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Public Health England

Protecting and improving the nation's health

Cardiovascular Disease Prevention Return on Investment Tool:

Technical appendix

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Contents

Executive summary

Introduction

Cardiovascular disease (CVD) prevention is a major public health priority in England. The NHS RightCare Optimal Pathway has highlighted 6 CVD high risk conditions that are currently underdiagnosed and insufficiently managed despite a range of available interventions, and therefore represent targets for improvement:

- high blood pressure
- atrial fibrillation (AF)
- high cholesterol/high CVD risk including Familial Hypercholesterolemia (FH)
- diabetes (Type 2 and Type 1)
- non-diabetic hyperglycaemia
- chronic kidney disease (CKD)

PHE has identified that whilst a number of tools currently exist for assessing return on investment (ROI) for CVD prevention, these use a variety of different evidence sources and assumptions and therefore there is no common platform for the assessment of ROI across different risk conditions and different interventions. There is therefore a need for an integrated, single platform ROI tool to support NHS and public health decision makers at both national and local level.

PHE commissioned a CVD prevention ROI tool, focussing on the 6 high risk conditions from the School for Health and Related Research (ScHARR) at the University of Sheffield. Prior to development of such a tool, it was recognised that a consistent and up to date evidence review was required. This was focussed primarily on finding the best quality evidence about the effectiveness and cost-effectiveness of interventions to identify people with currently undetected risk factors, and to manage and reduce levels of risk factors or progression of risk conditions. This included reviewing information about cross-cutting interventions that impact on more than 1 risk condition; the differential impact of interventions in people with different risk conditions; and the interaction between multiple interventions in a single individual who may have 1 or more risk conditions. It also involved identifying local data to inform current care usage of those interventions chosen to be incorporated in the tool.

ScHARR has developed the ROI tool based on a modification of an existing type 2 diabetes prevention model (the School for Public Health Research [SPHR] Diabetes Prevention Model), which has been previously made into a PHE tool to model the ROI of the NHS Diabetes Prevention Programme (NHS DPP). This model already included simulation of CVD risk and events through the validated and widely used QRISK2 10 year risk framework, which incorporates the relationship between risk factors/conditions

and the probability of having CVD events, including the joint impact on CVD risk of having multiple risk factors already present. Adaptation of this model was necessary to incorporate the CVD high risk conditions not currently included (primarily AF, FH and CKD), which required some reviewing of the modelling literature to identify key methodology and parameter values commonly used in models of these conditions.

Aims and objectives

The aim was to assess the feasibility of the CVD prevention ROI tool given the availability of evidence, then to adapt the existing SPHR Diabetes Prevention Model to develop a CVD ROI tool that can evaluate the identified prevention interventions.

The objectives were to:

- review evidence for effectiveness and cost-effectiveness of interventions that impact on the CVD high risk conditions, to identify a set of interventions for which there is good quality evidence for inclusion in the tool and in an accompanying database of interventions
- review the literature to identify where possible, evidence of cumulative or multiplicative interactions between interventions and their impacts on CVD risk reduction
- review the literature to identify modelling studies that can support decisions about the design of model additions and adaptations
- collate and compile the evidence together with input from potential tool users to propose a formal plan and conceptual model of a CVD prevention ROI tool
- adapt the NHS DPP user-friendly ROI tool based on the School for Public Health Research Diabetes Prevention Model, to a CVD ROI tool that can be updated with local information to support implementation
- carry out a set of exemplar analyses to model the potential return on investment of CVD prevention interventions in 1 or more CVD high risk groups

Evidence reviews for intervention topics

Consultation with the steering group led to the agreement that interventions that are currently recommended by NICE for detection or management of the 6 high risk conditions should be prioritised for inclusion in the tool. Whilst of potential interest, the tool would not include policy and structural interventions that improve uptake of and adherence to current NICE guidelines, or novel interventions (not currently NICE recommended) for detection or management of high risk conditions.

Selection of intervention topics for review was guided by recommendations within relevant NICE guideline documents for the 6 high risk conditions. Interventions were limited to those recommended for individuals without pre-existing CVD, those that specifically contributed to prevention of CVD (ie interventions for control of symptoms

that do not impact on CVD were excluded), and excluded interventions that were relevant to only a very small number of individuals with serious disease.

Following selection of topics, a review question was formulated for each included topic which enabled identification of effectiveness data for each intervention in silo or in combination with other included interventions, relating to each relevant high risk group. As an initial step, any existing evidence relating to the effectiveness of recommended interventions was extracted from NICE guideline documentation. If such evidence was relevant to the review question, had been reviewed within the last year and contained outcomes of relevance to the tool then no further reviewing was required. For other topics, searches were designed to identify recent evidence relating to effectiveness of the intervention. Searches were initially aimed at identifying relevant systematic reviews, but if none were found, a second set of searches was carried out to identify relevant randomised controlled trials or observational studies. A review protocol was designed to enable rapid reviewing for each search topic. In most cases multiple potentially useful studies were identified. Selection of studies for inclusion in the tool and database of interventions was based on an assessment of study quality, relevance to the topic question and input from the steering group.

A series of other intervention parameters were also reviewed including cost-effectiveness data, intervention costs, current intervention usage (a composite of proportion offered, uptake and discontinuation) and duration of intervention effect. Where possible information about current intervention usage and about current detection of high risk conditions was obtained from local data sources. Inclusion of topics within the tool and database of intervention was informed through evidence of both effectiveness and cost-effectiveness, together with steering group input. The following topics were included:

- lipid modification therapy (Primarily Atorvastatin 20 mg)
- anti-hypertensive therapy (primarily combination therapy for hypertension and ACEi/ARB therapy for CKD)
- anticoagulant therapy for AF
- blood glucose lowering medication for Type 2 diabetes
- NHS Diabetes Prevention Programme
- structured education programmes for diabetes
- weight management
- smoking cessation
- individualised nutritional advice for CKD
- continuous subcutaneous insulin infusion (Insulin Pump) for Type 1 diabetes
- blood pressure self-monitoring for management of hypertension
- pharmacist Medicines Use Review
- NHS Health Checks
- cascade testing for FH
- opportunistic detection (including for AF, type 2 diabetes and hypertension)

- annual review for detection and management

For several topics it was not possible to identify relevant, good quality or significant effectiveness or cost-effectiveness data. These topics were highlighted as evidence gaps that meant that they could not be included in the tool at the current time:

- exercise referral
- screening and brief intervention for alcohol
- brief advice for diet and physical activity
- individualised nutritional advice for FH

Additional evidence gaps related to intervention combinations, for which little specific effectiveness evidence was identified.

Tool user group and conceptual modelling

A group of potential tool users was recruited from amongst CCG and local authority public health representatives, PHE regional leads with responsibility for CVD, health professionals with CVD as a special interest and relevant charitable organisations. The tool user group was invited to a 1-day workshop to discuss what users would want from an ROI tool. A conceptual model detailing proposed tool inputs and outputs was constructed based upon tool user group responses and modelling constraints. Feedback from the tool user group about the conceptual model was obtained through email and an online questionnaire, and changes were made to the conceptual model to incorporate this user feedback. Tool users also provided feedback on the final tool.

Model adaptations

A series of model adaptations were carried out to convert the SPHR Diabetes Prevention model into the CVD Prevention model. The Health Survey for England 2014 was used to provide baseline characteristics for the model. The survey weights were used to enable the model to simulate the population characteristics of England. Calibration weighting was carried out to develop a set of alternative weights for each local area, based on local demographics (age, sex, deprivation and ethnicity).

Some of the high risk groups including diabetes, non-diabetic hyperglycaemia and hypertension were already adequately modelled in the SPHR Diabetes Prevention Model. Inclusion of type 1 diabetes, AF, FH and CKD required additional modelling work to be carried out; this was informed through a series of model reviews, designed to find any useful information such as risk equations, CVD risk, utilities and costs, used in previously published models. Modelling of type 1 diabetes was informed through the Sheffield type 1 diabetes model. AF risk in the baseline population was modelled using the Framingham AF risk equations, with eligibility for anticoagulation being assessed using a modelled version of the CHA_2DS_2-VASc score. CKD risk in the general

population was modelled through a risk equation developed from an observational analysis of CKD prevalence in England. Progression of CKD (by stage and by albumin creatinine ratio) was modelled using transition probabilities found through the model reviews. FH was randomly assigned to individuals with the highest cholesterol levels from HSE 2014.

QRISK2 and QStroke algorithms were used to model annual risk of first CVD event. Calculation of both risks in each simulated individual enabled a value for cardiac risk to be estimated separately from stroke risk. A series of modifications were applied to cardiac and stroke risk to enable CVD event rate to take account of additional high risk conditions and interventions not included in the original QRISK2 and QStroke algorithms. This included modifications to cardiac risk for FH; to cardiac and stroke risk by CKD stage and ACR category; to cardiac and stroke risk by HbA1c value in people with and without diabetes; and to stroke risk for AF and anticoagulation. Additional modifications to cardiac and stroke risk were carried out to take account of the known impact of statin and antihypertensive treatment in reducing CVD risk. Following model validation against current incidence of MI and stroke from Hospital Episode Statistics, additional adjustments were applied to stroke and cardiac risk separately to ensure that the model was accurately estimating the absolute number of CVD events. The type of stroke or cardiac event suffered by each individual was assigned using age and sex dependent probabilities from a statins HTA. Subsequent CVD events were modelled dependent upon age, sex and prior event only.

A range of other conditions were pre-existing in the SPHR Diabetes Prevention model and modelling of these was retained in the CVD Prevention model. This included congestive heart failure; microvascular retinopathy, ulcer and amputation in people with diabetes; breast and bowel cancer, osteoarthritis, depression and dementia. Risk of major bleeding (upper gastrointestinal bleed and intercranial bleed) is increased significantly through usage of anticoagulants and so this was added to the model, together with information about mortality rates following major bleed. Mortality from CVD, cancer and bleed were modelled separately, with other cause mortality modelled through life table information.

The range of detection and management interventions identified as part of the Phase One work was added to the model. Detection was modelled through NHS Health Checks, annual review, cascade testing and opportunistic detection. Opportunistic detection was modelled as a process to identify all remaining individuals who should be detected following the other 3 mechanisms, rather than through usage of the specific mechanisms identified as part of the evidence review. This enabled increases in detection through unspecified mechanisms to be included as part of the tool. A model structure was set up whereby the proportion of individuals detected, managed or using an intervention could be maintained at a specific user-defined value over time, despite dynamic changes in the numbers of people eligible. Management for each condition was defined through usage of key management interventions. These included

continuous interventions (pharmacological treatments, insulin pump and blood pressure self-monitoring), 1-off interventions (lifestyle interventions including NHS DPP, weight management, nutritional advice and educational interventions for diabetes) and repeated interventions (medicines use review and smoking cessation).

All model costs were reviewed and updated, with new costs added where required to model the new health states. Utilities were retained from the SPHR Diabetes Prevention model, with new utility decrements added to model major bleed. Following model development, a series of tests and validations were carried out to ensure that the model was behaving as expected.

Acronyms used in this document

ACEi/ARB: Angiotensin Converting Enzyme Inhibitor/Angiotensin II Receptor Blockers

ACR: Albumin to Creatinine Ratio (measure of kidney function)

AF: Atrial Fibrillation

AMSTAR: (A MeaSurement Tool to Assess systematic Reviews)

BMI: Body Mass Index

BNF: British National Formulary

BPSM: Blood Pressure Self Monitoring

BWMP: Behavioural Weight Management Programme

CASP: Critical Appraisal Skills Programme

CCG: Clinical Commissioning Group

CKD: Chronic Kidney Disease

CSII: Continuous Subcutaneous Insulin Infusion (Insulin Pump)

CVD: Cardiovascular Disease

DAFNE: Dose-Adjustment for Normal Eating

DESMOND: Diabetes Education and Self Management for Ongoing and Newly Diagnosed

DPP: NHS Diabetes Prevention Programme

ECG: ElectroCardioGram

eGFR: Estimated Glomurular Filtration Rate (a measure of kidney function)

EPIC: European Prospective Investigation into Cancer and nutrition

FH: Familial Hypercholesterolaemia

GP: General Practitioner

HDL: High Density Lipoprotein (cholesterol)

HSE: Health Survey for England

HTA: Health Technology Assessment

ICER: Incremental Cost-Effectiveness Ratio

IMD: Indices of Multiple Deprivation

INLIQ: Indicators No Longer In QOF

IPF: Iterative Proportional Fitting

JBS3: Joint British Societies for the prevention of cardiovascular disease

LA: Local Authority

LDL: Low Density Lipoprotein (cholesterol)

LSOA: Lower Super Output Area

MECC: Making Every Contact Count

MI: Myocardial Infarction

MUR: Medicine Use Review

NCVIN: National Cardiovascular Intelligence Network

NDH: Non-Diabetic Hyperglycaemia

NHANES: National Health and Nutrition Examination Survey (US)

NICE: National Institute for Health and Care Excellence

NMB: Net Monetary Benefit

NOAC: Novel Oral AntiCoagulant

NR: Not Reported

NRT: Nicotine Replacement Therapy

ONS: Office for National Statistics

PBO: Placebo

PCKS9: Proprotein Convertase Kexin/Subtilisin Type 9 inhibitor (lipid modification drugs such as Ezetimibe)

PDF: Portable Document Format

PICO: Population; Intervention; Comparator; Outcomes

PSSRU: Personal Social Services Research Unit

QALY: Quality Adjusted Life Year

QOF: Quality and Outcomes Framework

QRISK: QResearch Cardiovascular Risk Calculator (score gives 10 year CVD risk)

RCT: Randomised Controlled Trial

ROI: Return on Investment

RR: Relative Risk

SBP: Systolic Blood Pressure

ScHARR: School for Health and Related Research

SPHR: School for Public Health Research

STP: Sustainability and Transformation Partnership

THIN: The Health Improvement Network

TIA: Transient Ischaemic Attack

UKPDS: UK Prospective Diabetes Study

Introduction

Rationale for a cardiovascular disease return on investment tool

Cardiovascular disease (CVD) prevention is a major public health priority in England. Currently there are over 2.6 million people in the UK on the Coronary Heart Disease Register and 1.2 million on the Stroke or Transient Ischaemic Attacks Register[1]. CVD mortality varies widely throughout the UK by deprivation, by gender and by regional area, eg the highest age-standardised CVD death rates in England are in the North West (320/100,000), compared to only 269/100,000 in the South West[2]. According to a recent European study it is estimated that CVD cost the UK economy €26 billion in 2015 of which €12 billion (46%) came from direct health care costs[3].

