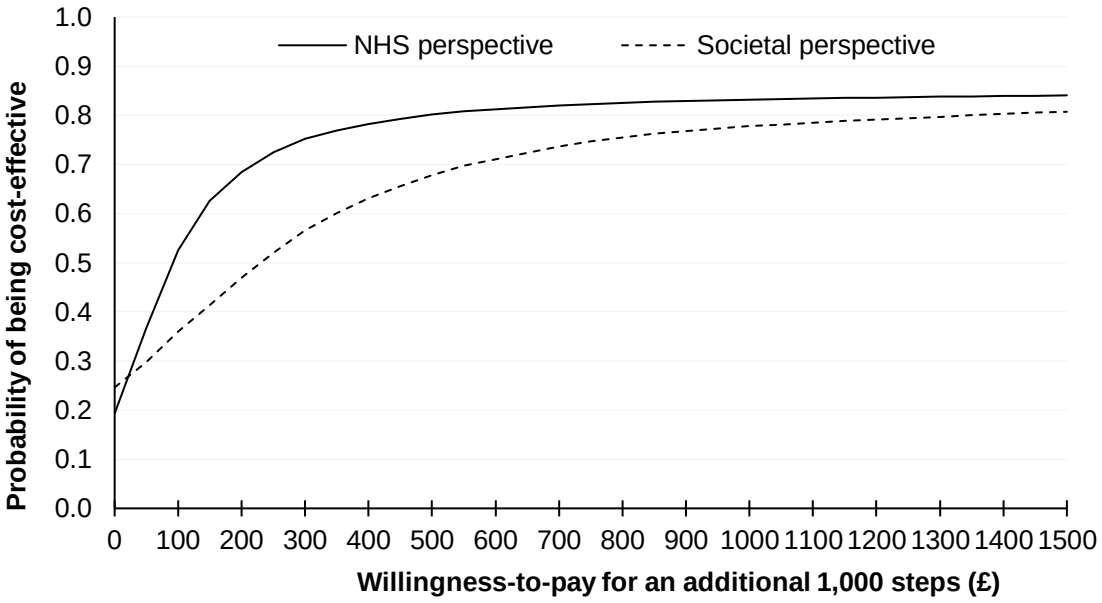

Figure 5-3: Cost-effectiveness acceptability curve

5.3.6.3 Value of lost productivity

On average 58% participants in the intervention (n=402) and 62% in control arm (n=422) were in work. Participants in the intervention group who were employed full time lost fewer work hours during the previous seven days compared to the control group (-0.06, 95% CI: -0.49 to 0.37) but the difference did not reach statistical significance. They also reported slightly higher presenteeism and overall better work impairment scores. On average 1% of the participants in both study groups missed work due to poor health. No significant difference in impairment while working due to health and overall work impairment due to health was observed between the groups (Table 5-9).

Table 5-9: Work productivity and activity impairment during the previous seven days

	Control				Intervention				Difference (95% CI)
	N	Mean	(SD)	[Min-Max]	N	Mean	(SD)	[Min-Max]	
Participants in work (n=824)	422	62.1	(48.6)		402	58.4	(49.3)		-3.6 (-10.3 to 3.1)
Percent work time missed due to health (absenteeism)	233	1.1	(9.4)	[0–100]	214	0.9	(6.8)	[0–75]	-0.22 (-1.7 to 1.3)
Percent impairment while working due to health (presenteeism)	249	4.9	(11.3)	[0–60]	221	6.0	(13.9)	[0–70]	1.1 (-1.2 to 3.3)
Percent overall work impairment due to health	229	5.0	(11.5)	[0–60]	210	6.7	(15.9)	[0–80]	1.7 (-0.9 to 4.3)
All participants (n=819)									
Percent activity impairment due to health	421	12.7	(23.2)	[0–100]	390	11.8	(21.7)	[0–100]	- 0.9 (-4.0 to 2.2)

Note:
N = number of observations, SD: standard deviation

5.3.6.4 Subgroup analysis

Table 5-10 reports the incremental cost, outcome (steps counts) and ICER between intervention and control group in subgroups. The absolute cost and outcome differ across subgroups; however there were no significant differences between study groups within any one subgroup.

Table 5-10: Cost-effectiveness analyses of 'Step It Up' versus Health Check only in patient-groups, using NHS perspective

Patient Subgroups		Incremental cost (95% CI)	Incremental step counts (95% CI)	ICER* (95% credible intervals)
Total (n=853)		21.55 (-26 to 69)	224 (-193 to 640)	96.32 (-996 to 1168)
Gender	Female (n=529)	-25.11 (-81 to 30)	130.15 (-367 to 628)	-192.89 (-1811 to 1526)
	Male (n=327)	83.92 (-2 to 170)	348.10 (-395 to 1092)	241.08 (-1799 to 2140)
Age	40–59 years (n=488)	30.04 (-15 to 75)	322.85 (-247 to 893)	93.04 (-834 to 1016)
	60–74 years (n=368)	1.88 (-91 to 95)	17.62 (-585 to 620)	106.99 (-2282 to 1653)
Educational qualification	None or GCSE (n=607)	-2.69 (-63 to 58)	292.27 (-216 to 801)	-9.20 (-736 to 835)
	Other (n=224)	19.84 (-10 to 50)	11.92 (-763 to 787)	1665.13 (-1012 to 838)
Marital status	Single (n=158)	98.79 (-17 to 214)	435.27 (-653 to 1523)	226.96 (-2105 to 2523)
	Married/cohabitating (n=647)	-4.04 (-60 to 52)	183.08 (-291 to 657)	-22.08 (-1699 to 1367)
Paid work	Paid work (n=479)	42.61 (-16 to 101)	275.09 (-292 to 842)	154.89 (-1370 to 1641)
	No paid work (n=370)	-6.81 (-85 to 70)	34.21 (-586 to 654)	-199.04 (-1366 to 1487)
Occupation	Manual (n=117)	107.29 (-105 to 319)	1080.21 (-356 to 2516)	99.32 (-597 to 1103)
	Not manual/other (n=384)	6.59 (-33 to 46)	49.39 (-536 to 635)	133.37 (-774 to 784)
Income	< £31,000 (n=319)	-34.22 (-113 to 45)	196.29 (-567 to 959)	-174.32 (-1693 to 1583)
	≥ £31,000 (n=537)	47.47 (-12 to 107)	217.98 (-274 to 710)	217.76 (-2127 to 2614)

Note: *incremental cost per 1000 additional steps, 95% non-parametric credible intervals (CrI) based on 10,000 bootstraps.

5.3.7 Discussion

The within-trial analysis showed no significant differences between groups in objectively measured physical activity (counts per minute, and step counts per day) and healthcare resource use at three-month follow-up. The 'Step It Up' intervention cost £18.04 per patient. When the NHS perspective was used, intervention participants increased their physical activity by 1000 step counts per day at an incremental cost of £96 above the control arm. An intervention is considered cost-effective if (a) it costs less and is more effective than the comparator intervention or (b) costs more and is more effective, but society is willing to pay for the additional benefit (step counts). In the latter scenario, the ICER is less than λ, i.e. the threshold value that society is willing to pay for additional steps.

Johnson et al. (478) evaluated the cost-effectiveness of a lifestyle based pedometer programme in primary care in Australia and reported a similar outcome to this study. However, their study included adults with type-2 diabetes where the 'Step It Up' intervention included apparently healthy adults. The ICER for Johnson et al. (478) study was AU$ 111 (£54, 2015 prices (134)) per 1000 step counts which was lower than the present study. Johnson et al. also estimated implied threshold value of AU$ 176 (£86, 2015 prices (134)) per additional 1000 steps. There is no such threshold value for additional step counts in England thus it is unclear if the society is willing to pay £96 for an additional 1000 steps. There was also uncertainty surrounding the point estimate, at a threshold value of £100 per additional 1000 steps, the probability that 'Step It Up' is cost-effective is 53% (NHS perspective) which increases to 84% (highest probability) at a threshold value of £1150 per 1000 additional steps.

The within-trial analysis was nested within a well-designed population-based pragmatic RCT and used individual patient level data (both cost and effectiveness data) collected at three-month follow-up. The trial captured both NHS resource use and patients' out of pocket expenditure on health and sports. However, the trial did not measure PA at baseline nor collect data on the quality of life impacts (such as QALY gains) of the intervention rather WPAI questionnaire was used to assess the effect of any health problems on the ability to work and perform regular activities.

The QALY is a common outcome used in the economic evaluation. As the VBI trial did not collect EQ-5D data, this limited the comparison of cost-effectiveness results from the within-trial economic analysis with other studies reporting cost per QALY outcome including results from the first iteration of the decision model described in Chapter 4. The cost of pedometer intervention used in the first iteration of the model (Table 4-31) was

£54.33 (£58 when inflated to 2015 price using the HCHS index (467)) which was higher than the cost of 'Step It Up' (£18.04, 2015 price). The higher cost of pedometer interventions used in the first iteration of the model was due to the fact that the pedometer interventions included in the Bravata et al. meta-analysis (151) were more intensive than 'Step It Up,' i.e. included > 5 minutes of PA consultation that increased the cost of the intervention. The model included both intervention and associated disease costs over a 10-year time horizon, with health outcomes measured in terms of QALYs. The within-trial economic analysis, however, included intervention and healthcare resource use costs over a 3-month period.

Previous studies indicated a positive association between PA and health-related quality of life in general and older adult population (443,479,480), but this evidence is mostly based on cross-sectional data which limits the generalisability. Baseline measurement in a pragmatic trial such as 'Step It Up' may preclude an intervention effect over behaviour (119,481,482). Furthermore, the earlier feasibility pilot (450) conducted as part of the VBI research programme showed that baseline measurement reduced health check uptake. In addition, this was not acceptable to GP practices, as health check constitutes routine care. The study population were healthy middle-aged adults (i.e. without pre-existing conditions) and who were already relatively active. This may have limited capacity for a VBI to have an effect over and above the health check alone. Although one would not expect much change in health-related quality of life in 3 months' time in an apparently healthy population post-intervention, it was not possible to report cost per QALY outcome as the trial did not use QALYs to value health outcomes. As a result, it is not possible to check if the ICER is above or below the NICE threshold value of £20,000 to 30,000 per QALY.

Previous meta-analyses indicated that pedometer-based interventions increase walking by 2,000 to 2,500 steps per day (151,436). The PACE-UP trial evaluated the effectiveness and cost-effectiveness of a pedometer-based 12-week programme to increase PA among adults aged 45-75 year olds in London and found a significant effect at 3 and 12 months (1173 and 677 additional steps respectively) (483). The PACE-UP trial included 20 minutes of consultation with the practice nurse compared to 5 minutes in the VBI trial.

The study found no evidence of the effect of a pedometer-based VBI ('Step It Up') regarding objectively measured physical activity at three-month follow-up compared to usual NHS Health Check only. The within-trial economic analysis showed a small added cost for a small and uncertain benefit, with a most plausible estimate of the incremental cost-effectiveness of £96 per 1000 additional steps.

Costs included in the decision model (Chapter 4) were intervention and disease costs. The trial included intervention costs and costs associated with healthcare resource use over 3 months that included any contacts in primary care (for example GP visits) and hospital care (outpatient, inpatient, day case procedures and A&E). The model used QALYs to value health outcome whereas health benefits were measured in terms of increase in step counts in the trial. Following the iterative framework, the next logical step is to incorporate the evidence from the VBI trial, i.e. updating the effectiveness evidence used and re-running of the decision model developed in Chapter 4.

The sections below describe updating the evidence base and model parameter for the second iteration of the model followed by cost-effectiveness and value of information analyses. The discussion section compares the results with the first iteration of the model and within-trial economic analysis. It also discusses the practical realities of applying the iterative approach.

5.4 Incorporating evidence from the VBI trial into the decision model reported in chapter 4

The VBI trial (456) was the first to consider pedometer-based VBIs compared to the NHS Health Check alone. The evidence from the VBI trial updates knowledge and understanding of the VBIs in primary care and their potential benefits. As per the decision analytic model for evaluating PA interventions, evidence from the VBI trial did not result in any structural changes to the model. Prior to the VBI trial, there was limited evidence on the effectiveness and cost-effectiveness of VBIs (less than 5 minutes) in primary care (113,149,451,452), and therefore the VBI trial has revised the knowledge and understanding of the (very) brief PA interventions in NHS Health Check population.

Despite the increasing number of PA interventions evaluated in the primary care and/or community setting (detailed in Chapter 2), little evidence on the effectiveness and cost-effectiveness of brief interventions in PA promotion were available for the first iteration of the decision analytic model presented in Chapter 4. In 2006, NICE endorsed the importance of PA as a means of promoting good health and preventing disease and produced guidance on four common methods used to increase the PA levels (112). The four interventions considered in this guidance were brief interventions in primary care, exercise referral schemes, pedometers, and community-based walking and cycling schemes. The guidance was subsequently updated in 2013, with separate guidance for brief PA interventions in primary care (448). The guidance aims to support the routine provision of brief PA advice in primary care practice. The review of economic evidence

conducted for the updated guidance on brief advice in primary care reviewed three papers including one study based on an Australian population indicated cost-effectiveness of brief advice on PA in primary care compared to usual care, but the evidence was based on weak effectiveness data and did not fully explore uncertainty.

5.4.1 The VBI trial evidence

As mentioned in above (sections 5.1 and 5.2), the VBI trial was conducted to assess the effectiveness and cost-effectiveness of a pedometer-based very brief advice to increase PA in primary care (456). Section 5.2 summarised the effectiveness evidence of the VBI trial, i.e. a mean increase of 242 steps per day (95% CI: -172 to 656) at three-month follow-up. However, this difference did not reach statistical significance at the conventional 5% level.

The effectiveness evidence used for pedometer BIs in the first iteration of the decision analytic model (Chapter 4) used evidence from a meta-analysis of 8 RCTs evaluating the effectiveness of pedometer interventions (151). The review reported that intervention participants significantly increased their PA by 2491 steps per day (95% CI: 1098 to 3885, $p<0.001$) than control participants. This meta-analysis compared the mean change in steps per day from baseline between study groups. To update the meta-analysis with the new evidence from the VBI trial, we require both baseline and follow-up PA measurement for both groups. One of the limitations of the VBI trial was that it did not objectively measure physical activity at baseline. As a result, to update the evidence base with new effectiveness data from the VBI trial, we require some assumptions regarding baseline activity levels.

A PubMed search was performed to identify any pedometer-based RCTs in the UK general practice. From the search hits, two RCTs of pedometer interventions were identified: the VBI pilot trial – a feasibility study (450) and the PACE-UP trial (484) which are described briefly below.

The VBI pilot trial (450) compared three VBIs with NHS Health Check. The three interventions compared (described in section 5.1) were motivational VBI, pedometer VBI and motivational plus pedometer VBI (combined). The follow-up duration of the pilot trial was four weeks, and PA was objectively measured using accelerometers at 4-week follow-up.

Harris et al. (484) conducted a three-arm parallel cluster RCT to assess the effectiveness of a pedometer-based walking intervention delivered by post or through primary care

nurse supported PA consultations (PACE-UP). The intervention group with nurse support received a pedometer, patient handbook, PA diary and three individually tailored nurse consultations on PA whereas post-intervention participants did not receive nurse support. The consultation duration ranged from 10 to 20 minutes. The intervention group with nurse support was of interest to this study. The trial recruited 1023 patients from six general practices in South London, UK aged between 45 to 75 years and assigned to either control group or one of two intervention groups (postal or nurse intervention). Physical activity was measured using an accelerometer at baseline, 3 months and 12 months.

Table 5-11 summaries the baseline characteristics of the VBI trial (457), VBI pilot trial (450) and PACE-UP trial (484). Both the VBI pilot and the main trial had a higher proportion of female study participants compared to the PACE-UP trial. VBI trial participants were more active than the PACE-UP trial when PA was (subjectively) measured at baseline. Both the VBI trial and PACE-UP trial used general practice physical activity questionnaire (GPPAQ) (485) to measure the baseline activity level. The GPPAQ was commissioned by the Department of Health and Social Care in 2006 and developed by the London School of Hygiene and Tropical Medicine (485). It is designed as a screening tool to assess PA levels within primary care and provides a simple 4-level physical activity index (PAI) reflecting an individual's current PA. The GPPAQ forms part of the NHS Health Checks (114,486).

Table 5-11: Baseline characteristics of pedometer-based studies conducted in the UK general practice and baseline PA measurement

	VBI trial (457)		VBI Pilot trial (450)		PACE-UP trial (483,484)	
	Intervention (N=505)	**Control (N=502)**	**Pedometer VBI (N=74)**	**Control (N=157)**	**Intervention* (N=346)**	**Control (N=338)**
Mean age (SD), years	55.7 (9.6)	56.5 (9.4)	53.3 (8.4)	53.9 (10.1)	–	–
Gender n (%) female	316 (63)	305 (61)	45 (61)	92 (59)	128 (37)	115 (34)
Ethnicity n (%) white	484 (96)	476 (95)	72 (97)	147 (97)	267 (80)	253 (78)
Employment status, n (%) employed	301 (62)	286 (61)	56 (79)	106 (68)	190 (56)	190 (57)
Physical activity status (GPPAQ), n (%)						
Inactive	69 (14)	63 (13)	–	–	156 (47)	159 (49)
Moderately inactive	81 (16)	97 (19)	–	–	83 (25)	69 (21)
Moderately active	178 (35)	176 (35)	–	–	60 (18)	50 (16)
Active	177 (35)	166 (33)	–	–	34 (10)	44 (14)
Baseline step-counts per day, mean (SD) †	–	–	–	–	7653 (2826)	7379 (2696)
Step-counts per day at 1m follow-up, mean (SD)	–	–	7844 (2863); n=37	7944 (3085); n=111	–	–

Note:

* Nurse support group

† accelerometry data adjusted for the week and day of wearing the accelerometer

The effectiveness evidence was updated using R package for meta-analysis 'meta' (487). As the VBI trial did not collect objectively measure baseline PA, the following assumptions were made while updating the evidence base (meta-analysis):

5.4.1.1 Base case assumption

In the base case, only PA measurement at follow-up was compared. This was done because objectively measured baseline PA data were not available for the VBI trial participants. For this, PA measurement at follow-up was extracted from the original pedometer meta-analysis (151) then VBI trial data were added in, and the meta-analysis was updated.

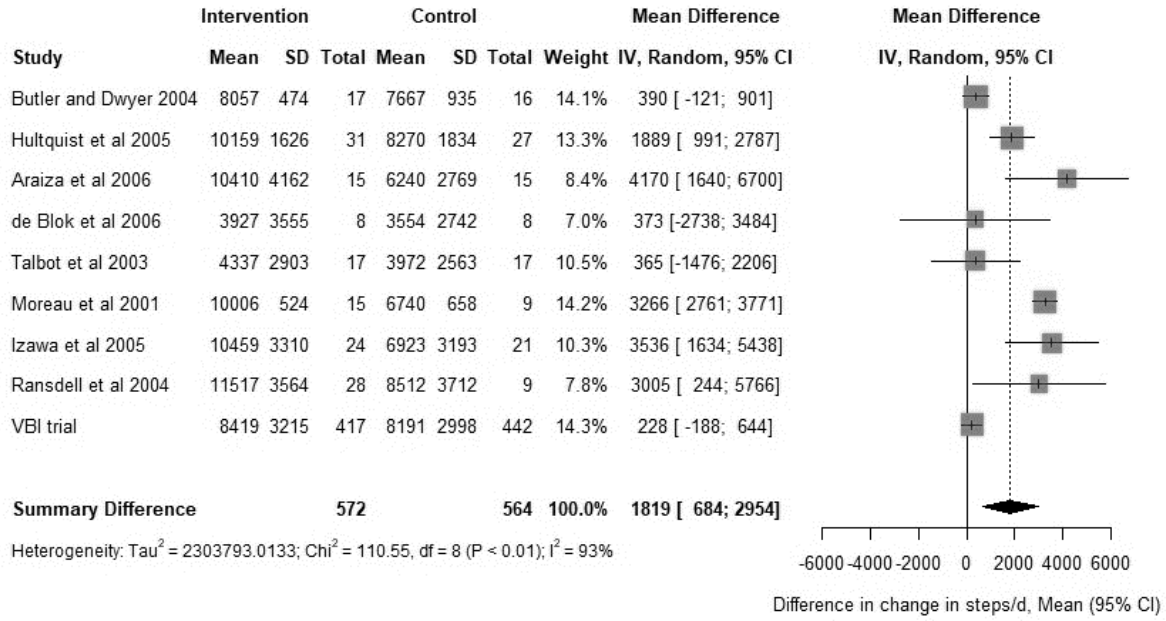

Figure 5-4: Forest plot of the difference in the change in step counts at follow-up among participants randomly assigned to pedometer interventions vs control (base case)

Source: Adapted from Bravata et al. (151) and Hardeman et al. (457).