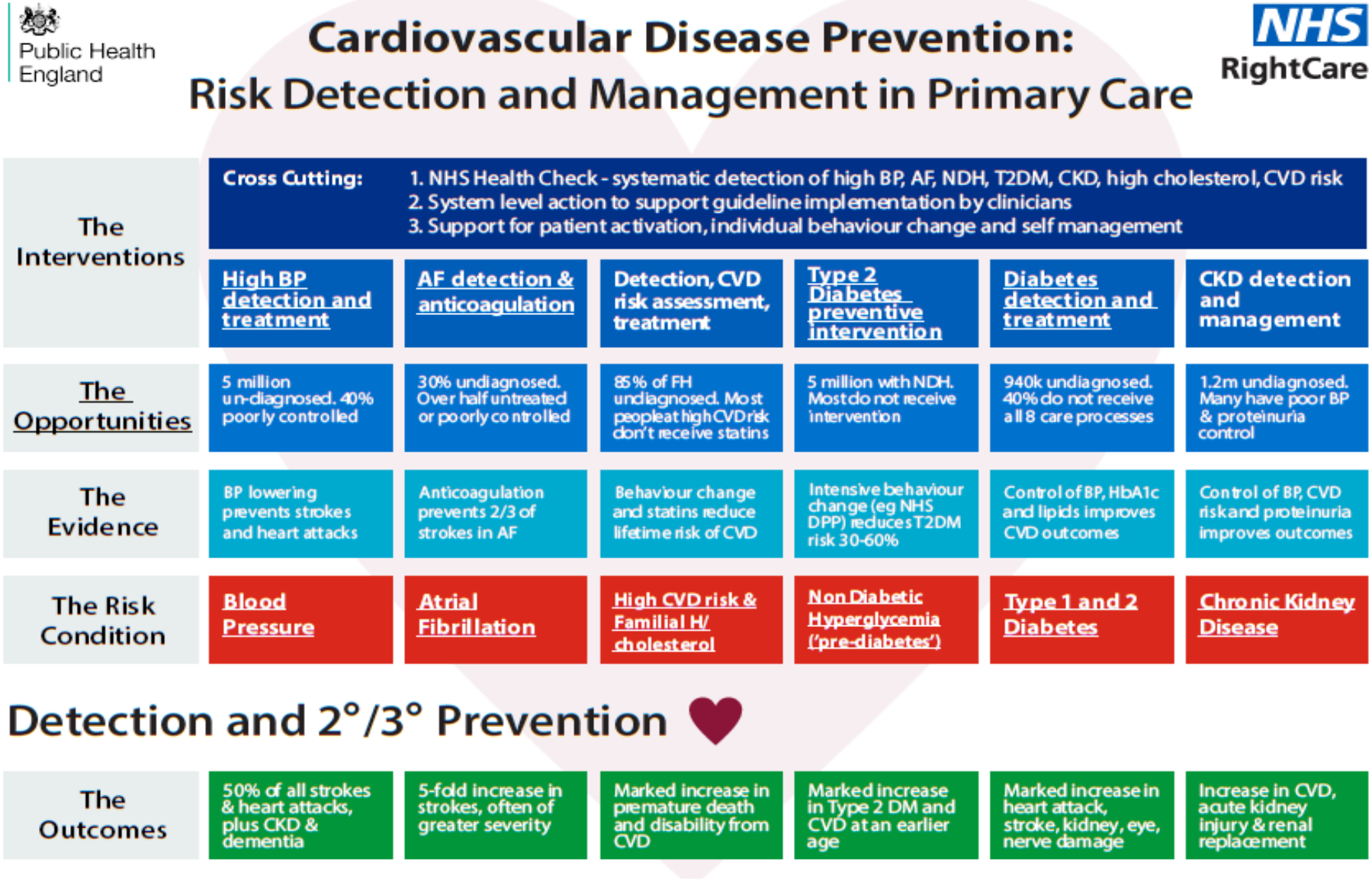
Recent declines in mortality mean that more people are living for longer with long-term conditions including CVD and other conditions that increase the risk of CVD. Despite the recent improvements, many CVD cases could be prevented through healthier lifestyles and through better risk factor detection and management[4]. Whilst some risk factors such as smoking have reduced in the population; levels of obesity and diabetes are increasing, and other risk factors such as hypertension and atrial fibrillation (AF) remain undiagnosed or poorly managed in many individuals.

For this project, PHE has chosen to focus on the 6 main risk conditions identified in the NHS RightCare Optimal Pathway[5]:

- high blood pressure
- atrial fibrillation (AF)
- high cholesterol/high CVD risk including Familial Hypercholesterolemia (FH)
- diabetes (Type 2 and Type 1)
- non-diabetic hyperglycaemia
- chronic kidney disease (CKD)

PHE as part of its process to develop an earlier CVD prevention opportunities toolkit[6], reviewed a number of existing tools or models for assessing cost-effectiveness or return on investment for CVD prevention across a variety of population subgroups. A variety of different evidence sources and assumptions have been used across these tools. This means that there is has not been a common platform for the assessment of ROI across different risk conditions. The results of existing assessments of ROI in the different interventions and different population risk groups are not therefore safely comparable. A holistic CVD ROI tool was needed in order to support NHS and public health decision makers at both national (eg PHE, Department of Health [DH], NHS England) and local (eg Clinical Commissioning Group [CCG], Local Authority [LA], Sustainability and Transportation Partnership [STP]) levels to assess the economic case for evidence based interventions to ensure efficient and targeted commissioning of interventions for at risk populations.

Figure 1: NHS RightCare Cardiovascular Disease Prevention Optimal Pathway[5]



Proposal

To enable development of an integrated single platform ROI tool, there was a need for a consistent and up to date evidence review. CVD is a huge component of public health and health services in England and there is an enormous and continuously evolving evidence base which covers its many different detailed aspects. In order to construct a valid and useful tool, evidence around the following aspects of CVD was required:

- distribution of risk factors and high risk conditions within the population of England/local areas
- the incidence/progression of these risk factors and risk conditions over time.
- the relationship between the risk factors/conditions and the probability of having CVD events including the joint impact on CVD risk of having multiple risk factors already present
- the effectiveness of interventions to identify people with currently undetected risk factors
- the effectiveness of interventions (behavioural/lifestyle changes, pharmacological, and other) to manage and reduce levels of risk factors or progression of risk conditions
- the combined effectiveness of multiple interventions to manage CVD risk within populations having 1 or more risk conditions
- information about the current utilisation of interventions (ie how many are offered/take-up/adhere to/discontinue) nationally and locally
- the costs of these interventions to the NHS and social care
- the immediate and ongoing costs of management to the NHS and social care of CVD events which can occur including myocardial infarction, stroke, TIA, angina and heart failure
- the increased mortality risks (and hence reduced life expectancy) associated with CVD events
- the health related quality of life reductions associated with the different risk conditions and CVD events

Given the time and resource constraints of the project, it was not feasible to systematically review all of these areas. To circumvent the need for this, it was proposed to make the ROI tool based on an adaptation of an existing model: The School for Public Health Research (SPHR) Diabetes Prevention Model[7-9], which has been previously made into a PHE tool to model the ROI of the NHS Diabetes Prevention Programme (NHS DPP)[10]. The model is an individual patient simulation model consisting of a representative sample of the English population with baseline characteristics obtained from the Health Survey for England 2014 (HSE 2014)[11]. Using an individual patient level model had several advantages as follows:

- distribution of CVD risk factors and high CVD risk conditions including correlations between them in individuals with multiple risk factors or comorbid conditions was already incorporated within HSE 2014 data and therefore data to inform this was not required for most risk conditions (with the exception of AF, FH and CKD which were not included in the previous versions of the SPHR Diabetes Prevention Model)
- the model enabled estimation of progression of metabolic risk factors over time (including Body Mass Index [BMI]; Systolic Blood Pressure [SBP]; blood glucose [HbA1c] and cholesterol) through statistical modelling of longitudinal UK datasets (described in more detail later in this report) − it also already incorporated progression of non-diabetic hyperglycaemia and type 2 diabetes
- the relationship between risk factors/conditions and the probability of having CVD events including the joint impact on CVD risk of having multiple risk factors already present, was already modelled through QRISK2[12]. This is a well validated and widely used algorithm to estimate CVD risk in primary care, based upon analysis of data from the English population[13]. In the model it is used not only to estimate CVD risk, but also to determine the probability of an individual having a CVD event. Its ability to combine multiple risk factors meant that the benefits of multiple interventions acting on 1 or more risk factors, on CVD risk reduction within 1 individual could be modelled without having to identify specific data about the CVD risk reduction of intervention combinations

The work was carried out in 2 phases. Phase 1 focussed on answering the following questions through a series of rapid reviews:

- What are the most effective and cost-effective interventions for identifying and managing the high CVD risk conditions, including cross-cutting interventions that impact on more than 1 risk condition?
- To what extent do combinations of interventions interact with each other within a single individual to impact on the overall effectiveness and cost-effectiveness?
- What strategies do existing cost-effectiveness models use for modelling AF, FH and CKD?
- What local and national data exists to inform current care usage of those interventions chosen to be incorporated in the tool?

In addition, a conceptual model was developed in consultation with potential national and local tool users. This enabled a feasibility report to be produced, laying out exactly how the ROI tool would be constructed.

In phase 2 of the project, the SPHR Diabetes Prevention model was modified to incorporate the additional high-risk factors/conditions and reviewed interventions. A web interface was developed for the CVD Prevention ROI tool and a series of exemplar analyses carried out to enable tool users to see which strategies were most likely to produce the highest return on investment. Following tool development, a period of user-testing was undertaken before general release of the tool; firstly by steering group

members and then by tool user group members. This enabled any glitches in the tool to be resolved and the user experience to be improved through feedback.

Project scope

The scope of this project was focussed on CVD prevention in people at high risk of CVD due to 1 or more of the following conditions:

- high blood pressure
- atrial fibrillation (AF)
- high cholesterol/high CVD risk including Familial Hypercholesterolemia (FH)
- diabetes (Type 2 and Type 1)
- non-diabetic hyperglycaemia
- chronic kidney disease (CKD)

It did not include people with pre-existing CVD. Some stakeholders were keen that cardiac rehabilitation in people with pre-existing CVD should be included in the ROI tool. However, it was not considered feasible to expand the scope within the resource constraints of the project for the following reasons:

- increase in the number of interventions to be reviewed (potentially double the number)
- QRISK2 is only valid for primary CVD events and this is the primary mechanism through which CVD risk and event rates are calculated in the model[13]. This meant that substantial data analysis and extra model adaptation would be required to model subsequent CVD events in a more complex way than at present (currently not based on modifiable risk factors)

Project governance

The project had 3 separate layers of project governance:

PHE Working Group: This was composed of individuals from PHE. The remit of the working group was to administrate the project from within PHE and to provide help and advice relating to project progression.

Steering Group: The steering group was composed of a large number of clinical and topic experts from within a range of interested organisations including PHE, NHS England, National Institute of Health and Care Excellence (NICE), British Heart Foundation, Academic Health Sciences Network, NHS RightCare and the Stroke Association. The remit of the steering group was to make decisions about the project direction and provide clinical expertise and advice.

Tool User Group: The tool user group was composed of a large number of potential tool users from different national and local settings including local public health commissioners from CCGs and LAs, regional PHE CVD leads, Consultant and GP CVD leads and NHS RightCare delivery partners. The remit of the tool user group was to provide suggestions about the type of question that they would like the tool to answer, what they would like to be able to modify, what the tool should look like and what type of outputs would be useful to them. However, they did not have the remit to make decisions about the direction of the project or the content of the tool. Input into conceptual tool development was provided through a tool user workshop in Phase 1, with feedback about the developed conceptual tool and testing of the final tool carried out by tool users in Phase 2.

Project aims and objectives

The aim of this project was to develop an integrated single platform ROI tool for CVD prevention in high risk individuals based on a consistent and up to date evidence review.

- to assess the feasibility of the CVD prevention ROI tool given the availability of evidence
- to adapt the existing SPHR Diabetes Prevention Model to develop a CVD ROI tool that can evaluate the identified prevention intervention

The objectives were to:

- review evidence of effectiveness and cost-effectiveness of interventions that impact on the CVD high risk conditions, to identify a set of interventions for which there is good quality evidence, for inclusion in the tool
- review the literature to identify where possible, evidence of cumulative or multiplicative interactions between interventions and their impacts on CVD risk reduction
- review the literature to identify modelling studies that can support decisions about the design of model additions and adaptations
- collate and compile the evidence together with input from potential tool users to propose a formal plan and conceptual model of a CVD prevention ROI tool to present to the steering group and other stakeholders
- adapt the NHS DPP user-friendly ROI tool based on the School for Public Health Research Diabetes Prevention Model, to a CVD ROI tool that can be updated with local information to support implementation
- carry out a set of exemplar analyses to model the potential return on investment of CVD prevention interventions in 1 or more CVD high risk groups

Intervention effectiveness review methodology

Selection of intervention topics for review

Categorising interventions and deciding upon tool focus

A sequential process was undertaken to select intervention topics for review and for use in the tool. The first step was to investigate sources of interventions and characterise them into different types before deciding which type of intervention should be included in the tool. The following sources of evidence were consulted:

- NICE guidelines and NICE health technology appraisal guidance[14]
- NHS RightCare website[15]
- NHS Evidence[16] search for policies and initiatives related to the high risk conditions.
- Scoping searches in Medline designed to find out the types of interventions for CVD prevention being published for each high risk condition, and for reviews of multiple/combinations of interventions or interventions in multi-risk individuals.

Interventions were categorised into the following types and their inclusion within the tool discussed with the steering group:

1. **Interventions that are currently recommended for detection or management of high risk conditions.** These may or may not be optimally implemented in practice. Effectiveness and cost-effectiveness evidence for many of these can be found in the supporting evidence within NICE guidelines (although this would need updating where out of date) and can be searched for in the published literature. Other intervention parameters associated with current care usage such as uptake, adherence and discontinuation would also be necessary to characterise current care and therefore identify the opportunities for improvement that would produce return on investment within the tool.

   The steering group decided that including these types of intervention within the tool should be prioritised and that most reviewing effort should go into finding good quality evidence around such interventions.

2. **Policy and structural interventions that improve uptake of and adherence to current NICE guidelines.** These interventions tend to be very cross-cutting. Several interventions falling into this category were identified through the NHS Rightcare website[15]. This includes interventions such as practice audits for detection of high risk individuals, setting up local structures for self-management,

commissioning of new services and healthcare professionals (eg diabetes nurse), agreeing national and local clinical consensus and pathways for optimal management, and building local primary care leadership to drive quality improvement. Finding evidence for the effectiveness of these interventions would be problematic as often the only evidence cited within NHS RightCare is case study evidence.