The updated evidence (Figure 5-4) gives an effect size of 1,819 steps per day (95% CI: 684 to 2954, p<0.01) which was lower than the one used in the first iteration of the evidence (2491 steps; 95% CI: 1098 to 3885).

5.4.1.2 Sensitivity analysis

Two sensitivity analyses were performed to test the base case assumption while updating the effectiveness of pedometer interventions. In the first scenario, VBI trial participants were assumed to have the same baseline PA levels reported for the PACE-UP trial participants (484). For this, baseline activity level for control group (mean= 7379; sd=2696

steps/day) and the nurse-support intervention group (mean=7653; sd=2826 steps/day) were used. Figure 5-5 shows that 572 intervention participants significantly increase physical activity by 2143 steps per day more than 564 control participants (95% CI: 936 to 3351 steps per day, p<0.01; I^2=93).

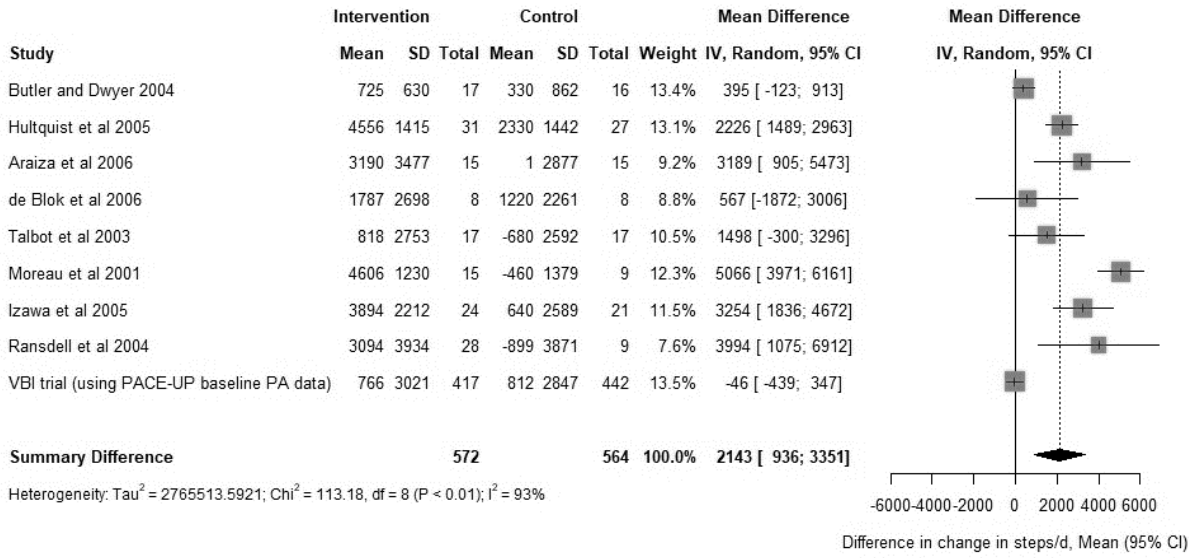

Figure 5-5: Forest plot of the difference in the change in step counts among participants randomly assigned to pedometer interventions vs control using baseline PA data from the PACE-UP trial (scenario 1)

Source: Adapted from Bravata et al. (151), Hardeman et al. (457) and Harris et al. (484).

In the second scenario, it was assumed that the baseline PA measures (steps/day) for both study groups in the VBI trial were similar and replaced by PA data for the of control group participants in the pilot trial (450). This assumption is based on the fact that baseline characteristics of study participants for both groups of the VBI pilot and main trial were similar (Table 5-11). As the baseline PA measurement was not available for the VBI pilot trial participants, accelerometer-measured step counts at one-month follow-up for the control group (health check only) of the VBI pilot trial (450) were used. Given the same patient population, i.e. NHS Health Check, similar baseline characteristics of study participants and study setting in both pilot and the main trial, it is reasonable to assume same PA levels for NHS Health Check population.

This assumption effectively gives the same mean difference in change in steps/day for the VBI trial, i.e. an increase of 228 steps/day. Figure 5-6 shows the difference between the increase in physical activity (step counts per day) among intervention and control group participants. The effect size for this scenario is 2172 steps per day (95% CI: 1019 to 3326; p<0.01).

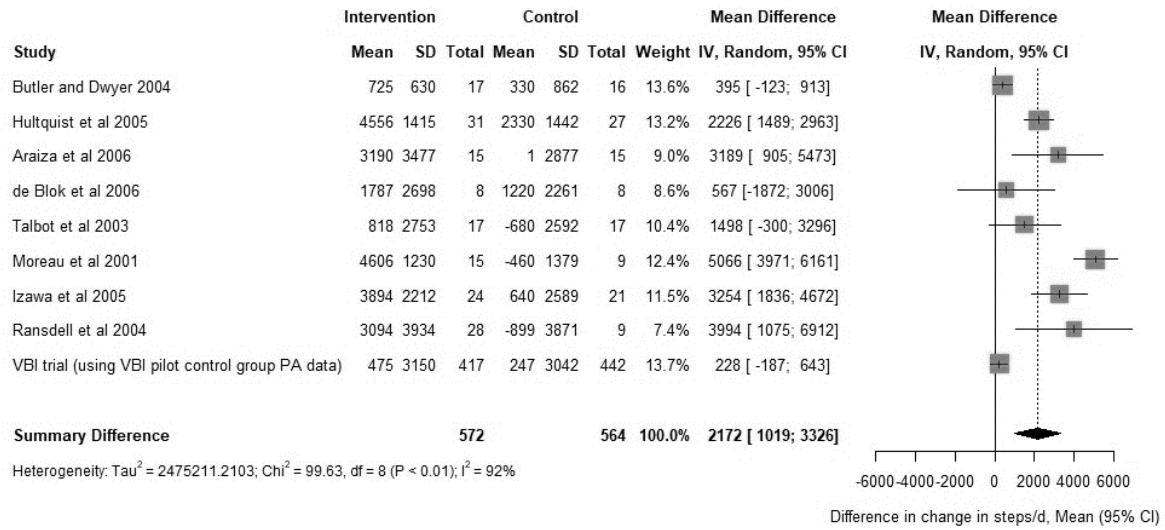

Figure 5-6: Forest plot of the difference in change in step counts among participants randomly assigned to pedometer interventions vs control while using control group PA level from the VBI pilot trial for VBI trial participants (scenario 2)

Source: Adapted from Bravata et al. (151), Hardeman et al. (457) and Pears et al. (450).

5.4.2 Changes to the decision analytical model

Prior to the VBI trial, there was limited evidence on the effectiveness and cost-effectiveness of VBIs in promoting PA in primary care. Incorporating the pedometer VBI evidence from the VBI trial into the decision analytic model developed in Chapter 4 did not require any structural adjustments to the decision model. The VBI trial provided the short-term effectiveness of a pedometer VBI and the cost of 'Step It Up' intervention.

5.4.3 Parameterisation of the decision analytical model

5.4.3.1 Short-term effectiveness of pedometer VBI

By using the method described above to update the evidence base for pedometer intervention, the short-term effectiveness of the pedometer intervention was updated. In the base case, i.e. using PA levels at follow-up (Table 5-12) shows that 572 intervention participants significantly increase their step counts per day by 1819 (95% CI: 684 to 2954, $p<0.01$) more than 564 control participants. However, this result was heterogeneous ($Q=110.55$, $p<0.0001$, $I^2 = 92.8\%$).

Table 5-12: Intervention effects and costs associated with implementing pedometers

Interventions	No of studies	Total number of participants	Effects in Steps/day, mean (95% CI)	Effects in MET-hours per day, mean (95% CI)
Pedometer (base case)	9	1,136	1,819 (684 to 2,954)	5.41 (2.03 to 8.79)
Pedometers (scenario 1)	9	1,136	2,143 (936 to 3,351)	6.38 (2.78 to 9.97)
Pedometers (scenario 2)	9	1,136	2,172 (1,019 to 3,326)	6.46 (3.03 to 9.89)
Current practice ('doing nothing')		–	–	–

In the scenario analyses where baseline PA measurement for VBI trial participants was assumed to have similar PA levels measured at baseline for the PACE-UP trial, an increase of 2143 steps (95% CI: 936 to 3351) was observed. When the baseline PA measurement for VBI trial participants was assumed to have the same PA levels of those control group participants at follow-up in the VBI pilot trial, the effect size of the pedometer intervention was 2172 (95% CI: 1019 to 3326). In these two scenario analyses, the effect size of the updated evidence was similar but higher than the base case scenario.

5.4.3.2 Cost parameters

The cost of the pedometer VBI was updated after updating the evidence as described in section 5.4.1. The updated meta-analysis now includes nine RCTs including the VBI trial. While running the first iteration of the model, the cost of the pedometer intervention was estimated based on the description of the intervention provided for individual studies included in the Bravata meta-analysis (151). The cost of the 'Step It Up' intervention was £18.04 (457). To update the cost of intervention, the original cost of pedometer intervention estimated in Chapter 4 was inflated to 2014-15 prices using inflation indices from the Hospital and Community Health Services (HCHS) (467). This gives the (revised) weighted average cost of the intervention of £28.30 per participant (Table 5-13).

Table 5-13: Estimates of cost per participant of pedometer intervention

Source	Intervention participant	Original cost estimated for the first iteration of the model*	Total cost, 2015 £
Araiza et al 2006	15	£14.96	£15.85
Butler and Dwyer 2004	17	£14.00	£14.83
de Bplok et al 2006	8	£82.96	£87.88
Hultquist et al 2005	31	£14.96	£15.85
Izawa et al 2005	24	£14.96	£15.85
Moreau et al 2001	15	£14.96	£15.85
Ransdell et al 2004 and Ornes et al 2005	28	£183.55	£194.43
Talbot et al 2003	17	£65.21	£69.08
Hardeman et al 2018 (VBI trial)	442	–	£18.04
Total	**597**		**£28.30**

Note:
* Price year used in the original estimation of intervention cost was for 2010-11 (as described in section 4.6.4).

The health state costs as per the original model are maintained but updated to reflect 2015 prices using the HCHS index (467).

5.4.3.3 Quality of life parameters

While running the first iteration of the model, there was limited evidence on the short-term improvements in quality of life associated with increased activity in general population as most of PA interventions focused on those with chronic conditions (442-444). As a result, the effect of short-term health gains (utility boost) was examined in the sensitivity analysis by adding a 'utility gain' in the first year of intervention to reflect short-term benefits of increased PA. For this data from a pragmatic RCT evaluating 'exercise referral' scheme in Wales (445) was used. The sensitivity analysis showed a parallel upward shift in NMB for the three BIs evaluated and did not change the adoption decision (Table 4.31).

As the VBI trial did not measure the effect of the intervention on quality of life, a PubMed search was performed using keywords 'pedometer' AND ('quality of life' OR 'EQ-5D') AND 'primary care' to identify any pedometer-based PA interventions measuring other health-related outcomes. The search found only one UK based study – the PACE-UP trial (483), a three-arm trial evaluating a pedometer-based walking intervention with or without nurse support (483). Harris and colleagues (483) measured the changes in health-related quality of life for the PACE-UP trial and found no significant effects on quality of life at either three months or 12 months follow-up. Utility changes at 3 months and 12 months for nurse support arm (pedometer plus nurse support) compared to the control arm were -0.01 (95%

CI: -0.03 to 0.01) and -0.01 (95% CI: -0.03 to 0.01) respectively (483). The health-related quality of life was measured via the EQ-5D-5L. This study (483) provided updated evidence on short-term health gains (utility boost) due to PA interventions. As the study did not find any significant short-term health gains from pedometer intervention (compared to control), the utility boost is not included in sensitivity analysis while updating the model.

5.4.4 The second iteration of the model

Similar to the analyses conducted in Chapter 4, the economic evaluation here is undertaken from the perspective of NHS with a ten-year time horizon. As per NICE recommendations, both costs and benefits (QALYs gained) were discounted at an annual rate of 3.5 per cent per year (2). The model was run probabilistically using a Monte Carlo simulation with 10,000 iterations to propagate the uncertainty in the individual model parameters. This gives a distribution of expected costs and expected outcomes (QALYs gains) associated with each PA intervention. The mean values of these 10,000 point estimates for costs and QALYs were used to calculate the mean cost-effectiveness ratio in terms of expected incremental costs associated with pedometer VBI compared to usual care per incremental QALYs gained. The joint distribution of incremental costs and incremental QALYs are presented through the cost-effectiveness plane (1) to illustrate the uncertainty associated with incremental costs and incremental QALYs.

The decision uncertainty associated with the cost-effectiveness of pedometer VBI compared to usual care is presented using CEAC (476). The CEAC shows the probability that pedometer VBI and usual care interventions are cost-effective at threshold values, i.e. the maximum willingness to pay threshold. A sensitivity analysis was performed around the assumptions on intervention decay rates and intervention repeat year. Two scenario analyses were performed around the assumptions on baseline PA measurement values for the VBI trial participants (as described in section 5.4.1). Finally, a value of information analysis was performed to re-address the research priority setting decision, i.e. whether there is value for collecting additional data.

The EVPI is the price that a decision maker would be willing to pay in order to completely resolving uncertainty in all input parameters that influence whether pedometer intervention is preferred as the result of CEA. The EVPPI gives the value of eliminating uncertainty in a subset of input parameters to the decision model (Chapter 3).

5.5 Cost-effectiveness analysis

Cost-effectiveness results were obtained from the 10,000 Monte Carlo simulations of the probabilistic model. The cost-effectiveness of pedometer VBI compared to usual care is estimated based on the updated meta-analysis of pedometer interventions (section 5.4.3.1). The base case analysis only uses PA measurement data at follow-up. In addition, the base-case analysis assumes that intervention effect is sustained for the first year then decays at a rate of 55% per annum.

5.5.1 Results of the base case analysis

Table 4-32 presents the mean costs, QALYs and net benefits at a willingness to pay threshold value of £20,000 per QALY and associated standard errors in the base case and scenario analyses. The base case results show that pedometer intervention was less costly (£11) and more effective (0.013 QALYs) than current practice. The 95% confidence interval around the incremental costs and benefits are -£229 to £202 and -0.017 to 0.043 respectively. Incremental costs and QALYs for two scenario analyses are similar to the base case results, i.e. pedometer intervention is less costly and more effective compared to usual care.

Table 5-14: Cost-effectiveness Results: Pedometer versus Usual Care (costs, QALYs and NBs)

	Mean cost (SE)		Mean QALY (SE)		Mean NB* (SE)	
Base case						
Current practice	£1,801	(618)	7.907	(0.236)	£156,340	(5,270)
Pedometer interventions	£1,790	(616)	7.920	(0.237)	£156,609	(5,289)
Scenario 1 - using baseline PA data from the PACE-UP trial						
Current practice	£1,801	(618)	7.907	(0.236)	£156,336	(5,271)
Pedometer interventions	£1,785	(614)	7.921	(0.238)	£156,643	(5,294)
Scenario 2 - using VBI pilot trial control group PA measurement at follow-up						
Current practice	£1801	(619)	7.907	(0.237)	£156,336	(5,272)
Pedometer interventions	£1787	(615)	7.921	(0.238)	£ 156,640	(5,293)

* NB at £20,000 per QALY gained

5.5.2 Probabilistic cost-effectiveness results (base case)

The Monte Carlo simulation produced a pair of 10,000 estimated cost and QALYS. The incremental costs and QALYs are plotted in the incremental cost-effectiveness plane (Figure 5-7). The incremental CE plane illustrates the existence and extent of uncertainty surrounding the incremental cost and effect (QALY gained). The plot shows that the points

scattered across all four quadrants of the CE plane indicating considerable uncertainty surrounding the extent of the differences in costs and QALYs.

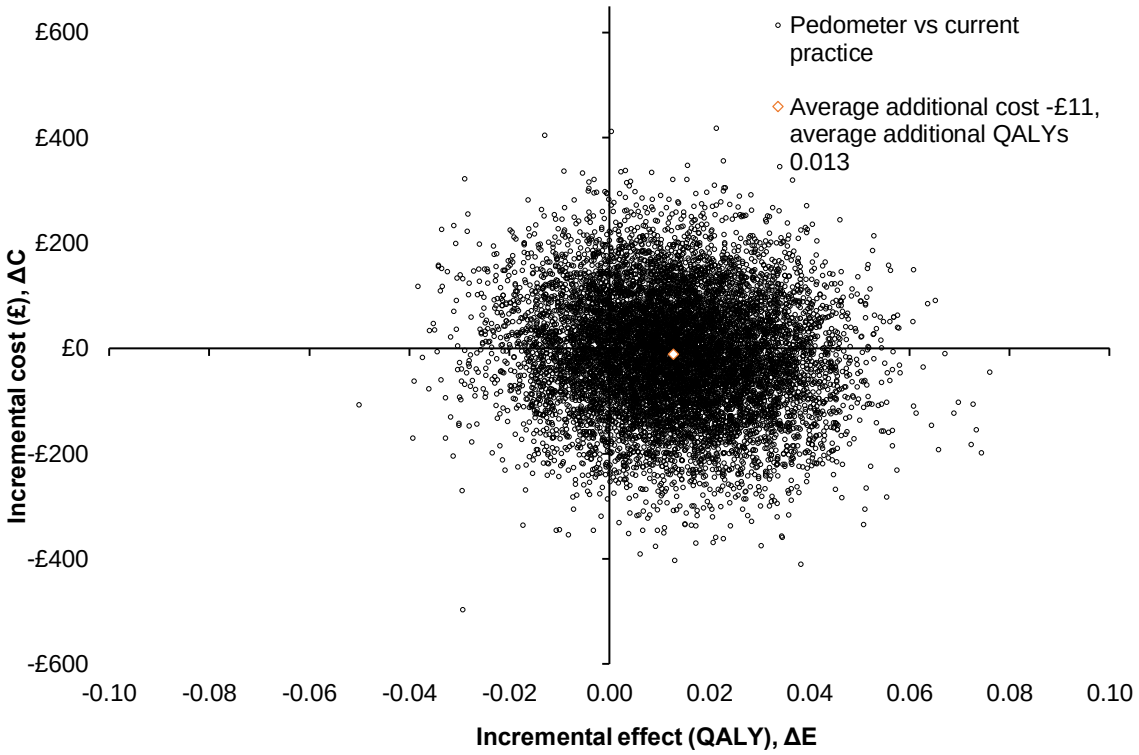

Figure 5-7: Incremental cost-effectiveness plane for comparison between pedometer and current practice

Of the 10,000 pairs of incremental costs and effects, almost half (43.9%) of the points are located on the South East quadrant indicating that pedometer intervention is likely to be more effective and less costly than current practice. Approximately one-third of the points (35.4%) are in the North East quadrant suggesting that pedometer intervention may be more effective and more costly than current practice. The remaining points are equally split between South West (10.1%) and North West (10.6%) quadrants.

The CEAC (Figure 5-8) represents the decision uncertainty surrounding the cost-effectiveness of pedometer intervention. In a situation where the decision maker is not prepared to pay any amount for additional QALY gains (i.e. the ceiling ratio is zero), the probabilities of pedometer and current practice being cost effective are 0.54 and 0.46 respectively. Assuming a ceiling ratio of £20,000 per QALY gained, the probability that pedometer intervention is more cost-effective than current practice is 0.78.