The steering group decided that whilst these interventions were potentially very interesting, they should not be explicitly included within the tool due to a lack of evidence and the wish that local areas would develop their own methods for achieving improvement. However, it was decided that it would be worth listing these interventions in the report, to help tool users decide what types of action they could take to improve the uptake and adherence of the NICE recommended and well evidenced interventions included within the tool.

3. **Novel interventions for detection or management of high risk conditions.** This includes a wide range of interventions that may have been assessed in a trial or observational study or may have been carried out by a particular CCG or local authority. The potential range of such interventions is huge and could include for example; novel intensive diet and lifestyle programmes for high risk groups, digital interventions to improve management, maintenance interventions to retain the benefits of lifestyle change for a longer period, new pharmacological treatments not yet recommended by NICE, dietary supplements. Evidence for these would be found through searches, but in many cases might have to come from only a single primary study.

   The steering group decided that inclusion of this type of intervention would widen the scope too much and would risk over-ruling NICE guidelines if the tool was suggesting that such interventions should be carried out.

4. **User defined interventions.** This was suggested by a member of the steering group. It would enable users to run their own query if they could input some data about the cost and effectiveness of an intervention not included in the tool. Inclusion of this would not add to the reviewing scope as users provide their own evidence.

   The steering group decided that this would be a useful addition to the tool.

Extracting interventions from NICE guideline recommendations

Given the decision that the focus of the tool should be the inclusion of currently recommended interventions for detection and management of high risk conditions, the next step was to identify which interventions are currently recommended from within the relevant NICE guidelines. NICE has developed guidelines related to each of the high CVD risk conditions as follows:

- CG127: Hypertension (last updated 2016)[17]
- CG180: Atrial fibrillation (last updated 2014)[18]
- CG71: Familial Hypercholesterolaemia (last updated 2017)[19]
- CG181: CVD Risk Assessment and Lipid Modification (last updated 2016)[20]
- NG17: Type 1 Diabetes (last updated 2016)[21]
- NG28: Type 2 Diabetes (last updated 2017)[22]
- PH38: Type 2 Diabetes Prevention (includes recommendations for non-diabetic hyperglycaemia; last updated 2017)[23]
- CG182: Chronic kidney disease (last updated 2015)[24]

Table 1 shows the list of interventions recommended for each condition that were extracted from the NICE recommendations.

Table 1: List of interventions for detection and management of high CVD risk conditions extracted from NICE guideline recommendations

High Risk Condition		List of Interventions
Hypertension:	Detection	• No specific routes to detection recommended in hypertension guideline (although included within NHS Health Checks for CVD assessment). • Regular assessment of blood pressure in people with other high risk conditions recommended.
	Management	• Anti-hypertensive treatment (many drugs, singly or combined). • Lifestyle advice (includes dietary advice, physical activity advice, weight management, stop smoking services, alcohol advice, salt intake, caffeine consumption). • Referral to specialist services for people with uncontrolled or secondary hypertension. • Annual review to manage condition.
Atrial Fibrillation:	Detection	• No specific routes to detection recommended in AF guideline apart from pulse palpation for symptomatic detection. • Opportunistic assessment for AF in patients with other risk conditions including hypertension and FH.
	Management	• Anti-coagulants to prevent stroke (Warfarin or Novel oral anti-coagulants [NOACs]). • Rate control drugs.

		• Referral to specialist services for people with uncontrolled symptoms. • Left atrial appendage occlusion if anti-coagulants contra-indicated. • Catheter or surgical ablation or pace and ablate or cardioversion in people with permanent AF. • Annual review to manage condition.
High CVD Risk (10 year QRISK ≥ 10%):	Detection	• Systematic detection strategy should be used. This has been operationalised as NHS Health Checks. • Opportunistic assessment of CVD risk in people with other high risk conditions, particularly hypertension and type 2 diabetes is recommended.
	Management	• Lipid modification therapy (primarily statins and in particular Atorvastatin 20mg as first line therapy). • Lifestyle advice (includes dietary advice particularly about lipid intake, physical activity advice, weight management, stop smoking services, alcohol advice). • Annual review to manage condition. • Referral to specialist services for people with cholesterol higher than 9mmol/L.
Familial Hyper-cholesterolaemia:	Detection	• People with particularly high cholesterol found during CVD risk assessment (see above) should be assessed for likelihood of FH according to Simon Broome criteria. • Cascade testing should be used to identify relatives of those diagnosed with FH.
	Management	• Lipid modification therapy (primarily statins but also newer drugs such as Ezetimibe). • Individualised nutrition and lifestyle advice from an expert (advice similar to that for people with high risk of CVD). • Annual review to manage condition. • Referral to specialist services for people with homozygous FH or insufficient control of cholesterol with treatment. • LDL apheresis in individuals with homozygous FH or progressive unresponsive FH. • Liver transplant in individuals with homozygous FH.
Chronic Kidney Disease:	Detection	• No specific routes to detection in the general population recommended in CKD guideline. • Opportunistic assessment for CKD in patients with other risk conditions including diabetes and hypertension.
	Management	• ACEi/ARB anti-hypertensive treatment to manage blood pressure and prevent progression. • Lipid modification therapy to prevent CVD (primarily statins). • Lifestyle advice (includes dietary advice, physical activity advice, weight management, stop smoking

		services, intake of salt, potassium and phosphate). • Referral to specialist services for people with end stage disease. • Kidney dialysis or transplantation for end stage CKD. • Annual review to manage condition.
Type 1 Diabetes:	Detection	• It should be considered that patients diagnosed with diabetes might have type 1 diabetes, particularly if they do not have risk factors for type 2 diabetes.
	Management	• Insulin treatment to manage blood glucose. • Self-monitoring of blood glucose. • Lipid modification therapy to prevent CVD (primarily statins). • Anti-hypertensive therapy to keep blood pressure below 135/85. • Structured education following diagnosis (eg DAFNE programme) including training in carbohydrate counting, blood glucose awareness and individualised nutritional advice. • Self-management (this is enabled by structured education and self-monitoring). • Obtain specialist advice for people with uncontrolled blood glucose. • Pancreas or islet transplantation if condition cannot be well managed. • Annual review to manage condition.
Type 2 Diabetes:	Detection	• Opportunistic assessment for type 2 diabetes in patients with other risk conditions including hypertension and as part of CVD risk assessment (NHS Health Check). • Active seeking out of individuals that may be at high risk for testing, both in health settings (eg GP, A&E, NHS walk-in centres, vascular surgery units, ophthalmology departments) and community settings (eg community pharmacies, dental surgeries, opticians, workplaces, job centres, local authority leisure facilities, shops, libraries, faith centres, residential and respite care homes and day centres). • Family members of people with type 2 diabetes should be encouraged to have a risk assessment. • Risk assessment using a validated tool should precede blood testing.
	Management	• Pharmacological treatment to manage blood glucose (ranges from Metformin as initial therapy to insulin as fourth line treatment). • Lipid modification therapy to prevent CVD (primarily statins) if they also have QRISK ≥ 10%). • Lifestyle advice (includes dietary advice, physical activity advice, weight management, stop smoking services, alcohol intake)

		• Structured education following diagnosis (eg DESMOND programme). • Annual review to manage condition and reassess cardiovascular risk. • Obtain specialist advice for people with uncontrolled blood glucose.
Non-diabetic hyperglycaemia:	Detection	• Active seeking out of individuals that may be at high risk for testing, both in health settings (eg GP, A&E, NHS walk-in centres, vascular surgery units, ophthalmology departments) and community settings (eg community pharmacies, dental surgeries, opticians, workplaces, job centres, local authority leisure facilities, shops, libraries, faith centres, residential and respite care homes and day centres). • Family members of people with type 2 diabetes should be encouraged to have a risk assessment. • Risk assessment using a validated tool should precede blood testing.
	Management	• Intensive lifestyle programme (NHS DPP). • Weight loss programme in addition if overweight. • Metformin may be considered if lifestyle advice contra-indicated or ineffective. • Annual review to manage condition and reassess diabetes status.

Some of the lifestyle interventions recommended for management of high risk conditions refer to other NICE guideline documents including:

- PH24: alcohol use disorders (last updated 2010)[25]
- PH44: physical activity brief advice (last updated 2013)[26]
- PH54: physical activity exercise referral schemes (last updated 2014)[27]
- PH10: stop smoking services (last updated 2013)[28]
- PH53: weight management (last updated 2014)[29]
- PH49: behaviour change individual approaches (last updated 2014)[20]

Some of the pharmacological interventions recommended for management of high risk conditions refer to other NICE guideline documents including:

- CG76: medicines adherence (last updated 2009)[30]
- NG5: medicines optimisation (last updated 2015)[31]

These additional guideline documents were used to help provide extra information about recommended interventions.

Steering group decisions around inclusion and exclusion of topics

The list shown in Table 1 was presented to the steering group. Following discussion with the steering group, several interventions were excluded from further consideration as follows:

- rate control drugs for AF − steering group members did not wish this to be included because rate control drugs are used to control AF symptoms rather than to prevent CVD
- self-monitoring of blood glucose − whilst recommended for people with type 1 diabetes, it was assumed that this was an integral part of insulin treatment and would therefore be included in effectiveness estimates
- referral to specialist services − the steering group agreed that this was relevant to only a very small number of individuals with serious disease and did not fall within the prevention remit of the project
- procedures including kidney dialysis, kidney transplant, pancreas or islet transplant, LDL apheresis, left atrial appendage occlusion, left atrial ablation, pace and ablate, cardioversion − the steering group agreed that these are relevant to only a very small number of individuals with serious disease and did not fall within the prevention remit of the project

Following discussion with the steering group, several other interventions were added as follows:

- blood pressure self-monitoring − this has no specific recommendation around it in the current version of 'CG127 - Hypertension'[17], but the steering group indicated that they wished it to be included in the tool
- continuous subcutaneous insulin infusion (insulin pumps) − it was indicated by the steering group that insulin pumps should be included as an intervention due to their potential for improving blood glucose in patients with type 1 diabetes; this is recommended by NICE in the 'Technology appraisal guidance TA151'[32].
- lifestyle advice − whilst lifestyle advice is recommended for each high risk condition, the extra information in the additional NICE public health guideline documents detailed above enabled lifestyle advice to be split into the following particular topics:
  - brief dietary advice
  - brief physical activity advice
  - screening and brief advice for alcohol
  - exercise referral
  - smoking cessation and weight management.

  This was in addition to the specific more intensive lifestyle advice recommended in the guidelines for each high risk condition:
  - structured diabetes education
  - individualised nutritional advice for FH and CKD

  - intensive lifestyle programme for non-diabetic hyperglycaemia
- pharmacist medicine use reviews − the steering group agreed that it could be important to include interventions by non-medical health professionals such as nurses and pharmacists; this topic was chosen for review given that new medicine reviews and medicine use reviews are recommended in NICE guidelines for medicines optimisation[31]
- opportunistic detection mechanisms − NICE guidelines are less informative about the type of mechanisms that should be used to detect new cases; the steering group suggested that a range of detection mechanisms were being used in practice including a variety of mechanisms to detect AF (Watch BP Home A blood pressure monitor, for which a NICE Medical Technologies Guidance [MTG] is available[33]; AliveCor[34] smartphone application & GRASP-AF[35] tool for case finding), PRIMIS[36] tools for case-finding of diabetes and community blood pressure testing to detect hypertension

Final list of topics for review

The final list of topics for review, plus the population of relevance to each topic is shown in Table 2.

Table 2: Final list of topics for review

Intervention	Population
MANAGEMENT INTERVENTIONS	
Lipid modification drugs	High cholesterol; FH; QRISK ≥ 10%; Diabetes
Anti-hypertensives	Hypertension; CKD; (Diabetes; QRISK ≥ 10%)
Anticoagulants	AF with CHA2DS2-VASc score ≥ 2
Blood glucose lowering agents	Type 2 diabetes (insulin obligatory for type 1 diabetes).
National Diabetes Prevention Programme (intensive lifestyle)	Non-diabetic hyperglycaemia
Structured, evidence based education programmes for type 1 or type 2 diabetes	Diabetes
Insulin Pump	Type 1 diabetes
Brief advice/ recommendations for physical activity	All high risk groups
Brief advice/ recommendations for diet	All high risk groups
Weight management programmes (tier 2-3)	Overweight/obese in all high risk groups.
Smoking cessation programme	Smokers in all high risk groups.
Alcohol brief intervention or extended brief intervention	Heavy drinkers in all high risk groups.
Exercise referral	Sedentary in all high risk

	groups.
Individualised nutritional advice	CKD; FH
Pharmacy based medicine use reviews	All high risk groups taking medication for their condition
Blood pressure self-monitoring	Hypertension
DETECTION INTERVENTIONS	
NHS Health Check	Age 40-74 without pre-existing risk/condition.
Cascade Testing	Relatives of FH patients
Opportunistic Detection methods including GRASP-AF, WatchBP Home A, AliveCor or pulse checking in over 65s for AF detection; Community blood pressure testing for hypertension; PRIMIS, risk assessment tool or community diabetes testing for type 2 diabetes.	Varies according to method.
Annual patient review to detect other conditions	All high risk groups

Effectiveness Evidence Review Protocol

Evidence from NICE guidelines

NICE recommendations are backed up by a series of high quality evidence reviews which are presented as part of the guideline documents. To avoid duplicating work already done to very high standard by NICE, the first step was to look at the available evidence, extract details relating to chosen topics and decide whether it would be sufficient to meet the purposes of the project or whether additional searches needed to be carried out.

There were 3 main reasons to carry out additional searches. Firstly, the topic of interest may not have been reviewed at all. An example of this is brief advice for diet. Whilst there is plenty of evidence about the benefits of improving dietary intake (eg salt reduction for hypertension or fat reduction for people with QRISK ≥ 10%), which have led to the development of NICE guidelines stating that patients should be given advice about diet; there is no evidence referenced in the NICE guidelines relating to CVD about the effectiveness of being given brief advice itself. Given that brief dietary advice is all that is recommended for many of the high risk conditions, it is essential that the tool does not contain an excessively optimistic estimate of the benefits of dietary advice taken from randomised controlled trials (RCTs) that compare 1 diet with another under controlled conditions. Secondly, the topic may have been reviewed but outcomes relating directly to CVD or to CVD metabolic risk factors may not have been gathered. Thirdly, in many cases the evidence provided was carried out some years ago and so it was important to search for more recent studies. For these 3 reasons, the majority of topics required carrying out at least 1 search.