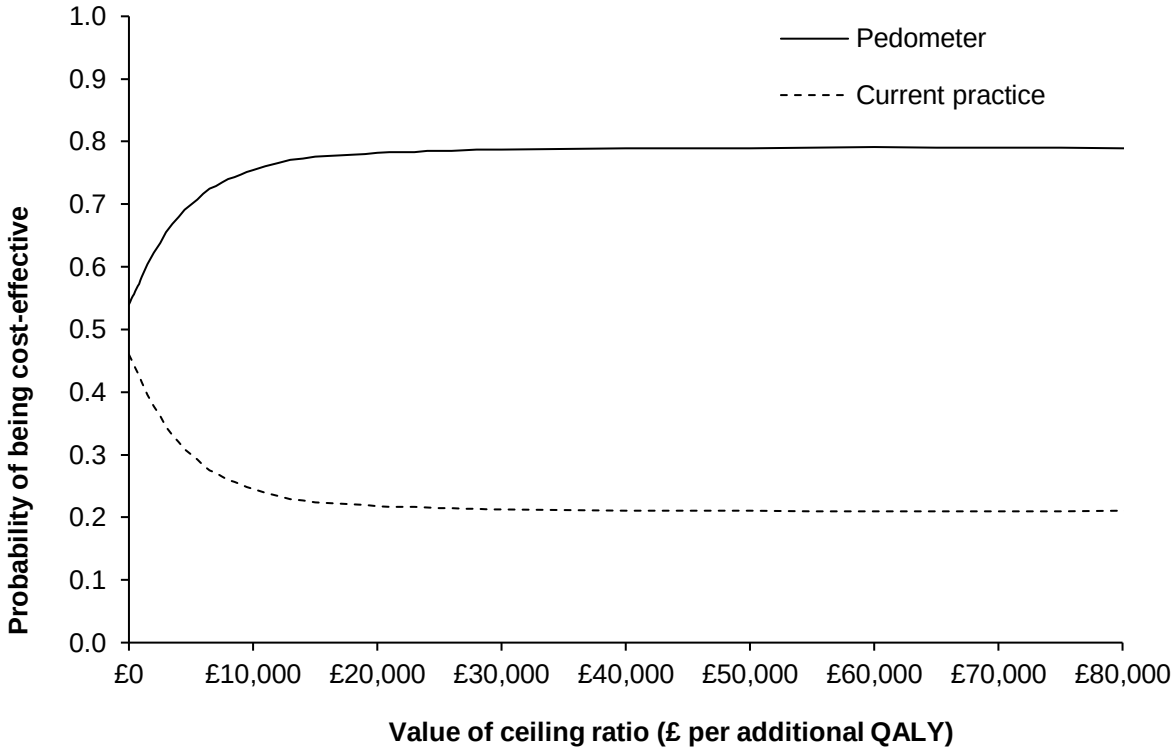

Figure 5-8: Cost-effectiveness acceptability curves (pedometer vs current practice)

5.5.3 Sensitivity analyses

Sensitivity analyses were performed to test the assumption used while updating the short-term effectiveness evidence (meta-analysis) of pedometer interventions. The results from the 10,000 Monte Carlo simulation using the updated evidence under two different scenarios (scenario 1 and scenario 2) are presented in Table 4-32. In addition, multiple CEACs were produced where the probability of pedometer intervention being cost-effective was plotted against the ceiling ratio (WTP threshold) for each assumption. The estimated NMBs for current practice and pedometer intervention under both assumptions were similar. Using baseline PA data from the PACE-UP trial (scenario 1) and using VBI pilot trial control group follow-up PA measurements (scenario 2) in the meta-analysis did not affect the general conclusion of pedometer intervention being less costly and more effective than current practice.

In the scenario analyses, the probability of pedometer-based VBI being cost-effective (Figure 5-9) was higher than the control group (health check only). This probability was slightly higher in scenario analyse 1 and 2 than base case assumption. It is because the intervention effect size was higher in both scenario analysis 1 and 2 than the base case

assumption. In addition, the effect sizes for scenario analysis 1 and 2 were similar (6.38 MET-hr and 6.46 MET-hr respectively).

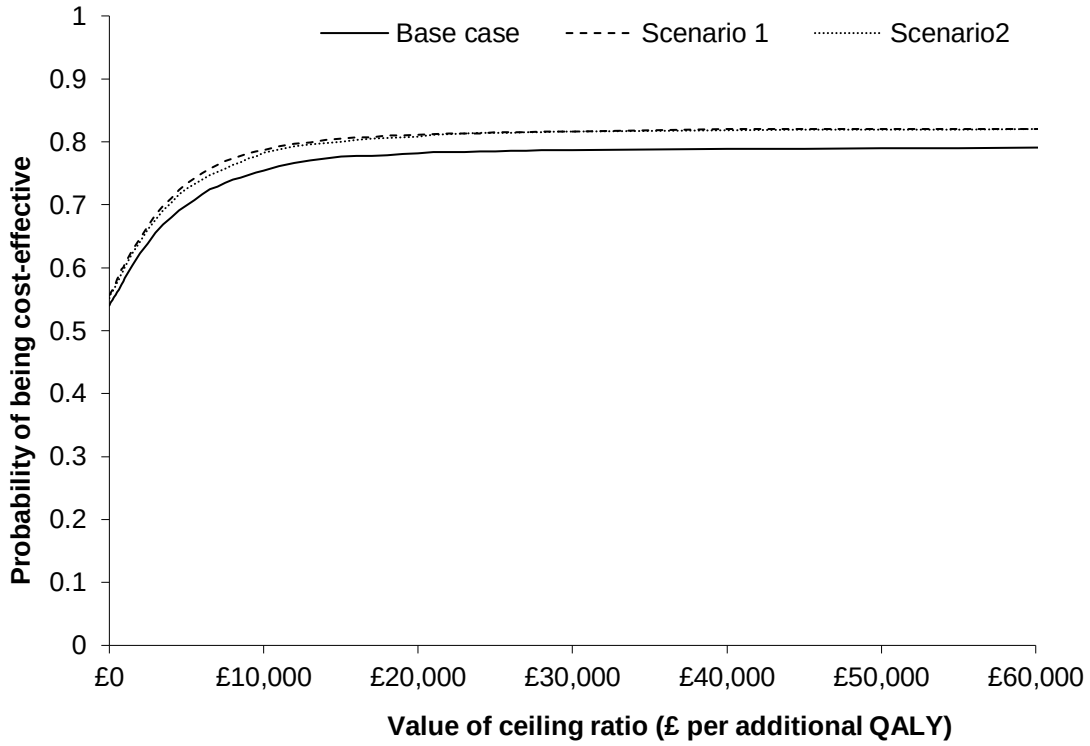

Figure 5-9: Multiple CEAC for different assumptions used while updating the evidence base for pedometers versus current practice

5.5.4 Scenario analyses

Scenario analyses were performed to test the effect of a change in intervention decay rate and intervention repeat years to expected net benefits. Figure 5-10 shows the effect of a change in intervention decay rates to expected NMBs. As expected, at a lower intervention decay rate the expected NMB of pedometer intervention was higher than the current practice. As the intervention decay rate increases, the intervention effects (MET-hour change) declines towards that of current practice. As a result, the expected NMB of pedometers and current practice are similar.

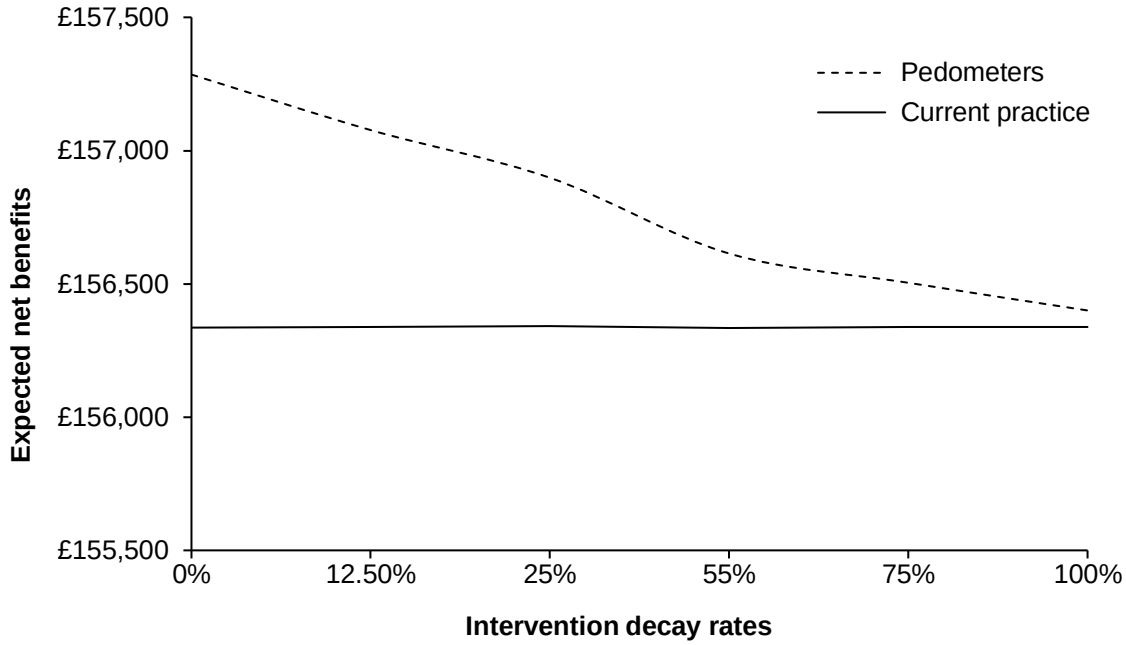

Figure 5-10: Sensitivity analysis of intervention cost-effectiveness to decay in intervention effects at a ceiling ratio of £20,000 per QALY

There is a lack of clarity on the extent of behaviour maintenance in PA interventions among the adult population (488), and PA interventions are not expected to have a lifelong change in PA behaviour. Scenario analyses were performed by varying the intervention repeat years (2, 5 and 10) to examine the optimal time to repeat pedometer intervention

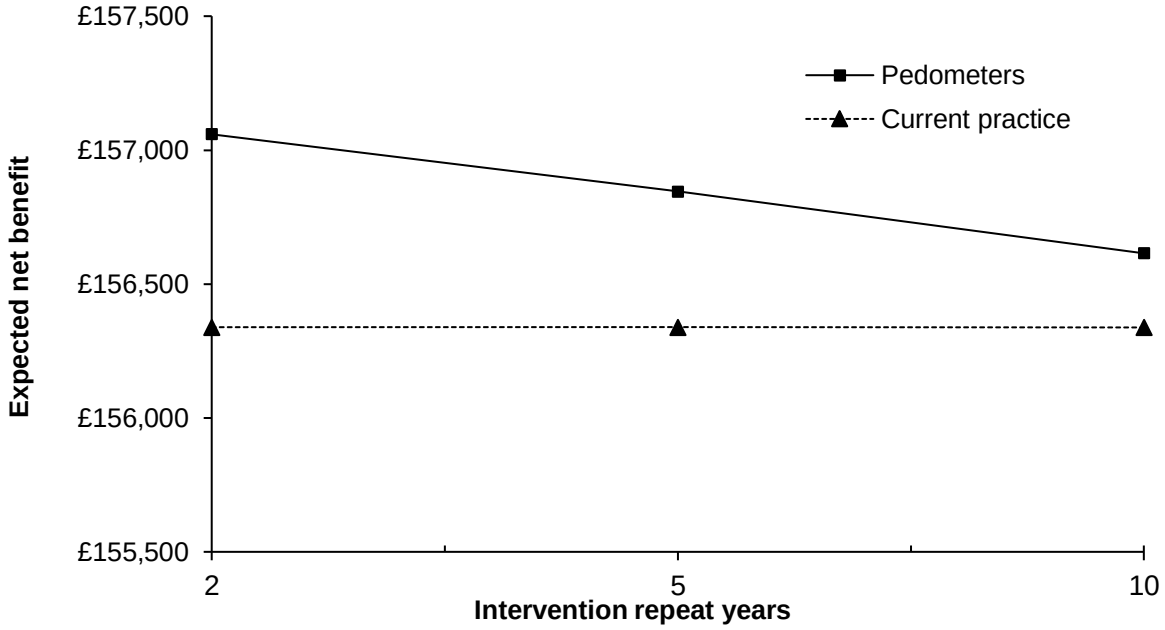

Figure 5-11: Sensitivity analysis – intervention repeat year: cost-effectiveness of pedometer intervention versus current practice at a ceiling value of £20,000 per QALY

Figure 5-11 shows the consequences of repeat years on expected NMBs. Pedometer intervention had the highest expected NMBs in all the three repeat year scenarios, and among the repeat years, pedometer intervention had highest NMB when the intervention was repeated once every 2 years.

5.5.5 Value of information analysis

Value of information is related to the value of reducing uncertainty such that a decision may include the option to acquire more information (see Chapter 3, section 3.3.3). The potential value of additional information is estimated by determining the value of acquiring perfect information (EVPI), as perfect information would eliminate the cost of uncertainty altogether. The per-patient EVPI when deciding between pedometers and current practice, over the ranges of NICE threshold values of £20,000 to £30,000 per QALY, ranges from £26 to £180 per NHS Health Check patient.

Figure 5-12 shows the relationship between population EVPI over 10 years and different values of the willingness to pay threshold per QALY. At a threshold value of £20,000 per QALY, the value of further research for the NHS Health Check population (19.06 million, Table 4.32) is £796 million. Here at a ceiling ratio of £20,000 per QALY, the probability that pedometer intervention is cost-effective is 0.78, and the probability that current practice is cost-effective is 0.22.

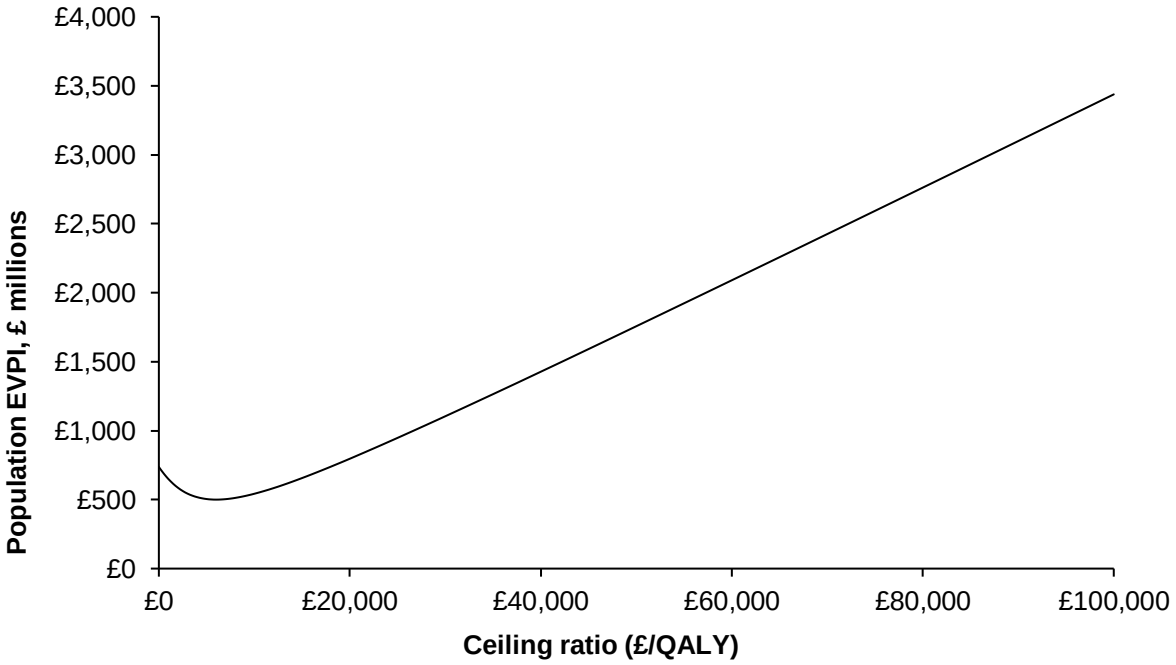

Figure 5-12: Population EVPI for pedometer intervention versus current practice (using updated evidence base)

As the population EVPI gives the upper limit for research into which the intervention is cost-effective, it is useful to consider which parameters this future evidence will be of most valuable. This is examined using EVPPI which provides the value of eliminating uncertainty in those individual or group of parameters. As in the first iteration of the model, six group of parameters are considered to indicate the maximum potential value associated with further data collection. The six groups of parameters are intervention effect, utility values, costs, the risk of MI, the risk of stroke, and parameters used in the SBP equation.

The computation of EVPPI requires a two-level Monte Carlo simulation, and an appropriate number of runs for inner and outer loops of the Monte Carlo Simulation should be chosen. Few runs in the outer loop result in a lack of precision while few runs in the inner loop result in a biased estimate of EVPPI (489,490). Furthermore, a larger number of interactions result in much longer computation time. Brennan et al. (159) carried out an empirical investigation on the impact of the number of inner and outer loop runs on EVPPI. They suggested that the number of inner and outer loops should not, in general, be equal and in most situations, 500 inner loops for each of the 100 outer loop iterations lead to convergence and sufficiently accurate EVPPI results. The EVPPI was run with a relatively high number of simulations – 1000 inner loops and 500 outer loops for each of the six parameter groups using a ceiling ratio of £20,000 per QALY.

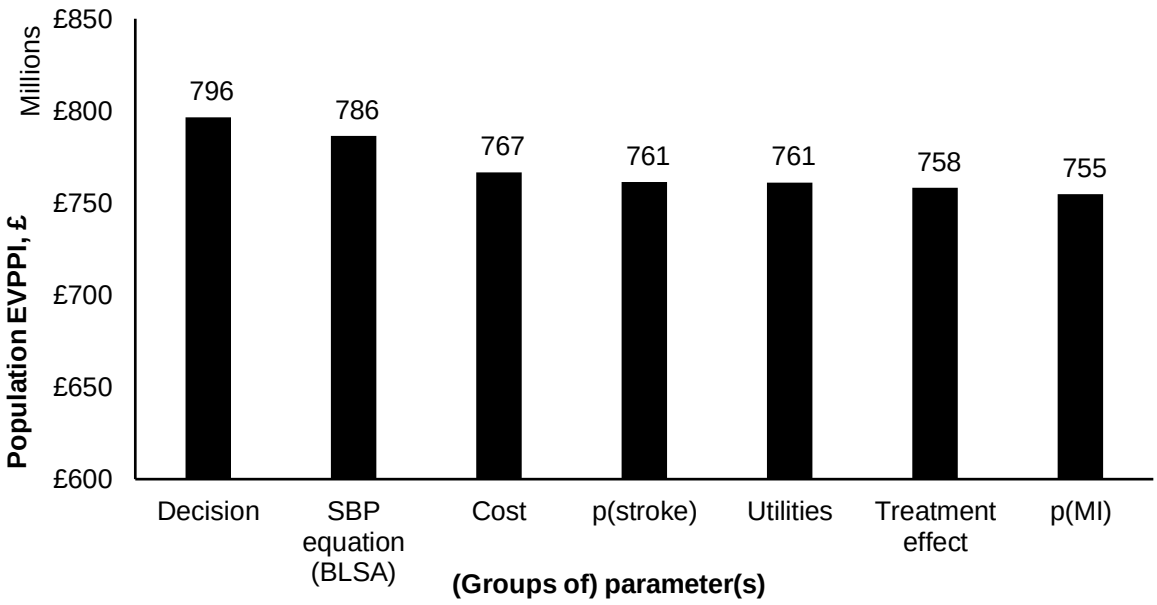

Figure 5-13: EVPPI results for the base case at a ceiling ratio of £20,000 per QALY: NHS Health Check population

Population EVPPI for different parameters with a threshold value of £20,000 per QALY is given in Figure 5-13. The results of the EVPPI analysis indicates that if further data collection were to provide evidence on the parameters used in the SBP prediction

equation would be worth a maximum of £786 million for the NHS Health Check population. Other group of parameters also had similar per-person EVPPI, but the population EVPPI for cost parameters was slightly higher (£767 million) than other parameters (risk of stroke, utilities, treatment effect and risk of MI).

5.6 Discussion

The decision model developed at the outset of this thesis has been employed iteratively to handle the developing and evolving evidence base of very brief PA interventions in primary care. This iterative approach started with reviewing the existing evidence on the cost-effectiveness of brief PA interventions (Chapter 2). The review included both trial- and model-based economic evaluations of PA interventions in primary care or community setting. The evidence in addition to effectiveness evidence of brief PA interventions was used to develop a decision model to estimate the long-term costs and benefits associated with brief interventions (BIs) promoting PA.

In this chapter, a second iteration of the decision analytic model was performed to re-address the adoption and research priority setting decisions. The first iteration of the model (Chapter 4) evaluated three BIs in PA promotion using effectiveness evidence from the meta-analysis of RCTs. In the original analysis, it was demonstrated that among the three BIs (exercise advice/counselling in primary care, action planning interventions, and pedometer interventions) considered, pedometer BI was the cost-effective way of promoting PA in primary care, i.e. had the highest expected net benefits amongst the BIs considered. The initial VoI analysis demonstrated there was value in collecting additional information particularly in the effectiveness of pedometer intervention. Following the collection of effectiveness evidence and analysis of data from the VBI trial, effectiveness and cost-effectiveness of pedometer-based VBI in primary care was evaluated, and the model was re-run updating the evidence base. The pedometer meta-analysis (151) used in the original analysis in Chapter 4 was updated using the effectiveness evidence from the VBI trial (457).

Results from the second iteration of the model showed that pedometer VBI is cost-effective, but there was increasing uncertainty surrounding the incremental costs and QALYs. The scenario analyses exploring the impact of model assumptions on the maintenance of intervention effects over time and intervention repeat year showed, as expected, similar results observed from the first iteration of the model. That is pedometer-based VBI become less cost-effective at higher intervention decay rates, and repeating the intervention once every two had the highest expected NMB.

Only two pedometer-based PA interventions estimated the long-term cost-effectiveness with QALY outcomes in primary care. In their PACE-UP trial, Harris et al. (483) estimated the long-term cost-effectiveness of the pedometer-based intervention. Their study reported an ICER of £16,368 per QALY for pedometer plus nurse support intervention compared to the control group. However, when postal delivered pedometer intervention was considered, the nurse-support intervention group was not cost-effective, i.e. postal delivery group dominated the nurse-support group. Harris et al. used previously published Markov model (136) which included two PA status – remained inactive and became active as a result of intervention in the run-in period (first year). The activity level was defined as achieving ≥150 minutes of MVPA per week. The classification of activity levels utilised self-reported data captured by the short International Physical Activity Questionnaire (IPAQ) to estimate the odds ratio for moving from inactive to an active health state. The VBI model included intervention effects (input) in terms of MET-hours and included more disease conditions that had known links to physical inactivity.

Over et al. (146) estimated the long-term costs and effects of counselling and pedometer use to increase PA in the Netherlands and reported an ICER of €11,100 per QALY (£9,910, 2015 price). At a ceiling value of €20,000 per QALY, the pedometer plus counselling intervention had a probability of 0.66 to be cost-effective which was similar to the present study. Both of the studies described above did not perform VoI analysis.

The VoI analysis conducted in this chapter suggested that there would be value in collecting additional evidence. The population EVPI at a threshold value of £20,000 per QALY was £796 million for the Health Check population over ten years. At the same ceiling ratio, the population EVPI in the original analysis was £1.85 billion – when converted to 2015 prices the value was £1.96 billion. The updating of the meta-analysis using data from the VBI trial reduced uncertainty surrounding the intervention effectiveness hence the lower population EVPI compared to the original analysis. Of the nine studies included in the updating of the pedometer meta-analysis, the VBI trial was the largest study (n=859). Population EVPPI values for six parameter groups were similar, but SBP prediction equation had slightly higher per-person EVPI than other parameters. It does not necessarily mean that we need a large RCT to collect additional information on the parameters used in the SBP equation. Instead, it would be much efficient to and cheaper to determine the parameter values for the SBP prediction equation from observational studies. As discussed in Chapter 4, an attempt was made to calculate the expected value of sample information and expected net gain of sampling, but it was not computationally feasible to generate meaningful and stable results.

Having conducted an iterative economic evaluation of (very) brief pedometer intervention, Chapter 6 presents the practical realities of applying iterative approach, lessons learned from the case study and the recommendations for future economic evaluation of very brief interventions promoting physical activity with evolving evidence.

Chapter 6 Discussion and Conclusions

6.1 Introduction

The aim of the thesis was to examine the feasibility of using an iterative framework for economic evaluation in healthcare. The thesis used a case study for this purpose and further explored the practical and methodological issues of applying an iterative approach to economic evaluation, and considered potential reasons as to why the framework has not been widely implemented.

The iterative approach to economic evaluation has been proposed as good practice to appraise health technologies or interventions (4-6,43,72,74,82,491). The implementation of this approach starts with evidence synthesis and decision analytical modelling to evaluate the cost-effectiveness of indicative studies, and progresses to more rigorous assessments, updating the decision over time as new evidence becomes available. Decision analytic models play a key role within the iterative framework and such modelling exercises carried out prior to conducting the primary research allow explorative evaluation of the cost-effectiveness of healthcare technologies or interventions. The PSA and VoI analysis enables an assessment to be made with regards to the sample uncertainty surrounding the cost-effectiveness decision (43). Using the PSA results, VoI techniques help to determine whether future research is worthwhile, help explore the type of research required to address uncertainty (feasibility or pilot studies) and help design a primary study to collect additional information. This framework allows incorporation of best available evidence at the time of decision making. Reiteration of the entire process provides greater confidence in cost-effectiveness estimates used to inform decisions, and it potentially can be performed throughout the lifecycle of the technology in order to optimise the use of health care resources (6,43,72,491). Despite the aforementioned benefits of applying the iterative framework in economic evaluations, the application of this approach for the purpose of informing policy decisions in healthcare is limited. Economic analyses developed alongside clinical trials are often conducted as a one-off exercise as they are usually funded to justify reimbursement decisions. Thus, such studies rarely use pre-trial economic modelling and VoI method.

This thesis explored the feasibility and benefits of applying the iterative framework in practice to evaluate the cost-effectiveness of healthcare interventions, using a case study example. This final chapter outlines the main results of this research project, discusses the methodological challenges, draws conclusions and makes recommendations for

further research. The first part provides an overview of the thesis by summarising aims, methods and main results. This is followed by a section that discusses the findings and relevant observations, as well as a discussion of the implications of the thesis and an identification of areas for future research.

6.2 Summary of the main findings and limitations

Chapter 1 introduced the basic concepts in economic evaluation in healthcare, the use of the iterative framework, the overall aims of the thesis and an overview of the structure of the thesis. The chapter started with providing a background to economic evaluations in health care along with key steps for conducting an economic evaluation. It also described the trial based approach to economic evaluation in which economic evaluation can be conducted using existing evidence on resource use, cost, intervention effects and quality of life. Economic evaluations provide a framework that helps decision makers in deciding which intervention or health technology to adopt from a list of alternative strategies. The process of decision making in health care should, ideally, be iterative (i.e. not static) to take account of new evidence and changes in circumstances. For example, there can be incremental innovations such as the availability of new therapies or novel approaches to the delivery of care. Consequently, the iterative approach to economic evaluation is purported to represent good practice for the appraisal of health technologies or interventions on an on-going basis.

As the research questions explored the current research gap, i.e. limited application of the iterative framework in economic evaluation of healthcare interventions, Chapter 2 assessed the current economic evidence on BIs promoting PA in primary care and community setting. This literature review included both economic evaluations conducted alongside trials as well as model-based economic evaluations and appraised them against the Drummond checklist (24). The review found that brief interventions such as exercise advice were inexpensive, can increase individuals' PA at reasonable costs and are cost-effective, given commonly accepted thresholds. This review highlighted methodological issues that limited the ranking of 'best bet' BIs from a list of interventions evaluated. Other issues identified were the quality of evidence used in model-based economic evaluations and assumptions around the maintenance of PA levels beyond the trial period. This suggested a need of a single framework so that all the interventions can be compared, i.e. a decision analytic model to transform the short-term (costs and intermediate disease-specific) outcomes into longer-term outcomes (QALYs). However, it was difficult to determine whether the interventions were truly brief, i.e. <30 minutes in duration according to the NICE definition (112).

Chapter 3 provided an overview of the iterative framework and described the stages involved in detail. VoI method has been proposed as a systematic decision analytic approach to understand the need for further research and play a key role within the iterative process to identify the focus of research and optimal research design. The merits and drawbacks of using such a method within the iterative framework were discussed. From the existing literature, it was not clear how the VoI method was used in an iterative process. Thus, a literature review was performed with an aim to explore how the VoI method was used within the iterative process to inform further research. The literature search found that when mapped with the 5 stages of the iterative framework, only two studies reported all the five steps of the iterative process. The analysis showed that the adoption and application of VoI approach in healthcare is still limited, and in most cases, studies do not proceed further after identifying future research priorities.

Chapter 4 corresponds with stages 2 and 3 of the iterative approach in economic evaluation involving the synthesis of evidence and development of a decision analytic model. This chapter described the decision problem, provided the rationale for using a decision model, detailed the development of this model to assess the cost-effectiveness of brief PA interventions in primary care and, in doing so, demonstrated the benefits of using an iterative process for synthesising existing evidence to inform the model. Additionally, the chapter examined the feasibility of including disease conditions that were shown to have links with physical (in)activity, the viability of modelling techniques given the availability of evidence and practical issues regarding the calibration of a complex decision model. A probabilistic microsimulation model was developed for this purpose using the available evidence in a systematic manner.

Following the development and calibration of the decision model, three ‘classes’ of brief PA interventions were evaluated. The effectiveness evidence for these ‘classes’ came from systematic reviews and meta-analysis of RCTs. Within the meta-analysis, the studies included were somewhat heterogeneous. Uncertainty in the model results was explored using probabilistic sensitivity analysis and scenario analyses. Cost-effectiveness acceptability curves were used to summarise decision uncertainty followed by the use of VoI techniques to examine the value in future research. The results of the VoI analysis supported a case of primary research. Having established that further research in this area is worthwhile, the EVPPI analysis found that treatment effect (of pedometer intervention) parameter had the highest EVPPI value. This finding indicates that primary research should focus on the collection of data to examine the treatment effect in order to reduce uncertainty associated with the decision problem. However, EVPPI value is the necessary but not sufficient condition for conducting further research as EVPPI results only give a value in reducing the uncertainty in a parameter or groups of parameter. EVSI

and ENBS provide sufficient condition as to whether it is beneficial to conduct further research on this parameter but these analyses were not performed due to computational burden.

In the context of this thesis, it would have been preferable to inform the design of the trial following an iterative approach whereby EVSI was undertaken. However, this was not feasible within the context of the VBI study due to timing issues. At the time when pilot trial (456) conducted as a part of wider VBI programme grant selected pedometer VBI to test in a full-scale trial, the VoI results from the first iteration of the model were not available. As a result, the VoI analysis was not able to inform the design of the trial by estimating the optimal sample size. Chapter 5 provided an overview of the case of VBI explanatory trial following the iterative process and evolving VBI evidence base. This chapter presented the within-trial cost-effectiveness results comparing pedometer-based VBI 'Step It Up' to usual care (i.e., NHS health check alone). The within-trial analysis showed no significant differences between groups in objectively-measured PA and healthcare resource use at three-month follow-up. The 'Step It Up' intervention costed £18.04 more per patient (using the NHS perspective), and participants receiving the intervention increased their PA level by 1000 step counts per day at an incremental cost of £96 above the control arm. As quality of life data, such as EQ-5D, was not collected alongside the VBI trial, within-trial cost-effectiveness results were not directly comparable with the results from the first model iteration (Chapter 4).

In addition to performing a within-trial economic analysis, Chapter 5 incorporated evidence from the VBI trial into the decision model reported in Chapter 4. The pedometer meta-analysis was updated to incorporate evidence from the VBI trial, and the model was re-run. This was done to readdress the adoption and research priority setting decisions following incorporation of new evidence. Results from the updated decision analytic model showed that pedometer VBI is cost-effective, but there was increasing uncertainty surrounding the costs and QALYs. The VoI analysis showed that there is value in conducting further research and EVPPI statistics indicated that conducting research to determine parameter values for SBP prediction equation would be much efficient. This does not necessarily mean that we need a large RCT to collect additional information on these parameters and it would be much more efficient to determine parameter values for the SBP predication equation from observational studies.

6.3 Reflections on the iterative framework in an economic evaluation

This thesis explored the feasibility of applying the iterative framework in evaluating healthcare interventions. This section now presents a reflection on the theoretical and conceptual understanding highlighted in Chapter 3 in relation to the application of the iterative framework in VBI study.

6.3.1 Time constraints

The main aim of the VBI programme grant was to develop and evaluate VBIs to increase PA that could be delivered in routine primary care consultations such as NHS health check. Before conducting a definitive trial, the VBI study conducted a pilot study (449) to test feasibility, acceptability and potential efficacy of promising VBIs. Parallel to the pilot study, a decision analytic model described in Chapter 4 was under development. However, the selection of pedometer VBI for the main trial happened before conducting the VoI.

The development of the model and calibration process took longer than expected. In the model, the effect of PA on the risk of CVD conditions occurring was mediated via changes in the risk factor values. Systematic reviews and meta-analyses of epidemiological studies (section 4.4.1.2) quantified a direct link between PA and health outcomes, i.e. reduced risk of diseases such as CVD and cancers with an increase in PA. Additionally, the model included more than ten co-morbidities, and varied sources were used to inform the model parameters. Model calibration ensured that model predictions are consistent with the observed data from epidemiological studies. The complexity of the decision model meant that model calibration process took a long time (approximately 80 processor days), even though it was developed in a modular form. Initially, the Nelder-Mead algorithm was used to calibrate the model, but it could not further minimise the goodness of fit value after 703 iterations with a weighted mean deviation of 18%. As a result, the random search method, a less efficient but widely used method in health economics was chosen. This resulted in a longer time to develop the model and perform VoI.

Although preliminary results from the early iteration of the model indicated that the pedometer intervention was a cost-effective intervention amongst the BIs compared, it was not possible to influence the design of the trial (in iterative fashion) and determine sample size. The sample size calculation for the trial was thus based within the context of a frequentist trial design. In the case of VBI study, funding was already secured to conduct

a trial. However, in practice, this may not be the case as once the modelling study identifies future research priorities, funding is sought for the research. In theory, VoI results could be used to determine the funding decisions or as an additional input in the research prioritisation process. In their pilot study, Claxton et al. (72) showed that with very short timeliness, it is possible to undertake VoI analysis that can feed into the priority setting process. The model they used in their case study were Markov models compared to patient-level simulation model developed in Chapter 4. Setting up and implementing Markov models are much easier and time efficient compared to discrete event simulation models, and the VBI model included more than ten comorbidities. Claxton et al. also highlighted the issues around time frames for carrying out VoI in the context HTA programme in the UK. Systematic reviews and decision analytic modelling that are typically carried out before conducting VoI analysis take time. In the case of VBI study, evidence synthesis and decision analytical modelling stages of the iterative process had a short time period to contribute in the design of the trial. As mentioned earlier, within the time frame of selecting a candidate VBI for exploratory study (main trial), it was not possible to fully explore VoI techniques and estimate the optimal sample size of the VBI trial.

6.3.2 Computation

Despite a strong case being presented in this thesis in support of using an iterative framework, there was difficulty in employing VoI methods particularly an EVSI approach. Conducting VoI analysis was time-consuming and computationally expensive. For example, conducting EVPPI for a parameter or a group of parameters took around 1,100 processing hours. Although the research had access to high-performance computing (HPC) cluster and the model codes were parallelised, it was still computationally expensive. Furthermore, model calibration was also computationally expensive. The more efficient Nelder-Mead search algorithm did not converge as a result a less efficient directed random search method was chosen which resulted in a longer processing time, approximately 80 processor days.

The EVSI analysis is a worthwhile and useful exercise to inform the design of a future trials. Although an attempt was made to conduct an EVSI analysis, it was not possible to generate meaningful and stable results given the limited resources available, i.e., time constraints and the number of computer nodes available per user on the HPC cluster. EVSI techniques are computationally heavy as the analysis require two-level expectations (Monte Carlo simulations) to be evaluated implies an additional level of computational burden (161). Previous literature reviews on the use of VoI methods also highlighted this challenge (166,167).

6.3.3 Practicality and ease of use

The application of the first two steps of the iterative framework, i.e. systematic review and decision analytic modelling, required a fair amount of time. There was a steep learning curve to start writing model codes in a new programming language, R. Most of the time was devoted to assessing the papers included in these reviews and translating PA outcomes into MET-hours. Systematic reviews and meta-analyses assessing the effect of BIs reported their effect size in mean difference or standardised mean difference. As a result, a common exposure metric, such as MET-hour was required to allow comparison of results. In addition, the PA exposure results reported in the meta-analyses were not comparable. Translating PA outcomes into METs took a considerable time. Besides this, structuring the decision model, populating the model and running PSA and VoI analyses took considerable amount of time. Calculation of EVPI was relatively straightforward. However, EVPPI analysis was more complex and time consuming. Initially, the model codes were implemented sequentially which meant that it took a considerable amount of time to run the EVPPI analysis. To reap the benefits of the HPC cluster, model codes were parallelised so that more than one computer node could be used to run the model. This required additional skills such as vectorising R codes and familiarisation with the cluster so that the operations occurred in parallel.

6.4 Strengths and limitations

In the context of a resource-constrained healthcare system, resource allocation decisions need to be guided by evidence on the expected costs and benefits of competing activities. An iterative approach to economic evaluation provides a framework that enables decision to be updated by incorporating new evidence when such evidence becomes available. This framework supports the process of gathering new information and, potentially, reducing uncertainty in order to improve decision-making. Clearly, if the VoI analysis suggested there is no value in conducting further research, the process stops at stage 3, and the model is updated once new evidence is available. Most of the studies identified that recommended further research did not proceed to explain the implications that this would have for the decision-making process. At the time the present analysis took place, the study was funded and on-going thus the practical application was carried out in a prospective manner.

There were limitations to the approach applied while carrying out this research. First, the baseline population parameters were determined mostly by age and gender that means it does not allow for interdependencies, for example, BMI may have a role in determining

SBP in addition to age and gender. This would require access to and analysis of data from longitudinal studies. Indeed, an attempt was made to get access to the Fenland Study, a cohort study that collects data on key lifestyle determinants of metabolic disease, however, the application did not receive a favourable outcome. As a result, baseline characteristics were sampled using the health survey for England summary statistics (368). The first iteration of the model used 2011 costings but the within trial and second iteration of the model used 2015 costings. It would have been preferable to use the same price year for both iterations and updating the base year used in the first iteration of the model. However, due to practicality issues, availability of time being the main factor, this was not possible.

A key assumption was made in the evaluation of BIs related to the sustainability of the intervention effect. There is little known about the sustainability of PA interventions beyond 12 months. The existing literature suggested that PA disengagement usually occurs six months after PA intervention ended (492) and cost-effectiveness of PA interventions decrease over time (143). In the base case analysis, it was assumed that the intervention effect decays at a rate of 55% after one year of receiving the intervention. This assumption was based on two previously published modelling studies conducted in this area (141,146). From the search of the literature in Chapter 2, it was clear that cost-effectiveness of BIs decrease over time unless there is continued contact so that activity levels are maintained over time. Thus, it is reasonable to assume that without continued contact, it is difficult to maintain the same PA levels post-intervention. Next, different PA interventions involve different behaviour change components, and it is possible that the same decay rates may not be true for all BIs. However, given the limited evidence available, the same rate was applied for all BIs, and different decay rates were tested in sensitivity analyses to explore the likely impact on the adoption decision. As expected sensitivity analyses suggested that BIs are more cost-effective at lower rates.

Due to time constraints and practical reasons, the second iteration of the model only used updated costs and intervention effects. A literature search was carried out to synthesise evidence concerning PA and health that captured studies published up to January 2015. In the past 2 years, five systematic reviews and meta-analyses were published. These recent studies examined the dose-response association between PA and risk of type2 diabetes (493-496), CVD (493), IHD (495), stroke (495), heart failure (497), breast cancer (495), and colon cancer (495). Four meta-analyses examining the incidence of type 2 diabetes and PA suggested a (non-linear) curvilinear dose-response curve for PA and incidence of type 2 diabetes. While calibrating the model, RRs of CHD and stroke were used, and these values were 0.86 and 0.86 for 11.3 METs and 11.5 MET-hr/week respectively relative to 0 MET-hr/week. In their meta-analysis, Kyu et al. (495) reported

an RR of 0.837 and 0.843 for IHD and stroke respectively for 600-3999 MET-minutes/week relative to inactive (<600 MET-minutes/week). The PA category included in this analysis (600-3999 MET-minutes/week) refers to the lower levels of activity category. The results of new meta-analyses that assessed the association between PA and cardiovascular, as well as results for the association between PA and stroke events, were similar to those employed in the model.

However, the effect of PA on the incidence of type 2 diabetes seemed more favourable than the value used in the model. The model used estimates derived in a meta-analysis by Jeon et al. (296) that were based on dose-response data and reported a reduction of 11% for type 2 diabetes among those who achieved 11 MET-hr/week relative to an inactive adult. However, the meta-analyses published after the study by Jeon et al. showed a reduction in risk ranging between 16% (495) to 26% (493,494). This suggests the benefits of PA on the incidence of type 2 diabetes were underestimated in the model. However, VBIs evaluated in the model did not have a large effect size and the dose-response equations used were not linear (i.e., curvilinear) so one would expect no significant changes in terms of health outcomes. The RR estimates from Kyu et al. (495) study for breast and colon cancer were similar to those used in the model. Additionally, the current analysis might have underestimated the potential impact of PA on other disease conditions, most notably mental health. Mental health was not included in the model as prevention of depression due to PA is still a subject of debate (440,441), and a clear dose-response relationship between PA and mental health outcomes was not identified.