Defining a search question

Search questions are usually defined using the PICO system, where P = population; I = intervention, C = comparator and O = outcomes. This system was used to generate search questions relating to each topic where:

- **population** = high CVD risk groups of interest
- **intervention** = 1 of the chosen topics
- **comparator** = control/placebo/usual care
- **outcomes** = CVD risk reduction or changes in metabolic risk factors

The resource constraints of the project meant that there was not time to carry out a full systematic review or meta-analysis for each topic. Instead, the focus was in obtaining the highest quality estimates of effectiveness from a published source. Initial searches therefore focussed on finding recent and high quality systematic reviews and meta-analyses about the topic. If this was not successful in identifying effectiveness estimates, a second search would be carried out for randomised controlled trials (RCTs) or large observational studies.

The outcome of interest varied between the reviews. For reviews of management interventions, CVD event risk reductions (including stroke reduction or MI reduction) are useful for validating model results. However, as the model calculates CVD risk through the QRISK2 risk equations[13], it was also useful for model purposes to obtain outcomes relating to QRISK2 inputs including changes in metabolic outcomes (ie systolic blood pressure, total cholesterol, BMI or HbA1c) and smoking. This method enables interventions to be combined in a single individual without needing to know what the combinatorial impact of multiple interventions on CVD risk is. Primary outcomes were therefore considered to be metabolic/smoking outcomes, with secondary outcomes relating to CVD reduction. The exception to this was anti-coagulants whose stroke reduction benefit is independent from the metabolic risk factors in QRISK2 and for which stroke reduction was considered to be a primary outcome. A range of other outcomes were gathered for particular interventions, including adherence to medicines as an outcome in the review of medicines use reviews, and the rate of detection of high risk conditions for detection interventions.

Ideally, a single best estimate of effectiveness of an intervention compared with placebo/control/usual care was required for each topic to parameterise the model. However, the searches were designed to enable reviews to be identified for each high risk group (and multi-high risk groups) eligible for the intervention, so that potentially different measures of effectiveness could be used in different high risk groups if valid differences were found. The searches were also designed so that any information about intervention combinations would also be found (in this case the comparator would likely

be 1 of the combined interventions). In summary this meant that a single search could be used to find information about:

- the overall effectiveness of an intervention
- the differential effectiveness of an intervention in different high risk groups
- the differential effectiveness of an intervention in individuals with multiple high risk conditions
- the combinatorial effectiveness of an intervention when combined with another intervention within the same individual

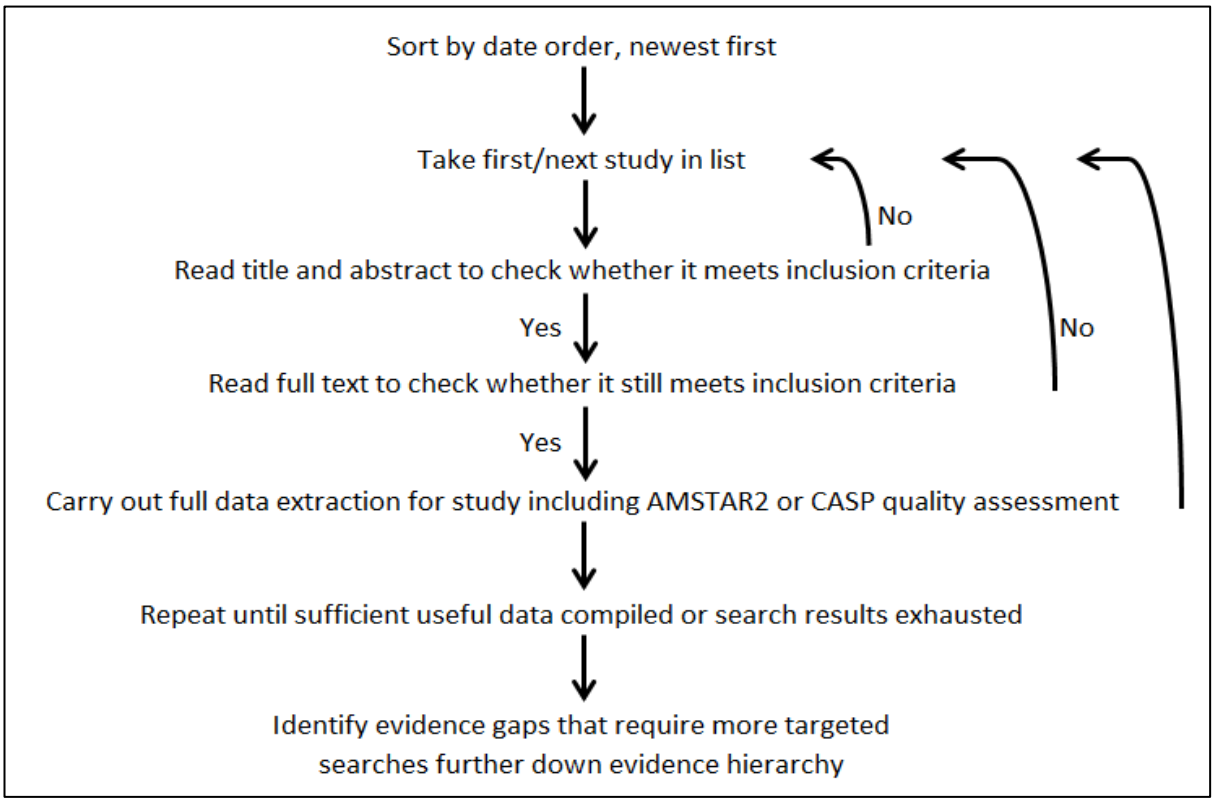
A set of search terms for each high risk group was defined and used repeatedly. Search terms were also constructed for each topic. Other search terms that were used where required included study type filters (eg systematic review, RCT), date filters (to limit searches to studies carried out since the last NICE review for example), UK/England filters (to limit searches for observational studies to relevant UK data), and some search terms for specific desired outcome measures. For example, searches for effectiveness data about anti-hypertensives included terms for systolic blood pressure (the metabolic blood pressure outcome used in the model) as this enabled studies with this particular outcome to be identified through the key word systolic. Due to resource constraints, searches were carried out only in Medline, as it was thought that high quality studies should be referenced in Medline. All search terms can be found in the Appendix.

Review protocol

A protocol was set out to enable the very rapid reviewing process required by the timescale (

Figure 2). First studies were sorted by date order, to enable newer studies to be prioritised. Then titles and abstract were scanned until a relevant study was identified. At this point the full text was checked to see whether it contained relevant outcomes and if so data was extracted and an informal assessment of study quality carried out. Data extracted for each study included the author; title; date; type of study (eg systematic review); setting (eg UK); relevant high risk population(s); intervention; comparator; number of studies reviewed (if systematic review); total number of patients; data about each outcome of interest including mean difference/relative risk; 95% confidence interval; time point; number of studies used to derive outcome and number of patients used to derive outcome. This process was repeated until sufficient studies had been identified to enable an informed choice to be made between them or search results had been exhausted. In practice this did often mean that all relevant studies returned by the search were extracted rather than just the most recent.

Figure 2: Rapid review protocol



Choice of study to go forward into the model and the database of interventions was determined partially by how comprehensive the study was (eg number of primary studies reviewed in a systematic review), partially by relevance to topic (eg interventions that closely resemble NICE guideline recommendations) and partially by date (more recent prioritised). The steering group were also consulted about study choice, and in some cases recommended sources of evidence for inclusion in the review. The chosen studies were formally assessed for quality. For systematic reviews a shortened version of the AMSTAR-2 tool (A MeaSurement Tool to Assess systematic Reviews)[37] was used for quality assessment including the following questions:

- Are the PICOs for the review question clear and defined?
- Was the literature search comprehensive?
- Did they satisfactorily assess risk of bias of included studies?
- How many studies were included, how large were they and of what design?
- Did they discuss heterogeneity when reporting results?

For RCTs, a shortened version of the Critical Appraisal Skills Programme (CASP) tool[38] was used for quality assessment including the following questions:

- Was the assignment of patients to treatments randomised (assessment of selection bias)?
- Were the groups similar at the start of the trial (assessment of confounding)?

- Were all of the patients who entered the trial properly accounted for at its end (assessment of attrition bias)?
- Were researchers collecting data blinded to treatment allocation (detection bias)?
- Was there a risk of selective reporting (reporting bias)?

Reports for each review can be found in the next section of this document.

Intervention effectiveness review reports

Lipid modification therapy

NICE recommendations

Recommendations about lipid modification therapy are found in NICE Guideline CG181, 2014; Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease[20], and are aimed at adults (18 years and over) with or without established CVD, with or without type 1 or 2 diabetes, and with or without chronic kidney disease (CKD). NICE has also developed specific guidelines on the use or effectiveness of lipid modifying drugs in people with specific risk conditions, including individuals with Chronic Kidney Disease (CKD) from NICE guideline CG182, 2014[24], and individuals with Familial Hypercholesterolemia (FH), NICE Guideline CG71, 2008[19]. In brief, the guidelines recommend that people with QRISK2 ≥ 10 be offered Atorvastatin 20mg for the primary prevention of CVD as a first line treatment, whilst individuals with FH may in addition be recommended a proprotein convertase subtilisin/kexin type 9 (PCKS9) inhibitor such as Ezetimibe[19].

Summary of evidence from the guidelines

A summary of the evidence from the guidelines is provided in Table 4. Briefly, the NICE guideline CG181, 2014[20], reported high quality evidence indicating that statins are associated with a -1.0 mmol/L reduction in LDL cholesterol at 5 years (16 RCTs with n=32,747). They found no evidence of a different effectiveness of statin therapy in people with type 2 diabetes, FH or CKD. Regarding Atorvastatin 20mg (the NICE recommended drug and dose), only 2 trials were included in the analysis (n=1,708); however a higher LDL cholesterol reduction of -1.7mmol/L was found. It is further noted that long term glycaemic control is associated with better outcomes; however, no study was found in the NICE review that exclusively investigated the efficacy of statin therapy or other LDL-cholesterol-lowering therapies in people with type 1 diabetes. Since CG181 was last updated in 2014 (and therefore reviews date from 2013), this rapid review therefore aimed at identifying any new studies examining effectiveness of lipid lowering drugs either as a class effect for statins, a class effect for PCKS9 inhibitors, or specifically for Atorvastatin 20mg. The primary outcome was change in cholesterol (total or LDL), with secondary outcomes of CVD event risk reductions.

Data from the NICE guideline CG181 indicates that 1 adverse effect of statin treatment is a small but significant increase in cases of new onset type 2 diabetes[20]. Whilst other adverse effects of statins were not included in the model, it was thought that this would

be particularly relevant given that type 2 diabetes is 1 of the high risk groups of interest. The review therefore also aimed to identify new studies examining the impact of statins on glycaemic control, with HbA1c change as a primary outcome and increased risk of new incident diabetes as a secondary outcome.

Review question: What is the effectiveness and the glycaemic impact of lipid modification therapy in adults, without established CVD, with 1 or more of: QRISK2 ≥ 10%, familial hypercholesterolemia, hypertension, atrial fibrillation, non-diabetic hyperglycaemia, type 1 or type 2 diabetes, or chronic kidney disease?

Search results and study selection

The review was conducted in 3 stages. In stage 1, the searches focused on identifying recent systematic reviews. The search for systematic reviews identified 191 articles. Six systematic reviews were included in the full text review[6 39-43]. In stage 2, a search was carried out to identify well conducted and large randomised controlled trials specifically comparing the effectiveness of Atorvastatin 20mg (the NICE recommended first line treatment[20]) with placebo. This was conducted as none of the systematic reviews found in the first search reported outcomes related specifically to this drug and dosage. The search for RCTs identified 134 articles; however, no relevant studies from this search were identified for inclusion in the review. A third search was also carried out to specifically identify systematic reviews about the impact of statin treatment on new diabetes incidence and glycaemic control. This identified 24 articles of which 4 were included in the full text review[44-47].

Individuals with QRISK2 ⩾ 10%

Two of the identified reviews[39 43] investigated the clinical effectiveness of statins in CVD prevention, whereas 1 review[42] investigated the effectiveness of PCKS9 inhibitors in preventing cardiovascular events, in adults with QRISK2 ≥ 10% and with no prior cardiovascular events (with or without other comorbidities). The number of studies included in each meta-analysis ranged from 19 to 136 randomised controlled trials (RCTs), recruiting between 8,883 and 134,537 patients (Table 3). Collins et al., 2016[39], and a Cochrane review (Taylor et al, 2013[43]) both reported the overall effect of statins as a class effect, versus placebo (PBO). Collins et al., 2016[39], in addition to crude data, also presented results for 4 different types of statins including Atorvastatin. Squizzato et al., 2017[42] conducted a meta-analysis investigating the effectiveness of PCSK9 inhibitors for treating dyslipidaemia in patients at different cardiovascular risk.

Individuals with CKD, Familial Hypercholesterolemia and diabetes

A well conducted systematic review and meta-analysis, Palmer et al., 2014[41], investigated the effects of statins on lipid profile in CKD. McDonagh et al., 2016[6] investigated the effectiveness of PCKS9 inhibitors in FH patients. A large systematic review and meta-analysis, Karlson et al., 2012[40], had data on lipid modification in

people with type 2 diabetes. In addition, Collins et al., 2016[39], also conducted a subgroup analysis of lipid changes in people with type 1 and type 2 diabetes. The search did not identify any reviews that investigated the effectiveness of lipid modification in people with atrial fibrillation (AF) or in people with hypertension.

Adverse effect of statins for glycaemic control

The 4 studies identified to inform the adverse effect of statins for glycaemic control included 3 reviews of statin treatment in individuals who already had diabetes (type 1 or type 2), reporting change in blood glucose (predominantly HbA1c) compared to control[45-47], and 1 review of statin treatment in individuals without diabetes, looking at the increased incidence of new onset diabetes[44]. Two of these studies performed subgroup analysis looking at different statin treatments including Atorvastatin, whilst another performed a subgroup analysis for high intensity statin treatment.