The model uses a time horizon of 10 years which may have excluded the long-term benefits of increasing PA. Using a longer time horizon would require additional assumptions, for example on the maintenance of PA and the study population demographics. Thus, a pragmatic approach was employed to avoid the additional computational burden and the additional structural uncertainty associated with a longer time horizon. Lastly, this study performed a decision analysis from a healthcare provider's perspective (i.e., NHS and personal social service), in order to inform policymakers in the UK. There may be costs that fall outside the scope of this approach such as costs associated with productivity loss or out of pocket expenditures incurred by the participants.

6.5 Areas for further research

6.5.1 Fully exploiting VoI within an iterative context

In this thesis, due to increased computational demands and timing issues, it was not possible to undertake EVSI or ENBS in order to determine an appropriate research design and sample size of a trial. The results from the original iteration of the model indicated that there is further value in collecting additional information to reduce decision uncertainty and the EVPPI results showed that, of the six parameters estimated, the treatment effect parameter had the highest population EVPPI value. An additional study to estimate this parameter would cost less than £708 million at a ceiling ratio of £20,000 per QALY. The EVSI analysis, which is the necessary condition, was needed to inform the design of the study. If funding were available for further research in this area (physical activity), the model developed here could be simplified and used to fully exploit the iterative framework by extending VoI analysis to undertake EVSI and ENBS. This will help to determine the design and sample size of a new study.

Furthermore, it would be ideal to update the decision model with newly available information, for example, updated information is available on the dose-response relationship between PA and health outcomes which the second iteration of the model did not incorporate for pragmatic reasons. Owing to the high computation costs associated with VoI analysis, in recent years that has been a progressive evolution and simplification of the methods (498-500), and development of a computationally efficient method for EVSI analysis are underway (169,501). When such computationally efficient methods are available, it will make the full exploitation of VoI methods within the iterative framework less burdensome.

Next, from the literature search conducted in Chapter 3, it was not clear how decision makers and funding bodies, such as the NICE, use VoI results to inform decisions or whether VoI results are helpful in research prioritisation and funding decisions.

6.5.2 Future economic evaluation of PA interventions

In this thesis, just one case study was employed to examine the feasibility and suitability of iterative framework to evaluate a public health intervention characterised by evolving evidence and uncertainty. More case studies in this area would provide further insight into the practicalities and other issues associated with applying the framework.

One of the issues in PA modelling is the maintenance of intervention effects over time. At the time of writing, there is a lack of accessible longitudinal data available for estimating changes in PA levels over the course of a lifetime. Cross-sectional studies, such as Health Survey for England provide a snapshot of the prevalence of PA in different age groups and gender. However, this approach is not able to quantify the trajectories of PA levels and very few economic evaluations of PA interventions estimating long-term costs and health outcome associated with PA intervention considered this aspect by applying different PA maintenance rates post-intervention. For example, in their base case analysis, Cobiac et al. (141) used 50% and Over et al. (146) used 55% decay in intervention effects after one year. Existing evidence suggests that maintenance of behaviour changes over time i.e. changes in activity levels, in the long-term is challenging (96,151). Furthermore, PA interventions are complex public health interventions involving different behaviour techniques such as goal setting, self-monitoring and motivational interviewing. Such interventions have different 'active ingredients' that bring about behaviour change. As a result, maintenance of PA effects over time may differ between BIs.

The VBI trial found no effect of pedometer-based VBI in the NHS health check population. The target population, i.e. apparently healthy 40-74 year olds were already relatively active compared to the general population, and as such, the intervention may have limited capacity to impact on PA. However, this does not take other effects that NHS health checks may have into account. Brief interventions could potentially lead to increases in PA levels in older adults and people with long-term conditions.

6.5.3 Policy implications

This thesis showed that application of the iterative framework would enable a more dynamic decision-making approach because it accounts for new evidence and changes in circumstances. The analysis showed that the two-year time point is the optimal time to repeat brief PA interventions in primary care. Given the fact that the NHS health check happens every five years, financial constraints in the NHS and recent innovation/application of digital technologies in health care, it could be possible that such digital interventions may support more patient engagement. This engagement would allow offering repeated VBIs or referral to follow-up support. Interventions such as mobile health apps have the potential to support people, for example, by offering advice on increasing their PA levels, using prompts or cues and signposting to PA services. However, the uptake of new interventions such as these would be conditional on the availability of robust evidence demonstrating that they represent a cost-effective use of NHS resources.

6.6 Conclusions

This thesis discussed and demonstrated the feasibility of applying an iterative framework in economic evaluation through a case study of practical application. The thesis showed that it is feasible to apply the framework while evaluating public health interventions and decision models could be employed at an early stage in this process. Decision modelling and value of information estimates in particular help to explore uncertainty and determine whether conducting further research is worthwhile. This approach provides a framework that allows the synthesis of existing available evidence and incorporates evolving evidence in order to reduce uncertainty and make informed decisions. Although there are several merits of applying this framework there are also a few drawbacks. These include time constraints, not being able to follow the steps of the iterative process sequentially and not being able to fully exploit the VoI methods. Undertaking VoI analyses, particularly EVSI, is challenging due to computational demands which limit their application in practice to inform the design of future trials. Development of new, computationally efficient methods for EVSI analysis may overcome this drawback.

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Appendix A: Literature review on economic evidence of brief PA interventions

A1 Search strategies for identification of literature on economic evidence of brief physical activity interventions

Medline, Embase, PsycINFO (via OvidSP)

1. physical exertion/
2. exp physical fitness/
3. exp Physical Education/ and exp Training/
4. exp Sports/
5. dance/ or exp recreation/
6. exp exercise/
7. exp Exercise/ or exp Physical Activity/
8. (physical* adj5 (fit* or train* or activ* or endur* or exert* or educat*)).ti.
9. (exercis* or danc* or sport* or walk* or bicycl*).ti.
10. ((lifestyle* or life-style*) adj5 activ*).ti.
11. ((lifestyle* or life-style*) adj5 physical*).ti.
12. inactiv*.ti.
13. (sedentary adj5 (lifestyle* or life-style* or population* or occupation* or behav*)).ti.
14. or/1-13
15. (increase* or promot* or improv* or prevent* or reduc*).ti.
16. (intervention* or advis* or advice or counsel* or prescri* or educat* or program* or scheme*).ti.
17. ((brief or opportunist$ or concise or short or direct or lifestyle or written or oral or verbal or personali?ed or individuali?ed) adj2 (advice or counselling or counselling or negotiation$ or guidance or discussion$ or encouragement or intervention$ or program$ or meeting$ or session$)).ti,ab.
18. (health adj5 (promot* or behav*)).ti.
19. (prevent* adj5 medicine).ti.
20. (behav* adj5 (chang* or modif*)).ti.
21. ((lifestyle* or life-style) adj5 chang*).ti.
22. ("motivational interview*" or "motivational counselling" or "motivational counseling" or "motivational intervention*").ti.
23. exp Health Promotion/
24. exp Health Behavior/
25. exp Preventive Medicine/

26. exp Counseling/
27. or/16-26
28. 14 and 15 and 27
29. economics/
30. "costs and cost analysis"/
31. (economic$ or cost or costs or costly or costing or price or prices or pricing).ti,ab.
32. (expenditure$ not energy).ti,ab.
33. value for money.ti,ab.
34. budget$.ti,ab.
35. or/29-34
36. ((energy or oxygen) adj cost).ti,ab.
37. (metabolic adj cost).ti,ab.
38. ((energy or oxygen) adj expenditure).ti,ab.
39. or/36-38
40. 35 not 39
41. 28 and 40
42. letter.pt.
43. historical article.pt.
44. editorials.pt.
45. or/42-44
46. 41 not 45
47. Animals/
48. Humans/
49. 47 not (47 and 48)
50. 46 not 49
51. limit 50 to english language
52. limit 51 to full text
53. remove duplicates from 52

CINAHL, EconLit, SPORTDiscus (via EBSCOhost)

S1 physical exertion+
S2 physical fitness+
S3 physical education AND training+
S4 ti sports
S5 dancing+
S6 ti exercise
S7 exercise therapy+
S8 TI (physical* n5 (fit* or train* or activ* or endur* or exert* or educat*))
S9 TI (exercis* or danc* or sport* or walk* or bicycl*)
S10 TI (lifestyle* OR life-style*) N5 activ*

S11 TI (lifestyle* OR life-style*) n5 physical*

S12 ti inactiv*

S13 sedentary n5 (lifestyle* or life-style* or population* or occupation* or behav*)

S14 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13

S15 TI increase* or promot* or improv* or prevent* or reduc*

S16 TI intervention* or advis* or advice or counsel* or prescri* or educat* or program* or scheme*

S17 TI (brief or minimal) n5 intervention*

S18 TI health n5 (promot* or behav*)

S19 TI prevent* n5 medicine

S20 TI behav* n5 (chang* or modif*)

S21 TI ((lifestyle* or life-style) adj5 chang*)

S22 TI ("motivational interview*" or "motivational counselling" or "motivational counseling" or "motivational intervention*")

S23 Health promotion+

S24 Health Behavior+

S25 Preventive medicine+

S26 Counseling+

S27 s16 or s17 or s18 or s19 or s20 or s21 or s22 or s23 or s24 or s25 or s26

S28 S14 AND S15 AND S27

S29 Economics+

S30 "costs and cost analysis"+

S31 TI (economic$ or cost or costs or costly or costing or price or prices or pricing)

S32 TI expenditure$ NOT energy

S33 TI value for money

S34 TI budget$

S35 (S29 or S30 or S31 or S32 or S33 or S34)

S36 (S28 and S35)

Cochrane library (NHS EED, HTA, CENTRAL, DARE)

#1 MeSH descriptor: [Physical Exertion] explode all trees

#2 MeSH descriptor: [Physical Fitness] explode all trees

#3 MeSH descriptor: [Physical Education and Training] explode all trees

#4 MeSH descriptor: [Sports] explode all trees

#5 MeSH descriptor: [Dancing] explode all trees

#6 MeSH descriptor: [Exercise] explode all trees

#7 MeSH descriptor: [Exercise Therapy] explode all trees

#8 (brief or minimal) intervention:ti,ab,kw

#9 MeSH descriptor: [Health Promotion] explode all trees

#10 MeSH descriptor: [Preventive Medicine] explode all trees
#11 MeSH descriptor: [Counseling] explode all trees
#12 (#1 or #2 or #3 or #4 or #5 or #6 or #7)
#13 brief:ti,ab,kw OR minimal:ti,ab,kw
#14 intervention:ti,ab,kw
#15 #8 or (#13 and #14)
#16 #9 or #10 or #11
#17 #12 and #15 and #16

CEA registry

“physical activity”

Physiotherapy Evidence Database (PEDro)

(physical activity) AND (cost effectiveness) AND (primary health care)

A2 Data extraction form

Table A-1: Data extraction table

Record No.	
Author, date	
Journal name	
Year of publication	
Title	
Country	
Study participants	
Age	
Setting	
Study period	
Intervention type	
Brief description of intervention(s)	
Comparator intervention included	
Number of interventions	
Number of brief interventions	
PA categories included	
Activity level	
Mode of intervention delivery	
Perspective of economic analysis	
Type of economic analysis	
Data source used	
Price year	
Cost and outcome discounted	Yes/No
Discount rate	
Model-based economic evaluation	Yes/No
Model structure	
Disease conditions included in the model	
Health outcome measured	
Source of effectiveness data	
Outcome reported	
Sensitivity analysis performed	Yes/No
PSA performed	
ICER point estimate	

Appendix B: Review of VoI Methods

B1 Search strategy

MEDLINE (MEDLINE in process & Other non-index citations) and Embase via OvidSP

#	Search terms
1	value of information.mp
2	value of perfect information.mp.
3	value of* information.mp.
4	expected net benefit of sampling.mp.
5	expected value of* information.mp.
6	(evpi* or evppi* or evsi* or enbs*).mp.
7	or/1-6
8	exp cost utility analysis/
9	exp cost effectiveness analysis/
10	exp cost benefit analysis/
11	exp decision making/
12	exp medical decision making/
13	exp decision theory/
15	exp decision model/
16	exp probability/
17	exp uncertainty/
18	or/8-17
19	(value adj4 information).mp.
20	7 or 19
21	18 and 20
22	decision making.mp.
23	trial design.mp.
24	research priorit*.mp.
25	priority setting.mp.
26	health priorit*.mp.
27	22 or 23 or 24 or 25 or 26
28	21 and 27
29	cost.mp.
30	28 and 29
31	remove duplicates from 30

Web of science

#1 TS = "value of information" OR TS = "value of perfect information" OR TS = "value of * information" OR TS = "expected net benefit of sampling" OR TS = "expected value of * information" OR TS = evpi* OR TS = evppi* OR TS = evsi* OR TS = enbs*

#2 TS = ("cost utility analysis" OR "cost effectiveness analysis" OR "cost benefit analysis" OR "decision making" OR "medical decision making" OR "decision theory" OR "decision model" OR "probability" OR "uncertainty")

#3 TS = ("decision making" OR "trial design" OR (research priorit*) OR "priority setting" OR (health priorit*))

#4 #1 AND #2 AND #3

#5 TS = cost

#6 #4 AND #5

CINAHL via EBSCOhost

S1 value of information OR value of perfect information OR value of * information OR expected net benefit of sampling OR expected value of * information OR evpi* OR evppi* OR evsi* or enbs* or engs*

S2 MH cost utility analysis OR MH cost effectiveness analysis OR MH cost benefit analysis

S3 MH cost* OR MH cost analysis+

S4 MH decision making* OR medical decision making OR MH decision theory OR MH decision model OR MH probability OR MH uncertainty

S5 MH decision making* OR MH trial design OR MH research prior* OR MH priority setting OR MH health priorit*

S6 S2 OR S3 OR S4

S7 (S2 OR S3 OR S4) AND (S1 AND S5 AND S6)

S8 S7 (limiters – Published Date: 19900101-20171231

EconLit via EBSCOhost

S1 value of information OR value of perfect information OR value of * information OR expected net benefit of sampling OR expected value of * information OR evpi* OR evppi* OR evsi* or enbs* or engs*

S2 MH cost utility analysis OR MH cost effectiveness analysis OR MH cost benefit analysis

S3 MH cost* OR MH cost analysis+

S4 MH decision making* OR medical decision making OR MH decision theory OR MH decision model OR MH probability OR MH uncertainty

S5 MH decision making* OR MH trial design OR MH research prior* OR MH priority setting OR MH health priorit*

S6 S2 OR S3 OR S4

S7 (S2 OR S3 OR S4) AND (S1 AND S5 AND S6)

S8 S7 (Limiters - Published Date: 19900101-20171231)

Cochrane Library (Cochrane Database of Systematic Reviews, CENTRAL, Cochrane Methodology register, DARE, HTA, NHS EED)

#1 "value of information" or "value of perfect information" or "expected net benefit of sampling" or (evpi*) or (evppi*) or (evsi*) or (enbs*)

#2 MeSH descriptor: [Cost-Benefit Analysis] explode all trees

#3 MeSH descriptor: [Costs and Cost Analysis] explode all trees

#4 MeSH descriptor: [Decision Making] explode all trees

#5 MeSH descriptor: [Decision Theory] explode all trees

#6 MeSH descriptor: [Decision Support Techniques] explode all trees

#7 MeSH descriptor: [Models, Economic] explode all trees

#8 MeSH descriptor: [Models, Statistical] explode all trees

#9 MeSH descriptor: [Decision Making] explode all trees

#10 MeSH descriptor: [Health Priorities] explode all trees

#11 MeSH descriptor: [Health Policy] explode all trees

#12 #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

#13 value near/4 information

#14 #1 or #13

#15 #12 and #14 Publication Year from 1990 to 2017

Health Technology Assessment (NIHR Database)

“Value of Information” OR “Iterative approach”

Scopus

TITLE-ABS-KEY (("value of information") OR ("value of perfect information") OR (evpi) OR (evppi) OR (evsi) OR (evsi)) AND TITLE-ABS-KEY (("cost benefit analysis") OR ("cost utility analysis") OR ("cost effectiveness analysis") OR ("cost analysis")) OR TITLE-ABS-KEY (("decision making") OR ("medical decision making") OR ("decision theory") OR ("decision model")) AND TITLE-ABS-KEY (("trial design") OR ("research prior*") OR ("priority setting") OR ("health priorit*")) AND SUBJAREA (mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal OR mult OR arts OR busi OR deci OR econ OR psyc OR soci) AND PUBYEAR > 1989

B2 Data extraction form for VoI Review

Table B-1: Data extraction table

Review ID	
Author, date	
Report title	
Publication type	
Journal	
Type of study	
Type of economic analysis	
Country	
Setting	
Study participants	
Sample size	
Intervention	
Comparators	
Study period (follow-up)	
Type of outcome measures	
Method of measure	
Main aim of the paper	
Disease or condition	
Source of effectiveness data	
Source of cost data	
Price year	
Currency	
WTP threshold	
Expected costs or outcomes discounted	
Model type	
Study perspective	
Time horizon	
Cycle length	
Decision uncertainty assessment	
Software used	
Sensitivity analysis	
ICER	
VoI type	
Individual EVPI	
Population EVPI	
Population discounted	
Life time of intervention	
EVPPI	
EVSI (n)	
ENBS or ENGS	
Author conclusions	
Future research recommendation	
Stages of iterative evaluation included	
Study funding source	

Appendix C: Cost-effectiveness of brief PA interventions

C1 Search terms for the methodological review

A. physical activity

1. epidemiology.mp.
2. exp "epidemiology"/
3. 1 or 2
4. model$.ti,ab.
5. 3 and 4
6. letter.pt.
7. editorial.pt.
8. historical article.pt.
9. 6 or 7 or 8
10. 5 not 9
11. Animals/
12. Humans/
13. 11 not (11 and 12)
14. 10 not 13
15. exp Physical Exertion/
16. Physical fitness/
17. exp "Physical education and training"/
18. exp Sports/
19. exp Dancing/
20. exp Exercise therapy/
21. (physical$ adj5 (fit$ or train$ or activ$ or endur$)).tw.
22. (exercis$ adj5 (train$ or physical$ or activ$)).tw.
23. sport$.tw.
24. walk$.tw.
25. bicycle$.tw.
26. (exercise$ adj aerobic$).tw.
27. (("lifestyle" or life-style) adj5 activ$).tw.
28. (("lifestyle" or life-style) adj5 physical$).tw.
29. or/15-28
30. Health education/
31. Patient education/
32. Primary prevention/
33. Health promotion/
34. Behavior Therapy/
35. Cognitive Therapy/
36. Primary Health Care/
37. Workplace/

38. promot$.tw.
39. educat$.tw.
40. program$.tw.
41. or/30-40
42. 29 and 41
43. 14 and 42

B. Type 2 diabetes mellitus

1. epidemiology.mp.
2. exp "epidemiology"/
3. 1 or 2
4. model$.ti,ab.
5. 3 and 4
6. letter.pt.
7. editorial.pt.
8. historical article.pt.
9. 6 or 7 or 8
10. 5 not 9
11. Animals/
12. Humans/
13. 11 not (11 and 12)
14. 10 not 13
15. exp Diabetes Mellitus, Type 2/
16. exp Diabetes Complications/
17. (obes$ adj6 diabet$).tw,kf,ot.
18. (MODY or NIDDM or T2DM).tw,kf,ot.
19. (non insulin$ depend$ or noninsulin$ depend$ or noninsulin?depend$ or non insulin?depend$).tw,kf,ot.
20. ((typ? 2 or typ? II or typ?2 or typ?II) adj diabet$).tw,kf,ot.
21. (diabet$ adj (typ? 2 or typ? II or typ?2 or typ?II)).tw,kf,ot.
22. ((adult$ or matur$ or late or slow or stabl$) adj6 diabet$).tw,kf,ot.
23. or/15-22
24. exp Diabetes Insipidus/
25. diabet$ insipidus.tw,kf,ot.
26. 24 or 25
27. 23 not 26
28. 14 and 27

C. Heart disease

1. epidemiology.mp.
2. exp "epidemiology"/
3. 1 or 2
4. model$.ti,ab.

5. 3 and 4
6. letter.pt.
7. editorial.pt.
8. historical article.pt.
9. 6 or 7 or 8
10. 5 not 9
11. Animals/
12. Humans/
13. 11 not (11 and 12)
14. 10 not 13
15. Heart Diseases.sh.
16. exp Heart Diseases/
17. *Cardiovascular Diseases/
18. *Arteriosclerosis Obliterans/
19. exp Arteriosclerosis/
20. *Embolism/
21. *Thromboembolism/
22. *Thrombosis/
23. *Coronary Thrombosis/
24. exp Hypertension/
25. *Vascular Diseases/
26. *Coronary Aneurysm/
27. *Heart Aneurysm/
28. heart*
29. myocard*
30. cardio*
31. cardia*
32. coronary*
33. pericard*
34. vascul*
35. (atrial and fibrillat*)
36. sick next sinus
37. tachycardi*
38. (ventricular and fibrillat*)
39. arrythmi*
40. endocardi*
41. angina
42. thromboembolism*
43. thrombosis
44. ischem*
45. ischaem*
46. or/15-45
47. 46 not exp animals/

48. 46 and humans/
49. or/47-48
50. 14 and 49

D. Stroke

1. epidemiology.mp.
2. exp "epidemiology"/
3. 1 or 2
4. model$.ti,ab.
5. 3 and 4
6. letter.pt.
7. editorial.pt.
8. historical article.pt.
9. 6 or 7 or 8
10. 5 not 9
11. Animals/
12. Humans/
13. 11 not (11 and 12)
14. 10 not 13
15. cerebrovascular disorders/
16. exp basal ganglia cerebrovascular disease/
17. exp brain ischemia/
18. exp carotid artery diseases/
19. stroke/
20. exp brain infarction/
21. exp cerebrovascular trauma/
22. exp intracranial arterial diseases/
23. exp intracranial arteriovenous malformations/
24. exp "Intracranial Embolism and Thrombosis"/
25. exp intracranial hemorrhages/
26. vasospasm, intracranial/
27. vertebral artery dissection/
28. aneurysm, ruptured/ and exp brain/
29. brain injuries/
30. brain injury, chronic/
31. exp carotid arteries/
32. endarterectomy, carotid/
33. *heart septal defects, atrial/ or foramen ovale, patent/
34. *atrial fibrillation/
35. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or isch?emi$ attack$ or tia$1 or neurologic$ deficit$ or SAH or AVM).tw.
36. ((brain$ or cerebr$ or cerebell$ or cortical or vertebrobasilar or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or MCA or anterior circulation or posterior circulation

or basal ganglia) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypox$ or vasospasm or obstruction or vasculopathy)).tw.

37. ((lacunar or cortical) adj5 infarct$).tw.

38. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or subarachnoid or putaminal or putamen or posterior fossa) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.

39. ((brain or cerebral or intracranial or communicating or giant or basilar or vertebral artery or berry or saccular or ruptured) adj5 aneurysm$).tw.

40. (vertebral artery dissection or cerebral art$ disease$).tw.

41. ((brain or intracranial or basal ganglia or lenticulostriate) adj5 (vascular adj5 (disease$ or disorder or accident or injur$ or trauma$ or insult or event))).tw.

42. ((isch?emic or apoplectic) adj5 (event or events or insult or attack$)).tw.

43. ((cerebral vein or cerebral venous or sinus or sagittal) adj5 thrombo$).tw.

44. (CVDST or CVT).tw.

45. ((intracranial or cerebral art$ or basilar art$ or vertebral art$ or vertebrobasilar or vertebral basilar) adj5 (stenosis or isch?emia or insufficiency or arteriosclero$ or atherosclero$ or occlus$)).tw.

46. ((venous or arteriovenous or brain vasc$) adj5 malformation$).tw.

47. ((brain or cerebral) adj5 (angioma$ or hemangioma$ or haemangioma$)).tw.

48. carotid$.tw.

49. (patent foramen ovale or PFO).tw.

50. ((atrial or atrium or auricular) adj fibrillation).tw.

51. asymptomatic cervical bruit.tw.

52. exp aphasia/ or anomia/ or hemiplegia/ or hemianopsia/ or exp paresis/ or deglutition disorders/ or dysarthria/ or pseudobulbar palsy/ or muscle spasticity/

53. (aphasi$ or apraxi$ or dysphasi$ or dysphagi$ or deglutition disorder$ or swallow$ disorder$ or dysarthri$ or hemipleg$ or hemipar$ or paresis or paretic or hemianop$ or hemineglect or spasticity or anomi$ or dysnomi$ or acquired brain injur$ or hemiball$).tw.

54. ((unilateral or visual or hemispatial or attentional or spatial) adj5 neglect).tw.

55. exp hypoxia-ischemia, brain/

56. or/15-55

57. 56 not exp animals/

58. 56 and humans/

59. or/57-58

60. and/14,59

E. Breast cancer

1. epidemiology.mp.

2. exp "epidemiology"/

3. 1 or 2

4. model$.ti,ab.

5. 3 and 4

6. letter.pt.

7. editorial.pt.
8. historical article.pt.
9. 6 or 7 or 8
10. 5 not 9
11. Animals/
12. Humans/
13. 11 not (11 and 12)
14. 10 not 13
15. exp breast neoplasms/
16. exp "neoplasms, ductal, lobular, and medullary"/
17. exp fibrocystic disease of breast/
18. or/15-17
19. exp breast/
20. breast.tw.
21. or/19-20
22. (breast adj milk).ti,ab,sh.
23. (breast adj tender$).ti,ab,sh.
24. or/22-23
25. 21 not 24
26. exp neoplasms/
27. and/25-26
28. exp lymphedema/
29. and/25,28
30. (breast adj25 neoplasm$).ti,ab,sh.
31. (breast adj25 cancer$).ti,ab,sh.
32. (breast adj25 tumour$).ti,ab,sh.
33. (breast adj25 tumor$).ti,ab,sh.
34. (breast adj25 carcinoma$).ti,ab,sh.
35. (breast adj25 adenocarcinoma$).ti,ab,sh.
36. (breast adj25 sarcoma$).ti,ab,sh.
37. (breast adj50 dcis).ti,ab,sh.
38. (breast adj25 ductal).ti,ab,sh.
39. (breast adj25 infiltrating).ti,ab,sh.
40. (breast adj25 intraductal).ti,ab,sh.
41. (breast adj25 lobular).ti,ab,sh.
42. (breast adj25 medullary).ti,ab,sh.
43. or/30-42
44. 18 or 27 or 29 or 43
45. exp mastectomy/
46. 44 or 45
47. exp "Analytical, Diagnostic and Therapeutic Techniques and Equipment"/
48. 25 and 47
49. 46 or 48

50. exp mammary neoplasms/
51. (mammary adj25 neoplasm$).ti,ab,sh.
52. (mammary adj25 cancer$).ti,ab,sh.
53. (mammary adj25 tumour$).ti,ab,sh.
54. (mammary adj25 tumor$).ti,ab,sh.
55. (mammary adj25 carcinoma$).ti,ab,sh.
56. (mammary adj25 adenocarcinoma$).ti,ab,sh.
57. (mammary adj25 sarcoma$).ti,ab,sh.
58. (mammary adj50 dcis).ti,ab,sh.
59. (mammary adj25 ductal).ti,ab,sh.
60. (mammary adj25 infiltrating).ti,ab,sh.
61. (mammary adj25 intraductal).ti,ab,sh.
62. (mammary adj25 lobular).ti,ab,sh.
63. (mammary adj25 medullary).ti,ab,sh.
64. or/50-63
65. 49 or 64
66. (breast adj25 self$).ti,ab,sh.
67. (breast adj25 screen$).ti,ab,sh.
68. exp mammography/
69. exp breast self examination/
70. or/65-69
71. mammograph$.tw.
72. 25 and 71
73. 70 or 72
74. humans/
75. 73 and 74
76. 14 and 75

F. Colorectal cancer

1. epidemiology.mp.
2. exp "epidemiology"/
3. 1 or 2
4. model$.ti,ab.
5. 3 and 4
6. letter.pt.
7. editorial.pt.
8. historical article.pt.
9. 6 or 7 or 8
10. 5 not 9
11. Animals/
12. Humans/
13. 11 not (11 and 12)
14. 10 not 13

15. (colorectal neoplasm or colorectal tumor or colorectal adenoma or colorectal cancer or colorectal carcinoma or colorectal disease or colonic or sigmoid neoplasms or rectal neoplasms or anus neoplasms).mp.

16. exp "Colorectal-Neoplasms"/

17. 15 or 16

18. 17 not exp animals/

19. 17 and humans/

20. or/18-19

21. 14 and 20

G. Kidney cancer

1. epidemiology.mp.

2. exp "epidemiology"/

3. 1 or 2

4. model$.ti,ab.

5. 3 and 4

6. letter.pt.

7. editorial.pt.

8. historical article.pt.

9. 6 or 7 or 8

10. 5 not 9

11. Animals/

12. Humans/

13. 11 not (11 and 12)

14. 10 not 13

15. renal.mp. or kidney$.tw. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]

16. (nephritis or nephrotic or nephrosis or nephropath$).tw.

17. 15 or 16

18. exp *kidney neoplasms/ or *ureteral neoplasms/ or *urethral neoplasms/

19. 17 and 18

20. (animals/ not humans/) and animals/

21. 19 not 20

22. 14 and 21

H. Lung cancer

1. epidemiology.mp.

2. exp "epidemiology"/

3. 1 or 2

4. model$.ti,ab.

5. 3 and 4

6. letter.pt.

7. editorial.pt.

8. historical article.pt.

9. 6 or 7 or 8

10. 5 not 9

11. Animals/

12. Humans/

13. 11 not (11 and 12)

14. 10 not 13

15. exp Lung neoplasms/

16. (NSCLC or SCLC).tw.

17. (lung or lungs or pulmonary or bronchus or brochogenic or bronchial or bronchoalveolar or alveolar).tw.

18. (cancer* or carcinoma* or adenocarcinoma* or malignan* or tumor* or tumour* or neoplasm*).tw.

19. 17 and 18

20. 15 or 16 or 19

21. 14 and 20

C2 Summary of resource use estimation and cost of intervention

Table C-1: Estimates of resource use and cost per participant of a pedometer intervention (k= 8 RCTs)

Study, year	Intervention participants	Resource use					Costs					
		Pedometers	Physical activity counselling	Information pack	Telephone calls	Diary	Pedometers	Counselling	Information pack	Telephone calls	Diary	Total
Araiza 2006	15	1	-	-	-	1	£ 14.00	–	–	–	£0.96	£14.96
Butler and Dwyer 2004	17	1	-	-	-	-	£ 14.00	–	–	–	–	£14.00
de Blok 2006	8	1	4x30 mins physiotherapist	-	-	1	£ 14.00	£ 68.00	–	–	£0.96	£82.96
Hultquist 2005	31	1	-	-	-	1	£ 14.00	–	–	–	£0.96	£14.96
Izawa 2005	24	1	-	-	-	1	£ 14.00	–	–	–	£0.96	£14.96
Moreau 2001	15	1	-	-	-	1	£ 14.00	–	–	–	£0.96	£14.96
Ransdell 2004 and Ornes 2005	28	1	2x120 mins exercise physiologist	1	6x3 mins exercise physiologist	-	£ 14.00	£ 136.00	£ 1.21	£ 32.34	–	£183.55
Talbot 2003	17	1	12x5 mins practice nurse	1	-	-	£ 14.00	£ 50.00	£ 1.21	–	–	£65.21
Total	155								Weighted average cost per participant			£54.33

Table C-2: Estimates of resource use and cost per participant of an advice or counselling intervention (k=9 RCTs)

Study, year	Intervention participants	Resource use				Costs				
		Counselling	Telephone calls	Postal contact	Written material	Counselling	written material	Telephone calls	Postal contact	Total
Chambers 2000	77	1x key messages reinforced in GP letter			1	£ 16.13	£ 1.21	-	-	£ 17.34
	76	1x individualised advice on exercise			1	£ 25.50	£ 1.21	-	-	£ 26.71
	78	1x exercise assessment, 4x small-group exercise sessions physiotherapist			1	£ 39.10	£ 1.21	-	-	£ 40.31
Halbert 2000	149	3x exercise advice sessions exercise specialist				£ 25.50	-	-	-	£ 25.50
Lamb 2002	131	1x group advice session	3x telephone calls physiotherapist		1	£ 2.83	£ 1.21	£ 20.90	-	£ 24.94
Elley 2003	226	1x 7 mins GP	3x 5 min calls by exercise specialist; 3x5 min calls by nurse		1	£ 21.54	£ 1.21	£ 22.15	-	£ 44.90
Van Sluijs 2005	97	2x counselling session with primary care clinician	2 telephone support call (practice nurse) x 5 mins		1	£ 72.00	£ 1.21	£ 7.80	-	£ 81.01
Kolt 2007	83		8x13 min (avg) phone call from exercise counsellor		1	-	£ 1.21	£ 72.45	-	£ 73.66
Kinmonth 2008	105	4x sessions	9 telephone support calls			£ 41.92	-	£ 73.12	-	£ 115.04
	109	1 session	6 telephone support calls	7	1	-	£ 1.21	£ 63.98	£.75	£ 73.94
Lawton 2008	544	2x 10 min practice nurse	5x 15 min practice nurse		1	£ 17.00	£ 1.21	£ 58.50	-	£ 76.71
Morey 2009	178	1x session health counsellor	12x 18 min phone call		1	£ 12.75	£ 1.21	£168.48	-	£ 182.44
Total	1,853			Weighted average cost per participant						£ 71.26

Table C-3: Estimates of resource use and cost per participant of an action planning intervention (k=14 RCTs)

Study, year	Intervention participants	Resource use				Costs			
		Material development / instrument	Implementation intention	Diary, log book etc.	Fitness membership	Material development / instrument	Implementation intention	Diary, logbook, brochures etc.	Total
Bycura 2009	40	–	10 min health worker, 6 min nurse	1	–	–	£ 6.88	£ 0.18	£ 7.06
de Vet 2009	138	–	5 min nurse	1	–	–	£ 0.87	£ 2.32	£ 3.19
Luszczynska 2006	104	–	15 min interviewer + 15 mins psychologist	1	–	–	£ 22.45	£ 0.26	£ 22.70
Milne 2002	93	1	10+5 min nurse admin	1	–	£ 1.34	£ 2.62	£ 0.34	£ 4.30
Murray 2009	29	–	15 min nurse, 30x6 min fitness supervisor, 9 wk gym membership	1	1	–	£ 127.00	£ 0.32	£127.32
Prestwich 2003 (a1)	18	–	15 min nurse, 5 min fitness advisor	1	–	–	£ 3.87	£ 2.08	£ 5.95
Prestwich 2003 (a2)	19	–	20 min nurse, 5 min fitness advisor	1	–	–	£ 6.07	£ 2.16	£ 8.3
Prestwich 2009 (b1)	29	–	15 min health worker	1	–	–	£ 7.75	£ 0.40	£ 8.15
Scholz 2006 (a)	103	–	15x2 min nurse, 9 min GP	1	–	–	£ 129.62	£ 11.32	£140.94
Scholz 2007 (b)	71	–	15 min nurse, 20 min interviewer	1	–	–	£ 10.68	£ 1.05	£ 11.73
Sniehotta 2005 (a)	56	–	25 min nurse, 15 min interviewer	1	–	–	£ 15.11	£ 11.26	£ 26.37
Sniehotta 2006 (b)	68	–	25 min nurse +15 min interviewer	1	–	–	£ 15.11	£ 15.06	£ 30.17
Thoolen 2009	78	1	2+5 min nurse	1	–	£ 1.60	£ 23.18	£ 1.06	£ 25.84
Waters 2006	54	1 digital timer	10 min nurse	1	–	£ 20	£ 1.75	£ 2.69	£ 24.43
Total	900						Weighted average cost per participant		£ 33.21

C3 Characteristics of the studies reviewed to inform the decision model

Table C-4: Data table for review of modelling studies

Author, year	Modelling method	Study description	Population used / data source	Interventions incorporated	Complications modelled	Time horizon	Software Used	Outcome measure	Strengths and weaknesses
Physical activity or life style intervention models									
Avenell 2004 (340)	Markov (cohort analysis)	An economic model of effectiveness of lifestyle interventions in preventing the onset of diabetes among people with Impaired Glucose Tolerance (IGT)	Cohort of individuals starting at the age of 55 years, preference scores from cost utility analysis database of Harvard university, CODE 2 study, FDPS[1]	Diet and exercise versus no intervention	IGT, onset of T2DM, continuing T2DM, and death	6 years	DATA 4.0	Cost per QALY	Only T2DM is included in the model.
Cobiac 2009 (141)	Markov (Monte Carlo simulation)	An economic model of interventions promoting physical activity using multi-stage lifetable analysis with 4 health states: healthy, diseased, dead from the disease, and dead from all other causes;	Australian population aged ≥15 years, RR of disease in each PA category drawn from meta-analysis(502) and HR from Asia pacific cohort study(503), cost data from Australia's ACE-prevention project and WHO-CHOICE	6 interventions • GP prescription • GP referral to exercise physiologist • Mass media-based campaign • TravelSmart • Pedometers & • Internet	IHD, Ischaemic stroke, T2DM, breast cancer-female and colon cancer	Life time	Microsoft Excel with add-in tool @RISK	Cost per DALYs averted	Details of model structure and parameter used are available,

[1] Finnish Diabetes Prevention Study (N Engl J Med 2001; 344:1343-1350)

Table C-4 (continued)

Author, year	Modelling method	Study description	Population used / data source	Interventions incorporated	Complications modelled	Time horizon	Software Used	Outcome measure	Strengths and weaknesses
Galani 2007 (337)	Markov (Monte Carlo simulation)	Model to quantify lifetime health and economic consequences of preventing and treating obesity with lifestyle interventions in Switzerland	Hypothetical cohort of 10,000 overweight or obese aged 25-65 years. Model adapted from Lindstrom 2005(504), transition probabilities based on disease progression with age, sex, BMI and cycle number	Standard care (no-intervention) vs. lifestyle intervention (regular PA and healthy eating including diet rich in vegetables and fruits)	overweight/ obese, hypertension, hypercholesterolemia, diabetes, stroke, CHD and death	Lifetime (over 60 years)	Microsoft excel	Cost per QALY	The model doesn't take smoking into consideration as risk factor
Matrix/ NICE 2006 (338)	Decision tree	Model to estimate health impacts, quality of life outcome and health care system costs and savings as a result of PA interventions.	Sedentary population, cost-estimates were based on resource use data extraction from selected studies	4 interventions • Brief interventions in primary care • Pedometers • Exercise referral • Walking and cycling programme in the community	CHD, stroke, T2DM and colon cancer	Not clear	Not mentioned	Cost per QALY	Assumed 50% drop off rates in PA, included PA only as risk factor and excludes other disease conditions
Nadeau 2011 (339) and Zucchelli 2010 (358)	Markov (discrete event, continuous time, Monte Carlo Micro-simulation)	A simulation model (POHEM) to project physical activity from 2001 to 2040 and its relationship to the onset of chronic conditions as well as the impact of health-adjusted life expectancy (HALE) in Canada.	Starting population from Canadian Community Health Survey (self-reported) 2000-01; other sources include NPHS, RPDB, BCLHD; aged 18+ years, 4 PA categories	Each intervention with 4 PA categories: none, 0-30 min/day, 30-60 min/day, 60+ min/day • leisure time PA • walking for errands • biking for errands and • overall level of PA	Diabetes, hypertension, cardiovascular disease and certain cancers	Not mentioned (40 years)	Modgen (Statistics Canada)	Health adjusted life expectancy (HALE)	Uses self-reported PA and health outcomes, risk equations and data source for chronic conditions were not described in detail

Table C-4 (continued)

Author, year	Modelling method	Study description	Population used / data source	Interventions incorporated	Complications modelled	Time horizon	Software Used	Outcome measure	Strengths and weaknesses
Type 2 Diabetes Mellitus – Diabetes progression and complications models									
Bagust 2001 (315)	Markov (deterministic)	Economic model of healthcare for T2DM for the UK assessing costs and complications of T2DM	UKPDS and CORE2 patients, cost data from South Glamorgan database and GPMDP[2], data source for retinopathy (WESDR as a function of HbA1c), neuropathy (Eastman), nephropathy (WESDR and Eastman)	4 broad classes of diabetic therapy: • Diet-only • First-line oral medication • Second-line (combination) therapy • Insulin-based therapy	nephropathy, neuropathy, retinopathy (9 morbid states), CHD and stroke	Lifetime	Microsoft excel	Cost per additional life year	Model designed in modular form
Brown 2000 (316)	Micro-simulation (continuous stochastic MCMM)	A model to predict medical events, longevity, quality of life and medical care expenditures for groups and individuals with T2DM. Transitional period of 1 year.	T2DM incidence and prevalence data from KPNW[3], UKPDS, NHANES II[4]; CVD events from Framingham Heart Study(373), statistical models derived from Kaiser Permanent Data, risk factors include SBP, HDL, LDL, TG, and blood glucose measure, HbA1c	Antihypertensive treatment (aspirin use) vs. placebo	CVD events (CHD, stroke, CHF, peripheral vascular disease), retinopathy, nephropathy, neuropathy, ESRD	Lifetime	Visual Basic	Cost per QALY	Details of risk equations, regression models, calculations etc. were provided, model includes most important risk factors