Table 3: Characteristics of included studies: Lipid modification therapy

Study	Type of Study	Intervention	Number of Studies	Total n
QRISK2 ≥ 10%				
Collins et al. 2016[39]	Review of Reviews & Meta-analysis	Statins (4 types)	136	134,537
Taylor et al. 2013[43]	Meta-analysis	Statins	19	56,934
Squizzato et al., 2017[42]	Meta-analysis	PCKS9	22	8,833
Chronic kidney disease (CKD)				
Palmer et al., 2014[41]	Meta-analysis	Statins	50	5,285
Familial Hypercholesterolemia (FH)				
McDonagh et al., 2016[42]	Systematic review	PCSK9 (ALI)	17	NR
Type 2 Diabetes				
Karlson et al., 2012[40]	Meta-analysis	Statins & Atorvastatin	37	32,258 (8,859)*
Adverse effect of statins on glycaemic control				
Casula et al., 2017[44]	Meta-analysis	Statins & Atorvastatin	19	NR
Cai et al., 2016[45]	Meta-analysis	Statins & High intensity statins	NR	6,875
Erqou et al., 2014[46]	Meta-analysis	Statins & Atorvastatin	9	9,696
Zhou et al., 2013[47]	Meta-analysis	Statins	26	3,232
PCSK9 = Proprotein convertase subtilisin/kexin type 9 (PCKS9) inhibitors; ALI = Alirocumab; * = number with diabetes; PBO = Placebo; NR = Not Recorded				

Review evidence

Lipid lowering drugs and reduction of cholesterol

Studies that reported the effectiveness of lipid lowering drugs on the reduction in cholesterol measured this either through an absolute reduction (in mmol/L) or as a percentage reduction from baseline. Note that the steering group indicated that a relative reduction was more clinically appropriate to use in the model. However, this did not constrain identification of studies for review or selection of the most appropriate study for use in the model, as the 2 can be easily interconverted if the baseline study cholesterol levels are known.

Taylor et al., 2013[43] reported absolute difference in LDL cholesterol reduction in statins versus placebo, which was very similar to that reported in the NICE CG181 guidelines[20]. However, the NICE evidence seems to suggest that the absolute reduction with Atorvastatin 20mg is much higher than this (1.70 mmol/L rather than 1 mmol/L). In the Collins et al., 2016 review this is reported as a percentage reduction instead39. Where total cholesterol reductions are also reported, these appear similar to the LDL cholesterol reductions indicating that cholesterol reduction is primarily due to reduction in LDL cholesterol.

Palmer et al., 2014[41] and Karlson et al., 2012[40] presented strong evidence that statins (and in particular Atorvastatin) significantly reduce LDL cholesterol in people with CKD and type 2 diabetes respectively. This seems to occur to a similar extent as that reported for the QRISK2 ≥ 10% population, indicating that statins may have a similar effectiveness in terms of cholesterol reduction in these subgroups.

McDonagh et al., 2016[6] suggests there is strong evidence that the PCSK9 inhibitor Evolocumab achieves a significant LDL cholesterol reduction among individuals with FH. A similar benefit is also observed among patients with homozygous FH.

Lipid lowering drugs and reduction of CVD outcomes

Three of the included studies reported the effectiveness of statin treatment on CVD outcomes (measured as relative risks [RR] for fatal CVD events, myocardial infarction [MI] or stroke) [39 41 43]. Reductions in CVD mortality with statin treatment in a QRISK2 ≥ 10% population ranged from 0.81 to 0.88; although the latter value was per 1mmol/L reduction in cholesterol. Higher reductions in CVD mortality were seen in a CKD population (RR = 0.77)[41]. Significant reductions in the rate of MI and stroke were also seen; again these were greater for individuals with CKD, although the stroke outcomes in the CKD population were not significant.

Lipid lowering drugs and glycaemic outcomes

Casula et al, 2017[44] found a much larger and more significant effect of statin treatment on incidence of new cases of type 2 diabetes than had been found in the NICE CG181

review[20]; this may be due to the inclusion of many more recent studies. Three studies reported an increase in HbA1c in people with diabetes taking statins of between 0.04% and 0.17%[45-47]; in the oldest review the change was not significant, but this also reviewed the fewest number of studies suggesting that inclusion of more recent studies has increased the significance of this result. The impact of Atorvastatin or other high intensity statins on HbA1c seems to be similar to that of statins in general.

Table 4: Evidence summary: Lipid modification therapy

Study	Intervention	Mean Difference	95% CI	Time Point	Total n	Number of Studies
Outcome 1: LDL Cholesterol						
QRISK2 ≥ 10%						
NICE Guideline CG181, 2014[20]	Statins	-0.99 mmol/L	-1.00; -0.97	Max 5.4 years	32,747	16
	Atorvastatin (20mg)	-1.70 mmol/L	-1.75; -1.65	Max 3 years	1,708	2
Collins et al. 2016[39]	Atorvastatin (20mg)	-43.0%	NR	Max 5 years	24,957	NR
Taylor et al. 2013[43]	Statins	-1.0 mmol/L	-1.16; -0.85	5.3 years	41,380	16
FH						
McDonagh et al., 2016[6]	Alirocumab (PCSK9)	-8.0%;-57.4%	NR*	12 weeks	99	2
	Evolocumab (PCSK9)	-44.1%;-61.3%	NR*	12 weeks	499	2
	Homozygous FH	-32.1%	-45.1; -19.2	12 weeks	50	1
NICE Guideline CG71, 2008[19]	Simvastatin	-14.9%; -46.5%	NR	4 weeks	NR	4
CKD						
Palmer et al., 2014[41]	Statins	-1.13 mmol/L	-1.39; -0.87	NR	2,054	22
Type 2 Diabetes						
Karlson 2012[40]	Atorvastatin 20mg	-41.8%	NR	>4 weeks	1,458	37
Outcome 2: Total Cholesterol						
QRISK2 ≥ 10%						
Taylor et al. 2013[43]	Statins	-1.05 mmol/L	-1.35; -0.76	5.3 years	34,122	14
Squizzato et al., 2017[42]	PCSK9	-48.80%	-54.1, -43.4	47 weeks	6,786	22
CKD						
Palmer et al., 2014[41]	Statins	-1.31 mmol/L	-1.71; -0.91	NR	2,105	25
Outcome 3: CVD Mortality						
QRISK2 ≥ 10%						
NICE Guideline CG181, 2014[20]	Statins	0.81 (RR)	0.77; 0.86	5.4 years	5,229	22
Collins et al. 2016[39]	Statins	0·88† (RR)	0·84; 0·91	1 year	10,177	NR
Taylor et al. 2013[43]	Statins	0.83 (RR)	0.72; 0.96	5.3 years	34,012	5
CKD						

Palmer et al., 2014[41]	Statins	0.77 (RR)	0.69; 0.87	NR	19,059	7
Outcome 4: Major Vascular Events (MI or Stroke)						
QRISK2 ≥ 10%						
Collins et al. 2016[39]	Statins	0.79† (RR)	0.77; 0.81	1 year	24,957	NR
Outcome 5: Myocardial infarction						
QRISK2 ≥ 10%						
NICE Guideline CG181, 2014[20]	Statins	0.69 (RR)	0.65; 0.73	5.4 years	91,482	21
Taylor et al. 2013[43]	Statins	0.73 (RR)	0.67; 0.80	5.3 years	48,049	14
CKD						
Palmer et al., 2014[41]	Statins	0.55 (RR)	0.42; 0.72	NR	9,018	8
Outcome 6: Stroke						
QRISK2 ≥ 10%						
NICE Guideline CG181, 2014[20]	Statins	0.78 (RR)	0.73; 0.83	5.4 years	109,244	19
Taylor et al. 2013[43]	Statins	0.78 (RR)	0.68; 0.89	5.3 years	40,295	10
CKD						
Palmer et al., 2014[41]	Statins	0.63 (RR)	0.35; 1.12	NR	8,658	5
Outcome 7: HbA1c						
Diabetes						
Cai et al., 2016[45]	Statins	0.10%	0.05; 0.15	NR	6,875	NR
	High Intensity statins	0.07%	0.02; 0.12	NR	NR	NR
Erqou et al., 2014[46]	Statins	0.12%	0.04; 0.20	NR	9,696	9
	Atorvastatin	0.17%	0.07; 0.27	NR	6,681	9
Zhou et al., 2013[47]	Statins	0.04%	-0.08; 0.16	NR	3,070	NR
Outcome 8: New Incident Diabetes Cases						
QRISK2 ≥ 10%						
NICE Guideline CG181, 2014[20]	Statins	1.09 (RR)	1.03; 1.17	5.4 years	3,504	10
Casula et al., 2017[44]	Statins	1.44 (RR)	1.31; 1.58	7.2 years	NR	19
	Atorvastatin	1.49 (RR)	1.31; 1.70	NR	NR	7

NR = Not reported; *= statistically significant. Where 2 figures (a range) have been provided for mean value, they represent different statin doses, † = Reduction in events per 1mmol/L reduction in cholesterol; NR = Not Recorded; RR = Risk Ratio

Conclusion

A large amount of relevant evidence about the effectiveness of statin treatment was found. For informing the QRISK2 equations it is necessary to input metabolic data (ie reduction in LDL cholesterol). Following discussion with the steering group it was agreed that for optimal treatment effect, this should be informed using the Atorvastatin 20mg data, and that a percentage reduction in cholesterol was more clinically relevant than an absolute reduction. The Collins et al., 2016[39] study was therefore considered the best source of evidence to inform this (43% reduction in LDL cholesterol) due to the large number of participants that the data had come from.

The benefit of statins in preventing CVD is thought to not come solely from the reduction in LDL cholesterol but also potentially through other mechanisms (steering group advice). It is therefore also necessary to take into account CVD reduction data when including the effectiveness of statins in the tool. The best source of data for this was thought to be the Collins et al., 2016[39] study as this was the most recent.

Finally, the increase in diabetes risk with statins will also be incorporated in the tool. This will be operationalised through a change in HbA1c, assuming that the increase in HbA1c observed in diabetic populations with statin treatment will also be observed in people at high risk of diabetes. Data from the Erqou et al., 2014[46] study will be used as this has specific analysis of people taking Atorvastatin. Quality assessment of chosen studies using key domains from AMSTAR-2[37] is shown in Table 5.

Table 5: Quality assessment: Lipid modification therapy

Study	Are the PICOs for the review question clear and defined?	Was the literature search comprehensive?	Did the authors satisfactorily assess risk of bias of included studies?	How many studies were included, how large were they and of what design?	Did they discuss heterogeneity when reporting results?	Overall quality?
Collins et al., 2016[39]	This is not a systematic review but is a review of reviews					
NICE Guideline CG181, 2014[20]	YES	YES	YES	21 RCTs	Unclear	HIGH
Erqou et al., 2014[46]	YES	Partial YES	YES	9 RCTs	YES	Moderate-HIGH

Anti-hypertensives

NICE recommendations

Recommendations about use of anti-hypertensive drugs are found in NICE Guideline CG127: Clinical management of primary hypertension in adults (2011)[17]. This was last updated in 2013. The guidelines recommend a target blood pressure for treated hypertension of below 140/90 mm Hg in people aged under 80 years and below 150/90 mm Hg in people aged over 80. NICE Guideline CG182: Chronic Kidney Disease (2014)[24], NICE Guideline NG17: Type 1 diabetes (2015)[21], and NICE Guideline NG28: Type 2 diabetes (2015)[22] separately recommend lower blood pressure targets for individuals with CKD, diabetes or a combination of the 2.

A range of different pharmacological treatments are recommended for achieving these targets including angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARBs), calcium channel blockers (CCBs) and thiazide-like diuretics. NICE Guideline CG127 (2011)[17] contains detailed recommendations for use of these drugs, including the order in which they should be used and the recommended combinations for individuals with different personal characteristics (eg age and ethnicity). Normally individuals will start on a single drug, but step up to combination therapy depending upon their response to treatment. Given the complexity of different treatment options, the steering group agreed that it was appropriate to treat anti-hypertensives as a single class with a single measure of effectiveness and that this should be considered to be represented by combination therapy rather than any single drug family.

Recommended therapy for treatment of CKD differs slightly from that for individuals with hypertension. NICE Guideline CG182 (2014)[24] recommends that individuals with CKD should be offered ACEi/ARB treatment even if they do not have clinical hypertension, as the drugs slow progression of CKD independently of their blood pressure effects. It is unclear whether combination therapy is appropriate for individuals with advanced CKD and hypertension due to potential safety issues.

Summary of evidence in the guidelines

NICE Guideline CG127[17] includes an extensive systematic review and meta-analysis of the effectiveness of anti-hypertensives that was carried out for the 2006 update. This reviews head-to-head comparisons for all classes of drugs, but does also include some meta-analysed evidence for the effectiveness of anti-hypertensive drugs against placebo in preventing mortality and CVD events. However, this is now over 10 years old and does not include systolic blood pressure outcomes. The 2014 update includes a summary of selected new evidence published since the 2006 update, but does not review this in detail. NICE Guideline CG127[17] is currently being updated and this

question is being revisited, but as it would not be published in time to inform the tool, it was necessary to search for more recent reviews of anti-hypertensive combination therapy.

NICE Guideline CG182 (2014)[24] includes a systematic review of evidence around the effectiveness of ACEi/ARB therapy for CKD, which includes some comparison against placebo. Outcomes tend to focus on CKD progression and CVD risk and do not include systolic blood pressure outcomes. It was therefore necessary to search for additional reviews for the effectiveness of ACEi/ARB therapy compared with placebo in individuals with CKD.

Review question: What is the effectiveness of anti-hypertensive combination therapy and ACEi/ARB therapy in reducing blood pressure and preventing CVD events in patients with hypertension, diabetes and CKD?

Study selection and search results

The review was conducted in 2 stages. In stage 1, the searches focused on identifying recent systematic reviews and found 550 studies. Four recent reviews comparing anti-hypertensives with placebo were retrieved (Table 6). One review (Brunstrom et al., 2016[48]) compared anti-hypertensive agents with placebo in people with diabetes; 1 Cochrane review (Musini et al., 2017[49]) assessed the effectiveness of anti-hypertensives compared with placebo or no treatment in adults <60 years; 1 review compared anti-hypertensive drug therapy with placebo in African or South Asian patients with hypertension (Brewster et al., 2016[50]); and 1 review assessed the effectiveness of anti-hypertensive monotherapy or combination therapy in non-resistant hypertensive patients (Paz et al., 2016[51]). A fifth review (Ettehad et al., 2016[52]) was added on the recommendation of the steering group.

In stage 2, searches focussed on identifying studies (reviews or RCTs) evaluating the effectiveness of ACEi/ARB therapy in individuals with CKD compared to individuals without CKD. Searches identified 133 studies, of which 2 systematic reviews were included. Huang et al., 2017[53] examined the efficacy and safety of blood pressure lowering drugs in individuals with diabetes; some of whom also had CKD, whilst the Blood Pressure Lowering Treatment Trialists' Collaboration (2013)[54] compared the effectiveness of anti-hypertensives in people with and without CKD.