[2] GPMDP – General Practice Morbidity Database Project

[3] Kaiser Permanente Northwest trial

[4] US National Health and Nutrition Examination Survey

Table C-4 (continued)

Author, year	Modelling method	Study description	Population used / data source	Interventions incorporated	Complications modelled	Time horizon	Software Used	Outcome measure	Strengths and weaknesses
CDC/RTI 1998 (391) and 2002 (317)	Markov	A model to estimate the cost-effectiveness of intensive glycaemic control, intensified hypertension control and reduction in serum cholesterol level for T2DM patients.	Cohorts aged ≥25 years (10 year age groups), initial patient distributions and transitional probabilities from UKPDS, previous diabetes progression models of T2DM and CHD	• Insulin or sulfonylurea therapy (intensive glycaemic control) • angiotensin converting enzyme inhibitor or β-blocker (hypertension control) • pravastatin (↓ serum cholesterol)	nephropathy, neuropathy, retinopathy, CHD and stroke	Lifetime	C++	Cost per QALY	
Chen 2008 (318)	Micro-simulation (probabilistic discrete event simulation)	A model (JADE) to project the long term impact on life expectancy and occurrence over 5, 10 and 40 years of microvascular and macrovascular complications of diabetes when using different HbA1c thresholds for intensifying treatment of T2DM.	UKPDS participants, contains 5 related modules – initial conditions, treatment, risk factor/adverse events, diabetes-related events, and cost/QoL	Six treatment regimens: • MF + SU • MF + rosiglitazone • MF + basal insulin • MDI (MF – metformin, SU – sulphonylurea, MDI – multiple-dose insulin)	Renal failure, blindness, amputation, IHD, MI, CHF and stroke	Not clear	Visual Basic 6.3 with Microsoft Excel	Cost per quality of life	Strategies that intensify therapy at lower HbA1c thresholds are associated with enhanced projected long-term health outcomes.
Clarke 2004 (319)	Micro-simulation (Probabilistic discrete time MC simulation)	A model-based on 14 risk equations; time varying risk factors (HbA_{1c}, SBP, TC: HDL-C and smoking status), patient history of complications to predict the occurrence	Data from UKPDS trial; 5,102 newly diagnosed diabetic patients, age 25-65 years (5 year age band)	UKPDS regimens of intensive and conventional blood glucose control	first occurrence of fatal or non-fatal MI, other IHD, stroke, HF, amputation, renal failure and eye disease	Lifetime	Microsoft Excel; C++	Disease events	Uses series of risk equations for long-term complications

Table C-4 (continued)

Author, year	Modelling method	Study description	Population used / data source	Interventions incorporated	Complications modelled	Time horizon	Software Used	Outcome measure	Strengths and weaknesses
Eastman 1997 (320)	Markov (probabilistic Monte Carlo simulation)	A model predicting rates of micro-vascular complications, CVD, and mortality that reflect the natural history of vascular and neuropathic complications of diabetes (NIDDM[5])	Cohort of 10,000 diabetic patients aged 25-74 in the US, model parameters and hazard rates based on epidemiological of diabetes in the US population, WESDR	A given treatment sequence where the number of switches are not clear	Retinopathy, nephropathy, neuropathy, CVD and mortality models	Lifetime (life span horizon of 95 years)	Microsoft Excel with add-in @Risk	Cost per QALY	Model includes independent sub-models with different health states
Eddy & Schlessinger 2003 (321) (Archimedes Model)	Micro-simulation	A mathematical model of the anatomy, pathophysiology, tests, treatments, and outcomes pertaining to diabetes	Population from T2DM and coronary artery disease (CAD) trials, risk equations from Framingham heart study, other sources include LIPID, HHS, 4S, SHEP, LRC, MRC, WOSCOPS, VA-HIT, UKPDS	Various management strategies for diabetes and CAD including prevention programme, screening tests, diagnostic test, treatment	microvascular complications of T2DM, MI, CHD death, coronary events, CAD events, stroke	Not clear	Smalltalk	Health outcomes (macro- and micro-vascular)	Limited information regarding model structure
Habacher 2007 (322)	Markov (cohort simulation)	A model to retrieve cost data for intensified treatment of diabetic foot ulcers and to estimate long-term outcome	Retrospective real-life data records of 119 patients with acute ulceration, Austrian life table & Ramsey et al(505) and other studies	Standard and intensified treatment groups	Ulceration, healed, minor amputation, major amputation, death	15 years	DATA 4.0	Average costs/patient-year, average life expectancy	Model limited to intensified treatment of diabetic foot ulcer

[5] NIDDM = Non-Insulin-Dependent Diabetes Mellitus

Table C-4 (continued)

Author, year	Modelling method	Study description	Population used / data source	Interventions incorporated	Complications modelled	Time horizon	Software Used	Outcome measure	Strengths and weaknesses
Icks 2007 (352)	Decision tree	A model analysing clinical and cost-effectiveness of primary prevention of T2DM patients in routine healthcare	60–74 year olds from KORA[6] survey 2000, DPP study applied to KORA population	3 interventions: Staff education; targeted screening and lifestyle modification; **OR** Metformin (60-74 years, BMI≥24 and pre-diabetic status) according to DPP trial	Pre-diabetes, no pre-diabetes	3 years	SAS and Stata	Costs per additional T2DM case prevented	
Lamotte 2002 (323)	Markov	A model predicting the complication rates and mortality of T2DM with and without Orlistat treatment assuming a 5 years catch up period; risk factors included in the model are HbA1c, BP and cholesterol, 6 monthly transitional probability	UKPDS population (obese T2DM patients without micro- or macro-vascular complications), clinical from Hollander trial(506), hypercholesterolemia data from Helsinki Heart Study (HHS) & UKPDS 34; cost data from CODE-2 study	Orlistat vs. no Orlistat	3 health states – without complication, with complications or death	10 years	DATA 3.5	Cost per LYG	

[6] Sub-study on cardiovascular risk factors and chronic diseases in inhabitants of Augsburg and surrounding counties (1998-ongoing); main aim - comparison with the WHO MONICA Augsburg surveys

Table C-4 (continued)

Author, year	Modelling method	Study description	Population used / data source	Interventions incorporated	Complications modelled	Time horizon	Software Used	Outcome measure	Strengths and weaknesses
McPherson 2007 (324)	Micro-simulation	A model to predict Predicts future level of obesity, consequences of health, health costs and life expectancy in English population. Risk factors included BMI, age, gender	Health survey for England 1993-2004 (cross-sectional) with epidemiological sources from literature review	BMI interventions – hypothetical reductions in BMI	CHD, stroke, diabetes, cancers (Colorectal, breast, kidney, oesophagus, endometrium), gall bladder, arthritis	50 years	C++	Disease incidence, costs and life expectancy	Model estimates obesity trends
Mueller 2006 (325) (EAGLE Model)	Micro-simulation	A model simulating diabetes-related complications and their impact on costs with type 1 and type 2 diabetes. Consists of 2 modules – epidemiological based on risk equations and a health economics model	Type 1 and T2DM patients in European countries, data from 3 large prospective studies: WESDR, DCCT[7] and UKPDS, mortality rates from WHO lifetables (adjusted).	A given treatment sequence – 5 switches (Ophthalmic disorders, kidney system, nervous system, short term outcomes, microvascular outcomes)	Hypoglycaemia, retinopathy, macular oedema, ESRD, neuropathy, diabetic foot syndrome, MI and stroke	Not clear (10 years?)	Delphi, C++	Short-term outcomes (hypoglycaemic event), long-term (macro- and microvascular disease event)	Uses series of risk equations for long-term complications
Ortegon 2004 (326)	Markov	A model to simulate onset and progression of diabetic foot disease in patients with newly diagnosed T2DM, 6 months transitional probability	Cohort of diabetic patients with mean age 61 years, source data from UKPDS (neuropathy), Dutch prospective cohort study on diabetic foot disease	Conventional glycaemic control (optimal foot care) and intensive glycaemic control based on UKPDS 33	13 health states: 3 risk health states, 6 wound type states, and 4 outcome states	Lifetime	DATA 3.5	Cost per QALAY, reduced incidence of foot complications, life expectancy	Model doesn't include chance of death for all health states

[7] DCCT = Diabetes Control and Complications Trial

Table C-4 (continued)

Author, year	Modelling method	Study description	Population used / data source	Interventions incorporated	Complications modelled	Time horizon	Software Used	Outcome measure	Strengths and weaknesses
Palmer 2004 (327) (CORE diabetes Model)	Micro-simulation	Model to determine the long-term health outcomes and economic consequences of implementing different treatment policies or interventions in type 1 and type 2 diabetes mellitus, 15 time-dependent inter-connected sub-models	Type 1 and type 2 diabetes patients in European countries, uses UKPDS and Framingham risk equations, cycle length of one year except foot ulcer (1 month) and hypoglycaemia (3 months)	Given treatment sequences	MI, angina, CHF, PVD, neuropathy, foot ulcer, retinopathy, macular oedema, cataract, nephropathy, hypoglycaemia, Ketoacidosis, Lactic Acidosis, non-specific mortality	1 to 90 years	SQL (database), C++, Data Pro (sub-models); Microsoft Excel	Cost per QALY	The model covers the widest range of complications
Waugh 2007 (328)	Markov	A model to investigate the order of magnitude of effects given different scenarios for T2DM screening policies; 2 sub-models – screening model and treatment model	Cohort based on Sheffield diabetes model[8]; risk equations from UKPDS (CHD & stroke) and Eastman (microvascular complications); prevalence figures from HSE; Δ in SBP, Cholesterol (UKPDS); HbA1c from diff sources	Screening of diabetes patients vs. treatment of diabetes complications	Retinopathy, CHD, stroke, nephropathy, PVD	Not clear	Not clearly mentioned	Cost per QALY	

[8] Yorkshire and Humber Public Health Observatory

Table C-4 (continued)

Author, year	Modelling method	Study description	Population used / data source	Interventions incorporated	Complications modelled	Time horizon	Software Used	Outcome measure	Strengths and weaknesses
Wilson & Fordham 2005 (329)	Micro-simulation	Estimates 10 years impact of changes in prevalence of obesity on incidence and prevalence of CHD, diabetes and mortality, and the NHS treatment cost; 3 scenarios – (1) continuation of BMI changes, (2) same level of BMI as of 2005 and (3) reduction of mean BMI by 4.3% over a period of 10 years	Cohort of 2,500 people sampled from Norfolk pop 2005, risk equations from Framingham study and other cross-sectional studies to estimate disease incidence	Public health campaign – healthy eating (5 a day community initiative)	T2DM, CHD, MI, stroke and death	10 years	Microsoft Excel	Life year gained	Main focus on T2DM, heart diseases and stroke
Zhou 2005 (330)	Semi-Markov with Monte Carlo techniques	A comprehensive computer simulation model to Predict the progression of diabetes and its complications and co-morbidities and its quality of life and costs; 4 sub-models: disease, health utility, cost and mortality models	T2DM patients, T2DM complications and co-morbidities derived from population based epidemiological studies and RCTs, and controlled clinical trials; largely used WESDR baseline and 4- and 10-year follow up data	Diabetes prevention and treatment strategies – screening, intensification of therapy with oral anti-diabetic medications and insulin	glucose tolerance, retinopathy, neuropathy, nephropathy, stroke and CHD	10 years	Not mentioned	Quality of life, cost	

Table C-4 (continued)

Author, year	Modelling method	Study description	Population used / data source	Interventions incorporated	Complications modelled	Time horizon	Software Used	Outcome measure	Strengths and weaknesses
Circulatory disease models									
Barton 2011 (331)	Not clear (Markov?)	Model to estimate cost-effectiveness of population-wide risk factor reduction programme aimed at CVD prevention.	40-90 year olds, ~50 million population (of England and Wales), ScHARR model adapted for costing(507), Framingham risk equation used to generate the expected pattern of first CV events according to age, sex and CVD risk	2 scenarios involving small reduction in pop level of blood pressure or TC concentration • Legislation to reduce salt intake • Legislation to ban industrial fats	Cardiovascular events	10 year	Microsoft Excel	QALY gained, CV events avoided, healthcare cost savings, estimates to achieve specific outcome	Lacks details on model structure and input parameters, doesn't include PSA
Hayashino 2007 (333)	Markov	A cost-effectiveness analysis to measure the clinical benefit and cost of CAD screening in asymptomatic patients with diabetes and additional atherogenic risk factors	Hypothetical cohort of 55-70 year old asymptomatic participant with T2DM and two additional atherogenic risk factors (hypertension, smoking or LDL), risk equation from FHS	• Screening strategies: • no screening • exercise electro-cardiography • exercise echocardiography • exercise single-photon emission-tomography	Normal, silent ischemia, symptomatic ischemia, history of MI, post-percutaneous transluminal coronary angioplasty,	Lifetime	DATA 3.5.9	Cost per QALY	

Table C-4 (continued)

Author, year	Modelling method	Study description	Population used / data source	Interventions incorporated	Complications modelled	Time horizon	Software Used	Outcome measure	Strengths and weaknesses
Jacobs-van der Bruggen 2007 (334)	Micro-simulation (**RIVM**[9] **C**hronic **D**isease **M**odel)	A model describing the development of long term disease over time of demography, risk factor (BMI, PA) incidence, mortality and health care costs in the Dutch population. BMI and PA are modelled in 3 classes each	A cohort of 20 to 85+ year olds representing Dutch population in 2004	Two interventions: Community-based lifestyle programme for general population, and intensive style intervention (health care) for obese adults	diabetes, CHD, CHF, CVA, cancers, musculosketal disorders	70 years	Not mentioned	Cost per QALY	Lifestyle interventions include diet and PA, details of model structure and inputs provided
Nelson 2005 (335)	Decision tree (with progression through Markov chains)	An epidemiological model to investigate the routine use of low dose aspirin in old people	A simulated cohort of 10,000 each men and women aged 70-74 years with no CV events, risk factor data from AusDiab study, incidence rates from VAED[10], MONICA, NEMESIS[11] trial	Routine use of low dose aspirin vs. no aspirin	1st MI/unstable angina, ischaemic or haemorrhagic stroke, and major gastrointestinal haemorrhage	Lifetime	Microsoft excel with add-in @Risk	health adjusted years of life lived	
Weinstein 1987 (336)	Markov model	A model to project future mortality, morbidity, and cost of CHD in the US – 3 sub-models: demographic-epidemiologic, bridge and disease history sub-models	Hypothetical cohort starting at age 35; data from the US census, HANES II, risk functions from Framingham Heart Study	Preventive (risk modification) or therapeutic	12 CHD (angina, MI, cardiac arrest, cardiac arrest with MI)	30 years	Not mentioned	CHD incidence, morbidity and mortality	Model structure and risk functions provided

[9] The Dutch National Institute for Public Health and the Environment

[10] Victorian Admitted Episodes Database (VAED)

[11] North East Melbourne Stroke Incidence Study (NEMESIS)

Table C-4 (continued)

Author, year	Modelling method	Study description	Population used / data source	Interventions incorporated	Complications modelled	Time horizon	Software Used	Outcome measure	Strengths and weaknesses
Breast cancer model									
Anderson 2006 (341)	Markov model	A model to evaluate the cost-effectiveness of the prevention strategies that are available to unaffected women carrying a single BRCA1 or BRCA2 mutation with high cancer penetrance	Unaffected carriers of a single BRCA1 or BRCA2 mutation 35-50 years of age; Data source: SEER; incidence rates, preference ratings and costs derived from the literature	6 Preventive strategies: Tamoxifen, Oral, ontraceptives, Bilateral salpingo-oophorectomy, Mastectomy, prophylactic bilateral mastectomy and oophorectomy, surveillance	Well, breast cancer, ovarian cancer, side effects, and death	lifetime	Data Pro (TreeAge)	Cost per life year or QALY	Model doesn't mention risk factors
Chen 2010 (342)	Markov model	A model to evaluate the cost-effectiveness of 70-gene MammaPrint Signature versus Adjuvant! Online software (AS)	Women aged ≤60 years with early stage breast cancer, base model with 70-gene signature validation study data and an alternative model using data from AS and SEER registry	70-gene MammaPrint signature versus Adjuvant! Online software (AS)	no recurrence, death from cancer and death from other causes	Not mentioned (10 year?)	TreeAge Pro	Cost per QALY gained	
Fryback 2006 (343)	Micro-simulation model	A discrete-event model that simulates breast cancer in a population over time generating cancer-registry like data sets. 4 interacting processes are modelled over time: natural history of breast cancer; breast cancer detection; breast cancer treatment; and competing cause mortality	Simulated 2.95 million women in the US from 1950-2000 in 6 month cycle, assuming all women in 1950 were cancer free, starting age 20 years (in 1950) to 100 years or until they die WCRS[12] and SEER[13] data	6 different adjuvant therapy with different time (2 or 5 year course)	In situ, localised, regional and distant stage	Lifetime	C++ using Microsoft Visual Studio Version 6	Observed change in cancer incidence and mortality	

[12] Wisconsin Cancer Reporting System (WCRS) state cancer registry

[13] National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) programme

Table C-4 (continued)

Author, year	Modelling method	Study description	Population used / data source	Interventions incorporated	Complications modelled	Time horizon	Software Used	Outcome measure	Strengths and weaknesses
Hanin 2006 (344)	Stochastic model (University of Rochester Model of Breast Cancer Detection and Survival)	A biologically motivated model of breast cancer development and detection allowing for arbitrary screening schedules and the effects of clinical covariates recorded at the time of diagnosis on post-treatment survival.	Women aged 40-59 years, simulated from CNBSS[14]-1 CNBSS-2 studies, follow-up at 7 and 11-16 years, Data source: SEER, Canadian National Breast Screening Studies (CNBSS)	Tamoxifen vs no treatment	Disease free, local, regional, and distant	Not clear	Pascal Delphi	Disease incidence, post-treatment survival	
Noah-Vanhoucke 2011(345)	Markov model (Archimedes Breast Cancer Model)	A continuous-time, mathematical model of breast cancer incidence, tumour growth, detection and spread, survival and healthcare processes associated with breast cancer used to simulate postmenopausal population	post-menopausal women aged <55 years (the US); data from SEER, and meta-analyses; cost data from previous studies	Tamoxifen treatment versus no treatment	Breast cancer (local, regional, distant), endometrial cancer, stroke, deep vein thrombosis	Lifetime	Not mentioned	Cost per QALY	Model takes risk factors (family history, BMI, CHRT use etc.) into account
Kidney cancer model									
Chien 2010 (351)	Disease prediction (Epidemiological) model	A clinical point-based model to estimate chronic kidney disease risk at 4 years using clinical variables (age, BMI, diastolic BP, history of T2DM, and stroke) and biochemical measures (postprandial glucose, HBA1c, proteinuria and uric acid); 2 models – clinical and biochemical	5,168 Chinese participants, mean follow-up duration 2.2 years, cox proportional hazard model to establish 2 parsimonious models according to backward selection strategy	NA	Chronic kidney disease risk	Not clear	SAS 9.1, R and Stata 9.1	Incidence of chronic kidney disease	Model structure details not given

[14] Canadian National Breast Screening Studies

Table C-4 (continued)

Author, year	Modelling method	Study description	Population used / data source	Interventions incorporated	Complications modelled	Time horizon	Software Used	Outcome measure	Strengths and weaknesses
Lung cancer model									
Das 2006 (349)	Markov	A model to estimate potential clinical benefits and cost-effectiveness of computed tomography (CT) for screening lung cancer in Hodgkin's lymphoma survivors. Screening starting 5 years after initial diagnosis and continuing until death or diagnosis of lung cancer	Hypothetical cohort of patients diagnosed with state IA-IIB Hodgkin's lymphoma at age 25; model parameters from SEER	Annual low-dose CT screening versus no screening in smokers and non-smokers	No lung cancer, non-small-cell carcinoma (localised, regional and distant), small-cell lung cancer and death	Lifetime	DATA	Cost per QALY	Stage distribution data based on short follow-up
Marshall 2001 (350)	Decision tree	A model to evaluate the potential clinical and economic implications of annual lung cancer screening programme based on helical computer tomography (CT); time horizon 5 years, disease stages (I, II, IIIA, IIIB and IV)	Hypothetical cohort of 100,000 patients aged 60-74 years, 5 year age grouping, Data from SEER and Early Lung Cancer Action Project (ELCAP)	• Screening strategies • low dose helicat CT scan • high resoluation CT scan • thoracoscopy, with biopsy • office visit	Local, regional and distant, metastatic	5 years	Microsoft Excel	Survival rate, cost per QALY	

Table C-4 (continued)

Author, year	Modelling method	Study description	Population used / data source	Interventions incorporated	Complications modelled	Time horizon	Software Used	Outcome measure	Strengths and weaknesses
Colorectal cancer model									
Allen 2005 (346)	Markov	A model to compare the cost-effectiveness of four diagnostic strategies in the evaluation of rectal bleeding; time horizon – patient's lifetime	Patients over age 40 with otherwise asymptomatic rectal bleeding Literature review, SEER	4 interventions • Watchful waiting • Flexible sigmoidoscopy (FS) • FS followed by air contrast barium enema (ACBE) • Colonoscopy	Small polyp, large polyp, Dukes disease (stages A, B, C, and D) and death	Lifetime	DATA 4.0	Cost per QALY	
Ladabaum 2010 (347)	Markov	A model to reflect the epidemiology of colorectal cancer (CRC) and estimate CRC incidence in persons at elevated risk of CRC conferred by a family history of CRC in a first-degree relative.	40-85 year, 1 year cycle interval, Screening was done from age 40 through age 80 years.	3 screening strategies • natural history • colonoscopy every 5 years • colonoscopy every 10 years	Normal; small adenomatous polyp; large adenomatous polyp; localised, regional, or distant CRC; and dead	Not clear	TreeAge	Cost per life year saved	
Loeve 2000 (348)	Micro-simulation model (MISCAN-COLON Model)	A patient level model to estimate costs and savings of endoscopic colorectal cancer screening	Patient aged 50—75 years, screening delivered at 5 years interval; Data from SEER, Kaiser Northern California screening programme	2 screening strategies • sigmoidoscopy and • surveillance colonoscopy	Normal; small polyp; large polyp; pre- and clinical stages (I, II, III, or IV); and dead	Cost and savings of endoscopic colorectal cancer	Not mentioned	Life year gained, savings of costs	

Appendix D: Within trial economic analysis

D1 Resource use questionnaire

Section E

NHS use, time off work and expenditure on physical activity Questionnaire

As a part of this study we are interested to know if you have visited your GP or the hospital, or incurred any expenditure related to physical activity over the past three months, for example membership of any health or sports clubs (e.g. fitness club, fitness centre, gym), or any other physical activity related expenditure.