Table 6: Characteristics of included studies: anti-hypertensives

Study	Type of Study	Intervention	Number of Studies	Total n
Hypertension				
Musini et al., 2017[49]	Cochrane systematic review	Anti-hypertensive drug therapy in adults aged 18-59	7	17,327

Brewster et al., 2016[48]	Systematic review	Anti-hypertensive drug therapy in African or South Asian patients with hypertension	African: 35 Asian: 16	African: 25,540 Asian: 1,719
Paz et al., 2016[51]	Systematic review	Antihypertensive monotherapy or combination therapy in patients with non-resistant hypertension	208	94,305
Ettehad et al., 2016[52]	Systematic review	Blood pressure lowering (all therapies)	123	613,815
Diabetes				
Brunstrom et al., 2016[48]	Systematic review	Anti-hypertensive drug therapy in patients with diabetes	49	73,738
Chronic Kidney Disease				
Huang et al., 2017[53]	Systematic review	Anti-hypertensive drug therapy in patients with diabetes	38	NR
Blood Pressure Lowering Treatment Trialists' Collaboration, 2013[54]	Systematic review	Anti-hypertensive drug therapy in patients with and without CKD	25	152,290
NR = Not Reported				

Review evidence

Blood pressure outcomes

Two reviews were identified that studied the effects of anti-hypertensives in general populations with hypertension (Musini et al., 2017[49] and Paz et al., 2016[51]). Paz et al., 2016[51] reported similar reductions in systolic blood pressure for ACE inhibitors, ARB and monotherapy in general compared to placebo (ACEi = -11.4 mm Hg, ARB = -12.9 mm Hg, monotherapy = -13,2 mm Hg) (Table 7). These were comparable with the reduction in systolic blood pressure found in Musini et al., 2017[49]. However, Paz et al., 2016[51] indicated that combination therapy showed a much greater reduction in systolic blood pressure (-20.2mm/Hg).

There was some suggestion from the steering group that different ethnic groups may respond differently to anti-hypertensive therapy. Brewster et al., 2016[48] found very different effectiveness for ACEi/ARB therapy in individuals of African versus South Asian ethnicity. However, they did not present results for combination therapy. Data from Paz et al., 2016[51] indicated that in contrast to specific drug classes, there was no significant difference in the effectiveness of combination therapy in African-American populations compared with the general population (Odds Ratio = 0.99 [0.96-1.02]), which may arise due to differences in treatment strategies in different ethnic groups (as recommended by NICE Guideline CG127[17]).

Data from the Blood Pressure Lowering Treatment Trialists' Collaboration, 2013[54] indicates that ACEi/ARB treatment results in a 4.7 mm Hg reduction in systolic blood pressure in populations with CKD (and a similar reduction in populations without CKD).

This is somewhat lower than that found by Paz et al., 2016[51] for ACEi or ARB monotherapy.

CVD outcomes

A range of other outcomes are reported including reduction in CVD mortality, MI, Stroke and combined CVD events (Table 7). Ettehad et al., 2016[52] reports reduction in CVD events per 10mm Hg reduction in systolic blood pressure. These suggest a slightly greater impact of anti-hypertensives on stroke (RR = 0.73) than on cardiac events (RR = 0.83); a result which was also seen in the 2006 evidence from NICE Guideline CG127[17]. Evidence from Brunstrom et al., 2016[48] and from the Blood Pressure Lowering Treatment Trialists' Collaboration, 2013[54], suggests that a similar magnitude of reduction is observed in individuals with diabetes and CKD.

Table 7: Evidence summary: Anti-hypertensives

Study	Intervention	Mean Difference	95% CI	Time Point	Total n	Number of Studies
Outcome No. 1: Systolic Blood Pressure						
Hypertension						
Musini et al., 2017[49]	Anti-hypertensives (class effect)	-14.98 mm Hg	-20.44; -9.52	1 year	14,845	3
Brewster et al., 2016[50]	ACE inhibitors (African)	-6.96 mm Hg	-9.64; -4.27	N/R	451	7
	ACE inhibitors (South Asian)	-22.51 mm Hg	-24.73; -20.29	4 weeks - 9 months	NR	NR
	ARB (African)	-3.63 mm Hg	-5.47; -1.78	N/R	933	4
	ARB (South Asian)	-10.41 mm Hg	-19.48; -1.34	4 weeks - 9 months	NR	NR
Paz et al., 2016[51]	ACE inhibitors	-11.4 mm Hg	-13.4; -9.4	Minimum 8 weeks	10,447	130
	ARB	-12.9 mm Hg	-14.6; -11.1	Minimum 8 weeks	27,129	157
	Monotherapy (class effect)	-13.2 mm Hg	-14.1; -12.2	Minimum 8 weeks	62,808	NR
	Combination therapy (class effect)	-20.2 mm Hg	-23.4; -16.7	Minimum 8 weeks	31,497	NR
Chronic Kidney Disease						
Blood Pressure Lowering Treatment Trialists' Collaboration, 2013[54]	ACE inhibitors	-4.6 mm Hg	NR	NR	42,896	NR
Outcome No. 2: CVD Mortality						
Hypertension						
Musini et al., 2017[49]	Anti-hypertensives (class effect)	0.78 (RR)	0.67; 0.91	1 year	17,278	6
Diabetes						
Brunstrom et al., 2016[48]	Anti-hypertensives in diabetes (class effect) Baseline SBP>150	0.75 (RR)	0.57; 0.99	3.7 years	NR	NR

Study	Intervention	Mean Difference	95% CI	Time Point	Total n	Number of Studies
	Anti-hypertensives in diabetes (class effect) Baseline SBP>140-150	0.87 (RR)	0.71; 1.05	3.7 years	NR	NR
Outcome No. 3: Total Major CVD Events						
Hypertension						
Ettehad et al., 2016[52]	Anti-hypertensives (class effect)	0.80 (RR)*	0.77; 0.83	NR	265,578	55
Diabetes						
Brunstrom et al., 2016[48]	Anti-hypertensives in diabetes (class effect) Baseline SBP>150	0.73 (RR)	0.53; 1.01	3.7 years	NR	NR
	Anti-hypertensives in diabetes (class effect) Baseline SBP>140-150	0.8 (RR)	0.66; 0.97	3.7 years	NR	NR
Chronic Kidney Disease						
Blood Pressure Lowering Treatment Trialists' Collaboration, 2013[54]	ACE inhibitors (without CKD)	0.81 (RR)	0.72; 0.91	NR	35,971	NR
	ACE inhibitors (with CKD)	0.81 (RR)	0.73; 0.89	NR	10,044	NR
Outcome No. 4: MI						
Hypertension						
NICE Guideline CG127 (2006)[17]	Anti-hypertensives (class effect)	0.75 (RR)	0.62; 0.91	NR	9,745	3
Ettehad et al., 2016[52]	Anti-hypertensives (class effect)	0.83 (RR)*	0.78; 0.88	NR	265,543	56
Diabetes						
Brunstrom et al., 2016[48]	Anti-hypertensives in diabetes (class effect) Baseline SBP>150	0.74 (RR)	0.63; 0.87	3.7 years	NR	NR
	Anti-hypertensives in diabetes (class effect) Baseline SBP>140-150	0.84 (RR)	0.76; 0.93	3.7 years	NR	NR
Outcome No. 5: Stroke						
Hypertension						
NICE Guideline CG127 (2006)[17]	Anti-hypertensives (class effect)	0.64	0.52; 0.78	NR	9,745	3
Ettehad et al., 2016[52]	Anti-hypertensives (class effect)	0.73 (RR)	0.68; 0.77	NR	265,323	54
Diabetes						
Brunstrom et al., 2016[48]	Anti-hypertensives in diabetes (class effect) Baseline SBP>150	0.77 (RR)	0.63; 0.87	3.7 years	NR	NR
	Anti-hypertensives in diabetes (class effect) Baseline SBP>140-150	0.84 (RR)	0.76; 0.93	3.7 years	NR	NR
RR = Relative Risk; NR = Not Reported; * = per 10 mm Hg reduction in systolic blood pressure						

Conclusions

A large amount of relevant evidence about the effectiveness of anti-hypertensive treatment was found. For informing the QRISK2 equations it is necessary to input metabolic data (ie reduction in systolic blood pressure). Following discussion with the steering group it was agreed that for optimal treatment effect, this should be informed using results for combination therapy for people with hypertension, and for ACEi/ARB therapy for people with CKD. The Paz et al., 2016[51] study was the only review we found that specifically reported outcomes for combination therapy, so these will be used to inform systolic blood pressure reductions in the tool. Data from the Blood Pressure Lowering Treatment Trialists' Collaboration, 2013[54] study will be used to inform the effectiveness of ACEi/ARB therapy in individuals with CKD.

Whilst the benefit of anti-hypertensives is assumed to work purely through blood pressure reduction, it is also useful to include estimates of CVD reduction for validation of the model. The Ettehad et al., 2016[52] study will be used for this purpose; firstly because it was specifically recommended by the steering group, secondly because it incorporates evidence from a very large number of participants and thirdly because of its standardised reporting of CVD reduction per 10 mm Hg. Quality assessment of chosen studies using key domains from AMSTAR-2[37] is shown in Table 8.

Table 8: Quality Assessment: Anti-hypertensives

Study	Are the PICOs for the review question clear and defined?	Was the literature search compre-hensive?	Did the authors satisfactorily assess risk of bias of included studies?	How many studies were included, how large were they and of what design?	Did they discuss heterogeneity when reporting results?	Overall quality?
Paz et al., 2016[51]	YES	Partial YES	YES	208 RCTs	YES	HIGH
Blood Pressure Lowering Treatment Trialists' Collaboration, 2013[54]	YES	YES	YES	25 RCTs	YES	HIGH
Ettehad et al., 2016[52]	YES	Partial YES	YES	123 RCTs	YES	HIGH

Anticoagulants for atrial fibrillation

NICE recommendations

NICE Guideline CG180: The Management of Atrial Fibrillation, 2014[18] recommends that stroke risk should be assessed in individuals with AF using the CHA2DS2-VASc score, and that anticoagulants should be offered to people with a score of 2 or above, and considered for men with a score of 1 or above. In practice this means individuals who have AF plus another risk factor such as diabetes, hypertension, prior CVD event or old age. A range of options are available for anticoagulant therapy, including treatment with either Warfarin or non-Vitamin K Antagonist Oral Anticoagulants (NOACs). Aspirin is not recommended for people with AF.

Summary of evidence from the NICE guidelines

The evidence review in NICE Guideline CG180, 2014[18] includes a meta-analysis of 5 studies comparing anticoagulant versus placebo which suggests that the relative risk of ischaemic stroke with treatment is 0.33 (95% CI 0.21; 0.53). This review does not distinguish between the different types of anticoagulant therapy.

The benefit of anticoagulants for CVD risk does not act through any of the metabolic or other risk factors included in the QRISK2 equations. The primary outcome of interest for the model from this review is therefore CVD risk reduction (and in particular stroke reduction) as reported in NICE CG180[18]. The review therefore sought to identify only more recent studies carried out since the NICE review. Given the recommendation that patients be considered for either Warfarin or NOAC treatment, evidence was sought for the effectiveness of either classes of drug against placebo.

The steering group noted that the adverse effects of anticoagulants in promoting bleeding risk were a particularly important consideration in AF treatment and that they should be included in the model. NICE Guideline CG180, 2014 suggests that the relative risk of major bleeding or haemorrhagic stroke with anticoagulant treatment compared to placebo is 1.56 and 1.87 respectively[18], although neither of these outcomes was significant. Bleeding outcomes were therefore also extracted as a secondary outcome.

Review question: What is the effectiveness of anticoagulants in reducing CVD events, and the risk of bleeding with anticoagulant treatment in patients with Atrial Fibrillation (AF)?

Search results and study selection

The review searches focused on identifying recent systematic reviews of anticoagulant treatment for AF versus placebo. The search identified 350 articles. A total of 3 studies met the inclusion criteria and were included in the brief review. One of these (Guo et al., 2017[55]) reviewed the effectiveness of anticoagulants in AF patients, and the other 2, Tan et al., 2016[56] and Dahal et al., 2016[57], reviewed the effectiveness of anticoagulants in AF patients who also had CKD. Whilst another 12 studies were identified, both for these population groups and for populations with AF and comorbid type 2 diabetes; all of these made head to head comparisons between NOACs and Warfarin, rather than comparing anticoagulants against placebo, and therefore could not be included in the review.

Guo et al., 2017[55] conducted a network meta-analysis of RCTs investigating the relative efficacy of 5 anticoagulants; Warfarin, Rivaroxaban, Apixaban, Edoxaban, Dabigatran, against placebo (PBO). They included 37 trials, which together recruited 251,147 patients. Tan et al., 2016[56] and Dahal et al., 2016[57] conducted meta-analysis of observational studies comparing Warfarin and PBO and prevention of stroke, MI, major bleeding, intracranial bleeding and other cardiovascular events among AF patients with CKD. Tan et al., 2016[56], included 20 well conducted real-world studies, with a total of 56,146 patients. Dahal et al., 2016[57] was smaller, with 11 observational studies and 48,500 patients. Dahal et al., 2016[57] was not available in full text and was not reviewed further given that Tan et al., 2016 was available, reviewed the same subject and considered a greater number of studies and participants (Table 9).

Table 9: Characteristics of the included studies: Anticoagulants

Study	Study type	Intervention	Number of Studies	Total n
AF				
Guo et al., 2017[55]	Network meta-analysis of RCTs	NOACs	37	251,147
AF plus CKD				
Tan et al., 2016[56]	Meta-analysis of observational studies	Warfarin	20	56,146
Dahal et al., 2016[57]	Meta-analysis of observational studies	Warfarin	11	48,500
NOAC = non-vitamin K antagonist oral anticoagulant				

Review evidence

Anticoagulants and CVD prevention

Warfarin, Rivaroxaban, Apixaban, Edoxaban and Dabigatran all significantly reduced occurrence of stroke to a similar extent among AF patients without any comorbidities in a review of RCTs[55] (Table 10). However, evidence from Tan et al, 2016[56] (a review of observational studies) indicated that Warfarin did not significantly reduce risk of stroke among AF patients with CKD. Only Guo et al., 2017[55] had data on effectiveness of

anticoagulants for MI; this suggested that there was no significant reduction. Guo et al., 2017[55] and Tan et al, 2016[56] also reported that anticoagulants reduced all-cause mortality but this was not significant.

Table 10: Evidence summary: Anticoagulants

Study	Intervention	Mean difference (OR)	95% CI	Time Point	Total n	Number of Studies
Outcome 1: Ischaemic Stroke						
Atrial Fibrillation						
NICE CG180 (2014)[18]	Anticoagulant (unspecified)	0.33	0.21; 0.53	1.2 to 2.2 years	1,175	5
Guo et al., 2017[55]	Warfarin	0.66	0.48; 0.80	4.1 years	127,967	37
	Rivaroxaban	0.47	0.29; 0.63	4.1 years	28,514	37
	Apixaban	0.45	0.27; 0.63	4.1 years	37,055	37
	Edoxaban	0.62	0.37; 0.85	4.1 years	18,482	37
	Dabigatran	0.53	0.32; 0.72	4.1 years	25,424	37
AF + CKD						
Tan et al., 2016[56]	Warfarin	0.92	0.74; 1.16	0.7 years	NR	15
Outcome 2: Myocardial Infarction						
Atrial Fibrillation						
Guo et al., 2017[55]	Warfarin	0.36	0.04; 2.36	4.1 years	127,967	37
	Rivaroxaban	0.37	0.03; 2.95	4.1 years	28,514	37
	Apixaban	0.27	0.02; 2.33	4.1 years	37,055	37
	Edoxaban	0.43	0.04; 3.44	4.1 years	18,482	37
	Dabigatran	0.25	0.02; 2.08	4.1 years	25,424	37
Outcome 3: All-cause mortality						
Atrial Fibrillation						
NICE CG180 (2014)[18]	Anticoagulant (unspecified)	0.82	0.53; 1.26	NR	NR	1
Guo et al., 2017[55]	Warfarin	0.85	0.61; 1.21	4.1 years	127,967	37
	Rivaroxaban	0.76	0.43; 1.36	4.1 years	28,514	37
	Apixaban	0.74	0.47; 1.17	4.1 years	37,055	37
	Edoxaban	1.07	0.61; 1.92	4.1 years	18,482	37
	Dabigatran	0.65	0.38; 1.13	4.1 years	25,424	37
AF + CKD						
Tan et al., 2016[56]	Warfarin	0.92	0.74; 1.16	0.7 years	NR	12
Outcome 4: Major bleeding						
Atrial Fibrillation						
NICE CG180 (2014)[18]	Anticoagulant (unspecified)	1.56	0.88; 2.75	NR	2,798	7
Guo et al., 2017[55]	Warfarin	1.73	0.57; 5.37	4.1 years	127,967	37
	Rivaroxaban	1.7	0.49; 5.96	4.1 years	28,514	37
	Apixaban	1.21	0.33, 4.37	4.1 years	37,055	37
	Edoxaban	1.19	0.31; 5.01	4.1 years	18,482	37
	Dabigatran	0.63	0.16; 2.52	4.1 years	25,424	37
AF + CKD						
Tan et al., 2016[56]	Warfarin	1.18	0.82; 1.69	0.7 years	NR	11
NOAC = non-vitamin K antagonist oral anticoagulant; NR = Not Reported; OR = Odds Ratio						

Anticoagulants and risk of major bleeding

Guo et al, 2017[55] found that Warfarin, Rivaroxaban, Apixaban and Edoxaban all increased risk of major bleeding, while Dabigatran may not. However, the confidence intervals were extremely wide indicating non-significance. Similarly, Warfarin was associated with an insignificant increase in risk of major bleeding in patients with AF and CKD[56].

Conclusions

The Guo et al., 2017[55] study was by far the best source of evidence found to inform this review question. Firstly, because it is very new and therefore includes the most studies and participants; secondly because it provides an analysis of all the major anticoagulant treatments currently recommended and thirdly because it reviews RCTs rather than observation studies. Evidence around the effectiveness of anticoagulants for preventing stroke will be included in the tool, but not the evidence around prevention of MI, due to its non-significance. Evidence around the risk of major bleeding will also be incorporated despite the non-significant findings, as the steering group highlighted this as being an important side effect of these drugs. Quality assessment of this study using key domains from AMSTAR-2[37] is shown in Table 11.

Table 11: Quality Assessment: Anticoagulants

Study	Are the PICOs for the review question clear and defined?	Was the literature search compre-hensive?	Did the authors satisfactorily assess risk of bias of included studies?	How many studies were included, how large were they and of what design?	Did they discuss heterogeneity when reporting results?	Overall quality?
Guo et al., 2017[55]	YES	YES	YES	37 RCTs	Unclear	HIGH

Blood glucose lowering medication for Type 2 diabetes

NICE recommendations

NICE Guideline NG28: Type 2 Diabetes in Adults (2015)[22] recommends that adults with type 2 diabetes should be helped to set an individualised HbA1c target, which may be achieved by diet and lifestyle alone, or more commonly through the use of blood glucose lowering medication. A 4 step medication pathway is recommended by NICE, with metformin generally used as first line treatment, stepping up to dual therapy, triple

therapy and finally insulin therapy if blood glucose is inadequately controlled at the previous step.

Note that NICE Guideline NG17: Type 1 Diabetes in Adults (2015)[21] recommends that adults with type 1 diabetes should aim to keep their HbA1c under 6.5%, which is achieved through use of insulin therapy. However, as insulin is essential for life in individuals with type 1 diabetes it was not appropriate to review the effectiveness evidence for this topic.

Summary of evidence from the NICE guidelines

NICE Guideline NG28 (2015)[22] includes results of a complex network meta-analysis comparing type 2 diabetes treatments at each step of treatment intensification. This indicates that metformin is the most effective drug for first line treatment, resulting in an average reduction in HbA1c of 0.83% compared to placebo. For subsequent treatment steps, the analysis compared different combinations of 2, 3 or more drugs against existing combinations of drugs rather than against placebo.

The SPHR Diabetes Prevention model already simulates a 3-step treatment regimen following diagnosis of type 2 diabetes[58]. First line treatment assumes use of low cost treatments such as metformin; a second treatment (assumed to be sitagliptin) is added if HbA1c levels rise above 7.4%. Initiation of insulin (third stage treatment) occurs if HbA1c rises above 8.5%. Effectiveness of these blood glucose lowering treatments is built into the model already through personalised trajectories of HbA1c that are based upon data from newly diagnosed diabetics within the UKPDS trial[59]. Following a diagnosis of diabetes individuals experience an initial fall in HbA1c due to changes in diet and lifestyle and initiation of medication; this is modelled conditional on HbA1c at diagnosis (as individuals with higher HbA1c at diagnosis tend to drop further before stabilising). After this initial reduction in HbA1c the longitudinal trajectory of HbA1c is estimated using the UKPDS outcomes model which can be used to predict HbA1c over time from the point of diagnosis[59]. Whilst the UKPDS data is now relatively old, this method represents a much more complex and nuanced way to model the effectiveness of blood glucose lowering medication than any updated analysis could provide within the timescale of this project. With the agreement of the steering group it was therefore decided that this topic would not be reviewed.

Conclusions

This topic was not reviewed given that blood glucose lowering for type 2 diabetes treatment is already incorporated in the model.

NHS diabetes prevention programme

NICE recommendations

NICE Public Health Guideline PH38: Type 2 Diabetes Prevention in People at High Risk (update 2017)[23] recommends that people confirmed as being at high risk of diabetes due to having an HbA1c between 6-6.4% should be offered a referral to a local, group-based intensive lifestyle change programme incorporating elements of dietary advice, physical activity and weight loss. Since publication of this guideline, NHS England has developed the NHS Diabetes Prevention Programme (NHS DPP); a centrally commissioned intensive lifestyle programme based on guideline principles and delivered locally by 4 different providers.

Summary of evidence from the NICE guidelines

NICE Guideline PH38[23] was updated last year with a new effectiveness evidence review and cost-effectiveness modelling (the latter carried out by ScHARR using the SPHR Diabetes Prevention Model). The systematic review looked at the effectiveness of pragmatic intensive lifestyle intervention programmes for diabetes prevention and found evidence to suggest that significant weight and HbA1c reductions could be achieved. Absolute changes in values of these depended upon the scenario considered, with the most pessimistic scenario based on excluding data from two large diabetes prevention programmes in other countries, which were considered to be potentially more intensive than the NHS DPP, and the most optimistic scenario including data from both of those studies (Table 12).

Table 12: Evidence summary: NHS DPP

Study	Intervention	Outcome	Mean change	95% CI	Time Point	Number of Studies
NICE PH38 (2017)[23]	Intensive Lifestyle Intervention: Optimistic Scenario	Weight	-2.97 kg	-4.75; -1.19	1 year	9
		HbA1c	-0.10%	-0.18; -0.03	1 year	6
		SBP	-1.33 mm Hg	-3.35; 0.70	1 year	6
		Total Cholesterol	-0.04 mmol/L	-0.10; 0.02	1 year	6
	Intensive Lifestyle Intervention: Conservative Scenario	Weight	-2.41 kg	-3.44; -1.38	1 year	8
		HbA1c	-0.07%	-0.12; -0.02	1 year	5
		SBP	-1.33 mm Hg	-3.35; 0.70	1 year	6
		Total Cholesterol	-0.04 mmol/L	-0.10; 0.02	1 year	6
	Intensive Lifestyle Intervention: Pessimistic Scenario	Weight	-2.15 kg	-3.14; -1.15	1 year	7
		HbA1c	-0.04%	-0.08; -0.01	1 year	4
		SBP	-0.06 mm Hg	-1.53; 1.40	1 year	5
		Total Cholesterol	-0.06 mmol/L	-0.13; 0.02	1 year	5
NHS DPP ROI Tool[10]	Intensive Lifestyle Intervention.	Weight	-3.24kg	-4.67; -1.81	1 year	35
		HbA1c	-0.20%	-0.29; -0.11	1 year	10
		SBP	-6.57 mm Hg	-9.47; -3.67	1 year	15
		Total Cholesterol	-0.28 mmol/L	-0.4; -0.15	1 year	15
SBP = Systolic Blood Pressure						

The Diabetes Prevention ROI tool[10] uses a different set of data taken from a PHE evidence review by Ashra et al. (2015)[60], combined with data from an older meta-analysis by Dunkley et al. (2014)[61]. Compared with the NICE study, these used slightly different search criteria, do not include some of the more recent trial data and rely on some assumptions around blood pressure and cholesterol which were not measured in the Ashra review, but were in the Dunkley review. The effectiveness estimates are higher for each of the 4 outcome measures.

An evaluation of the NHS DPP itself is currently underway; however this is not due to report for several years. Given that these 2 reviews were of high quality and carried out fairly recently, it was not thought worth investigating other review evidence and therefore no searches for this topic were performed.

Conclusions

Whilst the review evidence in the recent NICE Guideline PH38 (2017)[23] is more up-to-date, the steering group thought that is was important that the CVD ROI tool should align with the DPP ROI tool where possible to provide consistency between the 2 tools. The effectiveness data from the DPP ROI tool was therefore used[10]. However, this should be updated (in both tools) once evidence from the NHS DPP evaluation becomes available.

Structured evidence-based educational programmes for diabetes

NICE recommendations

Recommendations about the use of structured education programmes for individuals with diabetes are found in NICE Guideline NG17: Type 1 Diabetes (2015)[21] and NICE Guideline NG28: Type 2 Diabetes (2015)[22]. NICE Guideline NG17 (2015)[21] recommends offering a structured education programme of proven benefit, for example the DAFNE programme (Dose-Adjustment For Normal Eating), within 6-12 months of diagnosis. This should be delivered by trained educators and include advice on self-management, insulin use, carbohydrate counting and blood glucose awareness. NICE Guideline NG28 (2015)[22] recommends that group-based structured education with an evidence-based curriculum should be offered at the time of diagnosis and annually reinforced. This should be delivered by trained educators and include advice on lifestyle and self-management.

Summary of evidence in the guidelines

Evidence for the effectiveness of structured education for adults with type 1 diabetes was reviewed in NICE Guideline NG17 (2015)[21]. A meta-analysis indicated that significant reductions in HbA1c of between 0.49% (< 6 months) and 1.09% (> 12 months) were seen in individuals who had undergone structured education compared with usual care. However, this information came from a very small number of studies and participants, and therefore searches were carried out to find further studies to inform this topic.

For type 2 diabetes, NICE Guideline NG28 (2015)[22] did not perform any new analyses, instead citing evidence from an HTA from 2008[62]. The 2008 review included 13 studies but did not include a meta-analysis. Searches were therefore carried out to identify more recent evidence to inform this topic.

Review question: What is the effectiveness of structured, evidence based education for individuals with type 1 and type 2 diabetes?

Search results and study selection

Searches for systematic reviews identified 153 search results. Two reviews of a range of educational interventions for populations with type 2 diabetes were retrieved. Odgers-Jewell et al., 2017[63] reviewed group-based education programmes for adults with type 2 diabetes, with HbA1c as its primary outcome at ≥6 months follow-up. Duke et al 2010[64] is a Cochrane review of individual-based education for people with type 2 diabetes. No reviews for educational interventions in individuals with type 1 diabetes were identified from the searches.

The steering group recommended a number of sources for further evidence. For type 1 diabetes, the original DAFNE RCT was thought to be the best source of evidence[65]. Further evidence sources were found as references within a Diabetes UK report about diabetes education[66], which was also recommended by the steering group. This included a systematic review for type 2 diabetes education from 2012[67] and an RCT (7 year follow-up of the DAFNE trial) for type 1 diabetes education from 2012[68] (Table 13).

Table 13: Characteristics of included studies: structured education for diabetes

Study	Type of Study	Intervention	Number of Studies	Total n
Type 1 Diabetes				
NICE Guideline NG17 (2015)[21]	Systematic Review	Structured education for type 1 diabetes	6	1,109
DAFNE Study Group 2002[62]	RCT	Structured education for type 1 diabetes (DAFNE)	1	169
Gunn et al., 2012[68]	RCT	Structured education for type 1 diabetes (DAFNE) 7 year follow-up	1	111
Type 2 Diabetes				
Loveman et al., 2015[62]	Systematic Review	Structured education for type 2 diabetes	13	NR
Odgers-Jewell et al. 2017[63]	Systematic Review	Group-based structured education interventions for type 2 Diabetes	47	8,533
Duke et al. 2010[64]	Systematic Review	Individual structured education interventions for type 2 diabetes	9	1,359
Steinsbekk et al., 2012[67]	Systematic Review	Group-based diabetes self-management education for type 2 Diabetes	21	1,827

Review evidence

Most of the included studies reported significant changes in HbA1c at time-points ranging from 6 months to 7 years (Table 14). For type 1 diabetes, estimates of HbA1c reduction ranged from -0.3% at 7 year follow-up[68] to -1.09% at 1 year follow-up as reviewed in NICE Guideline NG17 (2015)[21]. For type 2 diabetes, a large range of follow-up time points were presented, with estimates ranging from -0.1% to -0.93%, with longer time-points tending to show a greater magnitude of HbA1c reduction. Duke et al., 2010[64] found HbA1c reduction to be both smaller and non-significant whereas the later (and larger) reviews generally found significant outcomes.