We are also interested in whether you have taken any time off work or felt your productivity was affected due to any ill health recently.

We would very much appreciate your help in gathering this information.

Please read the questions carefully and tick (✓) or provide information in the relevant boxes where requested.

Please try to answer every question, except when there is a specific request to skip a section. If you cannot remember the exact answer to a question, please enter your best estimate.

The information that you provide will be made anonymous and completely confidential. Your answers will be combined with the answers of other participants involved in the study and reported in such a way that they will not identify you or influence any NHS care you may receive.

Please return the questionnaire in the enclosed pre-paid envelope.

V1, dated 11/12/2014

Primary Care Visits

1. In the **past 3 months**, have you been seen by or spoken to your GP, a practice nurse or a health care assistant in person or on the telephone? Yes ☐ No ☐

   Please do not include your recent health check appointment.

   Please tick (✓) one box.

   (If NO, please go to Question 2)

   If **yes, please write** in the boxes below the number of times you have been seen or spoken to. Please complete each line. If none, please put a zero in appropriate box.

	Number of times:		
	at your GP's surgery	at your home	over the phone
your general practitioner (GP):			
a practice nurse:			
Other health care professional:			

   If you ticked 'other health care professional', please provide details below

   For example, '*physiotherapist*':

   _____

Hospital Visits

2. In the past 3 months, have you been to the hospital (NHS services) for any reason related to your health?

   Please tick (✓) in one box Yes ☐ No ☐

   (If NO, please go to Question 3)

   If yes, please write the number of times you have been into hospital and reasons:

No. of visits		***Reasons***
for an **outpatient appointment** (e.g. check-up, laboratory test, x-rays)		
for a **day case procedure** (e.g. inguinal hernia, varicose veins)		
admitted as an **inpatient** (involving overnight stay)		
Attended **Accident and Emergency** (A & E / emergency room)		
Other *(please specify)* _____ _____		

If you had one or more inpatient stays, how many nights did you stay at the last visit? **Please write** the number of nights spent in the box.

		nights

Expenditure on health, sports clubs or other physical activities

3. In the past 3 months, have you been a member of any health or sports clubs/centres (e.g. local sports club, fitness club, fitness centre or gym)? Please tick (✓) the appropriate answer.

   (If NO, please go to Question 10)

   Yes ☐ No ☐

4. When you travel to the fitness centre, sports club or gym, how do you normally get there? **Please tick** (✓) the box that best describes how you travelled. If you used more than one form of transport, please indicate the way you travelled for the **main** (longest in terms of distance) part of your journey.

Walk or cycle	☐	Hospital or community transport	☐	Car	☐
Public transport (bus, train)	☐	Taxi	☐	Park &ride	☐
Other (*please specify*)	☐	_____			

5. How much does the trip normally cost you? **Please write** the total amount spent on any bus, train or taxi fare or car parking. (For fares please write the total cost for the round trip, there and back). Please write zero if you did not incur any bus, train or taxi fare or car parking.

   Cost of fares and/or parking (£) ☐☐ – ☐☐ pence

6. If you normally travel by private car, about how many miles do you travel each way? **Please write** the number of miles in the box. Please put zero if you did not travel by private car at all.

   Miles one-way ☐☐

7. In the last 3 months, on average **how many visits** did you make to a fitness centre, gym or other sport activity **each week**? If you do more than one activity please write the total number of visits. For example, if you go to the gym twice a week and a sports club once a week, write '3' in the box.

   Number of visits per week ☐☐

8. On average, **how much time** did you spend at **each visit** including travel time? **Please write** the number of hours and minutes in the box.

   Time taken in hours ☐☐ – ☐☐ Minutes

9. How much money did you spend on fitness centre, sports club or gym memberships over the past three months? Please write details below including any membership or joining fees as well as any regular payments for each attendance. If none, please write 'none'.

Details	**Total Amount spent in the last 3 months**
	£
	£
	£
	£
	£
	£

10. Have you incurred **any other out of pocket expenditure** relating to physical activity over the last three months? For example, purchase of sportswear or footwear? If none, please write 'none'

Details	**Total Amount spent in the last 3 months**
	£
	£
	£
	£
	£
	£

Productivity at work and time off work due to ill health

The following questions ask about the effect of any health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

11. Are you currently employed (working for pay)? ____ NO ____ YES

    If NO, check "NO" and skip to question 15.

The next questions are about the **past seven days**, not including today.

12. During the past seven days, how many hours did you miss from work because of any health problems? Include hours you missed on sick days, times you went in late, left early, etc., because of any health problems. Do not include time you missed to participate in this study.

    _____HOURS

13. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

    _____HOURS

14. During the past seven days, how many hours did you actually work?

    _____HOURS (If "0", skip to question 16)

15. During the past seven days, how much did any health problems affect your productivity while you were working?

    Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

    Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from working

    CIRCLE A NUMBER

16. During the past seven days, how much did any health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

Consider only how much <u>health problems</u> affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from doing my daily activities

CIRCLE A NUMBER

Questions 11 to 16 are based on an adapted version of the Work Productivity and Activity Impairment Questionnaire (Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. PharmacoEconomics 1993; 4(5):353-65).

Thank you for filling this questionnaire.
Please post it back to us in the envelope provided.
No postage stamp required.

Appendix E: Conference Abstracts and Posters

E1 Joint iHEA and ECHE World Congress (July 2014) – Abstract

Development and validation of a decision model for very brief interventions promoting physical activity

GC V, Wilson E, Suhrcke M, on behalf of the Very Brief Interventions (VBI) study team

Word count: 479

Background

Physical inactivity is associated with a significant burden of chronic disease and a significant proportion of healthy life years lost in the UK. Evidence from clinical trials suggests that "(very) brief interventions" (VBIs) e.g. brief advice and/or exercise on prescription are effective in increasing physical activity in a primary care setting. However, these trials are insufficient on their own to inform decisions regarding the longer term cost-effectiveness of interventions. Decision analytic modelling can help synthesising all relevant data for the cost-effectiveness evaluation of health care interventions in an explicit manner.

Complex multi-disease decision models need validation and calibration in order to ensure predictive validity. In this paper, we first briefly describe the development of a model to estimate the cost-effectiveness of VBIs promoting physical activity in primary care. However, the primary focus of this paper is on the approach taken to validate and calibrate the model.

Methods

The VBI model is a discrete-event micro-simulation model developed in the 'R' programming language. It estimates long term cost and health consequences (including QALYs) from changes in physical activity (in MET-hours per week), specifically focusing on VBIs. The effect of increased physical activity is mediated through biomarkers (e.g. blood pressure, cholesterol levels and HbA1c), ultimately modelling their effect on development of conditions such as diabetes, cardiovascular disease (CVD), and certain cancers, and calculating lifetime cost and QALYs gained.

The model development comprised three stages: 1) Identification of relevant factors impacting on long term cost and outcomes 2) Review of the literature to identify both pathways linking the risk factors as well as data/risk equations with which to populate the model and 3) Validation and calibration of the model to ensure predictive validity.

Information on both direct and indirect estimates of relevant parameters was collected from a large range of sources, presenting a challenge of making consistent use of both types of effect estimates. For example, data are available linking physical activity to the risk of CVD, and CVD to mortality as well as data linking physical activity directly to mortality. The direct data was used to validate the indirectly modelled pathway.

A weighted mean deviation (WMD) is used to describe the overall fit of the model to all the identified 'sub-pathways'. Using an appropriate search algorithm (Nelder and Mead

1965), we then systematically calibrated all the model inputs iteratively to locate a set of inputs that minimised the WMD.

Results

Whilst computationally expensive, the Nelder-Mead algorithm proved a useful approach to calibrating the VBI model, increasing confidence in its predictive validity. Particular issues raised included defining the weights for each outcome in the 'sub-pathways', and determining a feasible sub-set of model inputs on which the Nelder-Mead algorithm can be conducted.

Conclusions

The process of developing the VBI model and validating a model presented in this paper could be a useful guide to increase transparency, credibility and acceptability of complex models.

Key terms: physical activity, decision model, brief interventions, model calibration

Past presentation history:

Never presented

Past publication history:

Never published

Disclosure:

None

Funding sources:

This work is part of the National Institute of Health Research (NIHR) funded (Grant Reference Number RP-PG-0608-10079) Very Brief Interventions programme to develop and test very brief interventions to increase activity which could be delivered by a practice nurse or other practitioner as part of a National Health Service (NHS) health check or routine consultation.

Conflict disclosure:

None

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On behalf of Very Brief Interventions (VBI) study team.

E2 EuHEA PhD Student-Supervisor and Early Career Researcher Conference (Sept 2014) – Poster

Are very brief interventions promoting physical activity in primary care cost-effective?

Vijay GC [1*], Ed Wilson [1,2] and Marc Suhrcke [1,3]

[1] Health Economics Group, University of East Anglia, [2] Cambridge Centre for Health Services Research, University of Cambridge, [3] Centre for Health Economics, University of York , * vijay.gc@uea.ac.uk

Introduction

Physical inactivity is associated with significant burden of chronic disease and a significant proportion of healthy life years lost.

Promotion of physical activity not only contributes to well-being, but is also essential for good health.

In England, adults aged 40-74 without pre-existing conditions are invited to receive a free "health check" at their general practice (NHS Health Check).

The majority of people in this age group do not meet the minimum recommended level of physical activity. The health check provides an opportunity to deliver brief interventions to increase physical activity.

Brief interventions involve opportunistic advice, discussion, negotiation or encouragement to promote physical activity, and are delivered by a range of primary care and community care professionals.

The present research aims to estimate the long-term cost and health consequences of brief physical activity interventions in a primary care setting.

Methods

A micro-simulation model of physical activity interventions where a cohort of participants was drawn at random using the UK population distribution of parameters (Source: Health Survey for England).

The model uses mathematical functions to predict disease events which are based on the changes in the values of risk factors (blood pressure, cholesterol levels and HbA1c).

The cost impacts and health outcomes of three brief interventions and usual care were compared.

GP advice on exercise: written physical activity prescriptions plus advice or counselling on physical activity

Implementation intentions: participants form their intentions (goals) into actions i.e. physical activity uptake

Pedometer use: encourage usage of pedometers as a motivational tool to increase physical activity

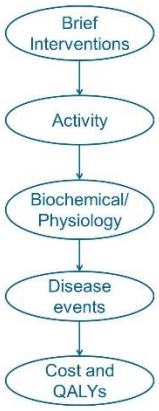

Figure 1. Conceptual structure of the model

The costs of disease treatment and interventions, transitional probabilities and health state utilities were taken from public data sources, and from a review of the literature.

Table 1. Model inputs (Intervention costs and effects)

	Cost of intervention*	Effect of intervention (MET-hour/week)	Source
GP advice	£ 73.21	0.277 (0.165 – 0.388)	Orrow et al., 2012
Implementation Intentions	£ 44.74	0.243 (0.127 – 0.358)	Belanger-Gravel et al., 2013
Pedometers	£ 53.33	7.41 (3.27 – 11.56)	Bravata et al., 2007

* Price year 2011, £

Results

A cohort of 10,000 participants entered the model. The sustainability of intervention health effects over time is evaluated by varying decay rates between 0% (lifelong behaviour change) and 100% (behaviour change reversed after the first year post-intervention) .

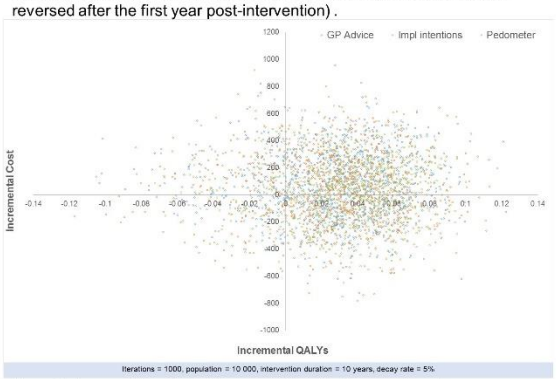

Figure 2. Incremental cost-effectiveness scatter plot (all versus 'none')

Not surprisingly, the incremental cost-effectiveness ratio increases with faster "decay rate". The Pedometer intervention appears to have the highest net benefit.

Table 2. Cost-effectiveness of brief interventions

Interventions	Total Cost*	QALYs gained*	Net benefit at £20,000	Net benefit at £30,000
None	£4,731 (4320 – 5184)	7.5084 (7.43 – 7.56)	£ 145,441	£ 220,526
GP advice	£4,799 (4418 – 5270)	7.5091 (7.43 – 7.56)	£ 145,378	£ 220,469
Implementation intentions	£4,734 (4379 – 5238)	7.5087 (7.43 – 7.57)	£ 145,444	£ 220,534
Pedometers	£4,711 (4368 – 5211)	7.5150 (7.44 – 7.57)	£ 145,511	£ 220,631

* Costs and QALYs are discounted at 3.5%; price year 2011 £; decay rate 5%. Figures are mean (95% interval).

Conclusions

A single brief intervention leads to virtually no difference in cost or outcome between any of the comparators; although point estimate results suggest that the use of pedometers could be the most cost-effective brief intervention. Future work will explore the impact of different "decay rates", and the effectiveness of repeated interventions and optimal time interval for repeats.

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Cost-effectiveness of a very brief pedometer-based intervention delivered in the NHS Health Checks: economic analysis alongside a randomised controlled trial

Vijay GC [1], Marc Suhrcke [2], Joanna Mitchell [3], Wendy Hardeman [4], Stephen Sutton [3], Ed Wilson [5] on behalf of the VBI Programme Team*

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BACKGROUND

- Physical inactivity is an important risk factor associated with significant burden of chronic disease[1] and considerable economic burden.[2]
- The financial burden to the National Health Service (NHS) has been estimated at £1.06 billion per year.[3]
- When objectively measured, only 6% of men and 4% of women in England meet current physical activity recommendations.[4]
- Very brief interventions (VBIs) such as brief physical activity advice in primary care could be relatively easy and inexpensive to implement into routine primary care consultations such as NHS health check.
- Although primary care based interventions promoting physical activity are considered good value for money, there is uncertainty about the potential effectiveness and cost-effectiveness of VBIs.[5,6]

AIM

To assess the costs and cost-effectiveness of a pedometer-based VBI implemented in general practice from healthcare and societal perspectives.

METHODS

Design: Economic evaluation alongside a randomised controlled trial (the VBI trial, ISRCTN72691150).[7]

Participants: 1,007 adults aged 40-74 years in the East of England eligible for NHS health check.

Intervention: Participants were randomly assigned to receive either standard health check plus pedometer-based VBI ('Step It Up') or standard health check only.

Resource use: We collected out of pocket expenditure on health, sports club or other physical activity, NHS resources use and work productivity via questionnaire.

Cost estimation: Costing comprised the cost of delivering the 'Step It Up' intervention itself plus the volume of resource use over the 3 months.

Main outcome measures: changes in accelerometer counts per minute, step counts per day, costs to the NHS and to the society, and incremental cost-effectiveness ratios.

RESULTS

- 864 participants returned the completed resource use questionnaire at 3 months follow-up.
- The intervention had an increase of 242 (95% CI: -172 to 656) steps per day.
- The cost of delivering the 'Step It Up' was £18 per participant.
- NHS healthcare resource use was similar between intervention and usual care groups. Much of the costs were driven by out-of-pocket expenditures incurred by participants.
- No statistically significant differences but on average participants had 2.5 visits per week to a fitness centre, gym or other sport activity.
- The 'Step It Up' intervention costed £19 more than usual care group (£59, societal perspective).

Table 1. Mean costs, mean number of steps per day and incremental cost-effectiveness ratio (ICER)

	N(usual care, intervention)	Usual care	Intervention	Difference	p	Point estimates
Intervention costs	(442, 422)		18.04			
Total NHS costs	(442, 422)	101.45	120.84	19.39	0.42	
Primary care costs	(432, 409)	35.40	31.93	3.47		
Secondary care costs	(429, 408)	68.87	74.32	5.45		
Total societal costs	(442, 422)	558.59	617.15	58.82	0.44	
Step counts per day	(442, 417)	8,191	8,419	242	0.25	
ICER of 'Step It Up intervention' (per 1,000 steps per day)						
Based on NHS perspective						80
Based on societal perspective						243

- On average 59% participants in intervention (n=408) and 62% in usual care (n=424) were in work. Among those employed, intervention group participants reported slightly higher impairment at work and overall work impairment scores.

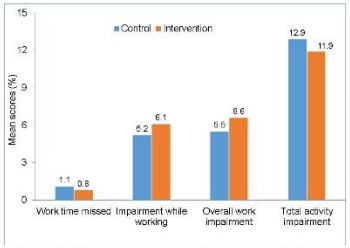

Figure 1. Mean work productivity and activity impairment scores by study groups

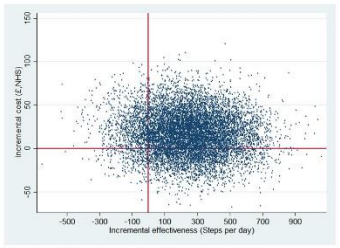

Figure 2. Bootstrap results on the cost-effectiveness plane (based on 10,000 replications)

SUMMARY / CONCLUSION

- No significant difference in resource use between study groups. However, much of the costs were attributed by out of pocket expenditure.
- Total NHS costs for 'Step It Up' intervention was £19 greater per participant than usual care over the 3-month follow-up.
- Intervention participants increased their physical activity by 242 steps per day at an additional NHS cost of £19 or approximately £80 per 1,000 steps per day (£243 per 1,000 steps per day from societal perspective) compared with usual care.

ACKNOWLEDGEMENTS

We are grateful to the twenty three general practices who supported this study, the health practitioners who delivered the intervention and all the patients who participated. This presentation presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Grant Reference Number RP-PG-0608-10079). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

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