For type 2 diabetes structured education, a range of other outcomes were presented including BMI, systolic blood pressure and cholesterol. However, none of these outcomes were found to be significantly reduced compared to usual care (Table 14).

Table 14: Evidence summary: structured education for diabetes

Study	Intervention	Mean difference	95% CI	Time Point	Total n	Number of Studies
Outcome No 1: HbA1c						
Type 1 Diabetes						
NICE Guideline NG17 (2015)[21]	Structured education for type 1 diabetes	-0.49%	-0.75; -0.22	6 months	716	3
		-1.09%	-1.28; -0.90	1 year	75	2
DAFNE Study Group 2002[62]	DAFNE (RCT)	-1%	-1.42; -0.58	6 months	169	1
		-0.5%	NR	1 year	NR	1
Gunn et al., 2012[68]	DAFNE (RCT)	-0.3%	NR	7 years	111	1
Type 2 Diabetes						
Duke et al. 2010[64]	Individual education for type 2 diabetes	-0.2%	-0.5; 0.03	6-9 months	295	3
		-0.1%	-0.3; 0.1	12-18 months	632	4
Odgers-Jewell et al. 2017[63]	Group based education for type 2 diabetes	-0.31%	-0.48; -0.15	6-10 months	4,107	30
		-0.33%	-0.49; -0.17	12-14 months	4,384	27
		-0.72%	-1.26; -0.18	18 months	194	3
		-0.33%	-0.82 to 0.17	24 months	1,106	8
		-0.93%	-1.52 to -0.34	36-48 months	1,436	5
Steinsbekk et al., 2012[67]	Group based education for type 2 diabetes	-0.44%	-0.69; -0.19	6 months	1,827	13
		-0.46%	-0.74; -0.18	1 year	1,503	11
		-0.87%	-1.25; -0.49	2 years	397	3
Outcome No 2: BMI						
Type 2 Diabetes						
Duke et al. 2010[64]	Individual education for type 2 diabetes	-0.2 kg/m^2	-1.0; 0.6	12-18 months	312	2
Odgers-Jewell et al. 2017[63]	Group based education for type 2 diabetes	-0.0 kg/m^2	-0.44; 0.44	6-10 months	2,035	18
		0.19 kg/m^2	-0.37; 0.75	12-14 months	2,044	13
		0.80 kg/m^2	-0.93; 2.54	24 months	998	6
Steinsbekk et al., 2012[67]	Group based education for type 2 diabetes	-0.21 kg/m^2	-0.86; 0.43	6 months	1,159	7
		-0.22 kg/m^2	-1.13; 0.69	1 year	1,092	7
Outcome No 3: Systolic Blood Pressure						
Type 2 Diabetes						
Duke et al. 2010[64]	Individual education for type 2 diabetes	-2 mm Hg	-5; 1	12-18 months	625	3
Odgers-Jewell et al. 2017[63]	Group based education for type 2 diabetes	0.12 mm Hg	-1.44; 1.67	6-10 months	2,577	17
		-0.49 mm Hg	-1.90; 0.92	12-14 months	2,170	11
		-0.68 mm Hg	-5.43; 4.07	24 months	528	4
		-1.71 mm Hg	-5.76; 2.34	36-48 months	1,319	4
Steinsbekk et al., 2012[67]	Group based education for type 2 diabetes	-0.34 mm Hg	-5.19; 4.51	6 months	814	5
		-2.61 mm Hg	-6.74; 1.52	1 year	327	2
Outcome No 4: Total Cholesterol						
Type 2 Diabetes						
Odgers-Jewell et al. 2017[63]	Group based education for type 2 diabetes	-0.01 mmol/L	-0.16; 0.14	6-10 months	2,270	15
		0.01 mmol/L	-0.12; 0.15	12-14 months	1,819	9
		-0.10 mmol/L	-0.56; 0.36	24 months	484	3
		-0.23 mmol/L	-0.65; 0.18	36-48 months	1,275	3

Study	Intervention	Mean difference	95% CI	Time Point	Total n	Number of Studies
Steinsbekk et al., 2012[67]	Group based education for type 2 diabetes	-0.04 mmol/L	-0.17; 0.10	6 months	1,161	7
		0.07 mmol/L	-0.09; 0.24	1 year	656	4
Outcome No 5: LDL Cholesterol						
Type 2 Diabetes						
Odgers-Jewell et al. 2017[63]	Group based education for type 2 diabetes	-0.03 mmol/L	-0.13; 0.07	6-10 months	1,131	12
		0.08 mmol/L	0.01; 0.15	12-14 months	731	5

Conclusions

There is little review evidence around the benefits of structured education for type 1 diabetes, with the highest quality evidence coming from the NICE Guideline NG17 (2015)[21] review. This evidence is very similar to that found in the DAFNE trial[62], and therefore represents an appropriate estimate to use in the tool. For type 2 diabetes, Odgers-Jewell et al. 2017[63] represents the most recent and largest study and therefore will be used as the source of evidence for informing the tool. In particular, evidence from the 12-14 month time period will be used as this is the most robust and reflects the annual cycles used in the model. Changes in BMI, systolic blood pressure or cholesterol will not be incorporated in the effectiveness estimates due to the non-significant changes seen in these outcomes. Quality assessment of these studies using key domains from AMSTAR-2[37] is shown in Table 15.

Table 15: Quality assessment: structured diabetes education

Study	Are the PICOs for the review question clear and defined?	Was the literature search compre-hensive?	Did the authors satisfactorily assess risk of bias of included studies?	How many studies were included, how large were they and of what design?	Did they discuss heterogeneity when reporting results?	Overall quality?
NICE Guideline NG17 (2015)[21]	YES	YES	YES	47 RCTs	YES	HIGH
Odgers-Jewell et al. 2017[63]	YES	YES	YES	15 RCTs	YES	HIGH

Insulin pumps for type 1 diabetes

NICE recommendations

NICE Guideline NG17: Type 1 Diabetes in Adults; Diagnosis and Management (2015)[21] advises that adults with type 1 diabetes should be considered for continuous subcutaneous insulin infusion (also known as CSII or insulin pump) if they are having real-time continuous glucose monitoring; recommended in a subset of the type 1 diabetes population who have high risk of or poor awareness of hypoglycaemia and who are willing to commit to using the device.

Summary of evidence from the NICE guidelines

A NICE Technology Appraisal Guidance (TA151): Continuous Subcutaneous Insulin Infusion for the Treatment of Diabetes Mellitus was published in 2008[32]. This included an effectiveness review, which concluded that there was some evidence (mostly from observational studies) for a reduction in HbA1c levels and in the rate of severe hypoglycaemic episodes in individuals using insulin pumps compared to the control of multiple daily injections.

Review question: What is the effectiveness of continuous subcutaneous insulin infusion compared to multiple daily injections, for reducing HbA1c levels in eligible individuals with type 1 diabetes?

Search results and study selection

This topic was not in the original scope, but was identified as an important intervention by steering group members towards the end of the reviewing process. There was insufficient time to carry out a series of formal searches and reviews, so instead, some rapid PubMed searches were carried out using keywords from the review question. This identified 2 studies; a systematic review and meta-analysis from 2012, which reviewed the effectiveness of insulin pumps in individuals with either type 1 diabetes or type 2 diabetes; and an RCT of the recent REPOSE trial from 2017[69], which examined the effectiveness of insulin pumps compared to multiple daily injections in individuals having equivalent training in flexible insulin treatment (note that this population was not specifically at risk of hypoglycaemia and therefore would not be recommended insulin pumps according to current NICE guidelines). An additional systematic review from 2008 was recommended by the steering group[70]. Although this is relatively old, it is particularly relevant is it only incorporates studies from a patient population that corresponds to NICE Guideline eligibility for insulin pumps.

Table 16: Characteristics of the included studies: Insulin pump

Study	Type of Study	Intervention	Number of Studies	Total n
Pickup et al., 2008[70]	Meta-analysis	Insulin pump for type 1 diabetes	25	NR
Yeh et al., 2012[71]	Meta-analysis	Insulin pump for type 1 and type 2 diabetes	33	NR
REPOSE study group, 2017[69]	RCT	Insulin pump for type 1 diabetes	1	317
NR = Not Recorded; REPOSE = Relative Effectiveness of Pumps Over MDI and Structured Education Trial				

Review evidence

All of the included studies reported changes in HbA1c outcomes (Table 17). NICE Guidance TA51 (2008) did not include a meta-analysis and therefore reported a range of values between -0.2% and -1.4% from the 18 reviewed studies[32]. Pickup et al., 2008 found an average reduction in HbA1c of 0.61%[70], whereas Yeh et al., 2012 indicated that the reduction in HbA1c was about half of this[71]; however, only 4 studies were included in their subgroup analysis for the effects of insulin pump in adults with type 1 diabetes (note that the subgroup analysis for children with type 1 diabetes resulted in an even smaller effect size – not shown). The REPOSE study found a non-significant reduction in HbA1c at 2 years, but the study population does not relate to the NICE eligible group for insulin pump[69].

Table 17: Evidence summary: Insulin pump

Study	Intervention	Mean Difference	95% CI	Time Point	Total n	Number of Studies
Outcome 1: HbA1c						
NICE TA51 (2008)[32]	Insulin pump for type 1 diabetes	-0.2% to -1.4%	NR	Varies	NR	18
Pickup et al., 2008[70]	Insulin pump for type 1 diabetes	-0.61%	-0.47; -0.76	NR	NR	25
Yeh et al., 2012[71]	Insulin pump for adults with type 1 diabetes	-0.3%	-0.58; -0.22	NR	NR	4
REPOSE study group, 2017[69]	Insulin pump for type 1 diabetes (RCT)	−0.24%	−0.53; 0.05	2 years	317	1

Conclusions

Review of this topic indicated that there is likely to be a significant drop in HbA1c with use of insulin pump in eligible individuals with type 1 diabetes. The Pickup et al., 2008[70] study will be used to inform this as it was recommended by the steering group, contains data from the largest number of studies and uses a patient population which reflects NICE Guidelines around usage. Quality assessment of this study using key domains from AMSTAR-2[37] is shown in Table 19.

Table 18: Quality assessment: Insulin pumps

Study	Are the PICOs for the review question clear and defined?	Was the literature search compre-hensive?	Did the authors satisfactorily assess risk of bias of included studies?	How many studies were included, how large were they and of what design?	Did they discuss heterogeneity when reporting results?	Overall quality?
Pickup et al., 2008[70]	YES	Partial YES	YES	25 RCTs	YES	HIGH

Brief advice for diet and physical activity

NICE recommendations

NICE guidelines for each of the high risk CVD conditions indicate that individuals should be advised about dietary and physical activity changes that may benefit their health. However, for most of the conditions, guidelines do not recommend referring individuals to intensive programmes aimed at diet and exercise change (exceptions include exercise referral, structured education for people with diabetes, the NHS DPP and specialised nutritional advice for CKD and FH, which have all been reviewed as separate topics).

The advice varies for each condition. NICE guideline CG127: Hypertension[17] suggests that patients with hypertension should be advised to follow a healthy diet with regular exercise, encouraged to keep dietary sodium intake low and to limit excessive consumption of caffeine. NICE guideline CG181: Lipid modification[20] suggests that patients with high CVD risk should be advised to eat a diet in which fat intake is 30% or less of total energy intake, saturated fats are 7% or less and dietary cholesterol is less than 300mg per day, to choose wholegrain foods, to limit intake of sugar, to eat at least 5 portions of fruit and vegetables per day, 2 portions of fish per week (1 oily) and 4-5 portions of unsalted nuts, seeds and legumes per week, and to do physical exercise in line with NHS Choices guidelines on physical activity. NICE guideline CG71: Familial Hypercholesterolaemia[19] indicates that people with FH should receive similar advice to people with high CVD risk; however there is a recommendation to refer them to individualised nutritional advice (more intensive than brief advice), so this has been reviewed separately. Equally, NICE guideline CG182: Chronic Kidney Disease[24] recommends that patients should be encouraged to take exercise, and that dietary advice about potassium, phosphate, calorie and salt intake should be offered as appropriate to the severity of CKD, but this may be offered as specialised nutritional advice rather than brief advice. NICE guideline CG180: Atrial Fibrillation[18] does not contain any recommendations for diet or physical activity, whilst NICE Guideline PH38: Type 2 Diabetes Prevention in People at High Risk[23] recommends raising awareness of the importance of physical activity, with dietary advice generally recommended as being provided as part of an intensive diabetes prevention programme. Advice for people with diabetes may be given as part of diabetes education particularly for type 1 diabetes; however recommendations within NICE Guideline NG28: Type 2 diabetes in Adults[22] include emphasising healthy balanced eating and physical activity as applicable to the general population, individualising recommendations for carbohydrate intake and discouraging the use of foods marketed specifically for people with diabetes.

Brief advice for diet and physical activity falls within the remit of Making Every Contact Count (MECC)[72]. MECC is an approach to behaviour change promoted by NHS England, which utilises the millions of day to day interactions that organisations and

people have with other people to encourage changes in behaviour that have a positive effect on the health and wellbeing of individuals, communities and populations. The current expectation is that all organisations within the NHS will commit to MECC.

Summary of evidence from the NICE guidelines

Whilst NICE guidelines contain plenty of evidence about the benefits of making changes to diet or physical activity, there is little evidence within NICE guidelines about the effectiveness of the brief advice itself. NICE Public Health Guideline PH44 (2013)[26], reviewed the effectiveness of brief advice interventions addressing physical activity versus usual care delivered in a primary care setting for the general population. However, meta-analysed outcomes focused on improvements in level of self-reported physical activity and cardio-respiratory fitness and did not report CVD risk reductions or metabolic outcomes. No NICE guideline reported evidence around the effectiveness of brief dietary interventions.

Review question: What is the effectiveness of brief advice (defined as a single advice session of no more than 30 minutes) for diet and physical activity as recommended by NICE guidelines, for individuals with QRISK ≥ 10%, familial hypercholesterolemia, hypertension, atrial fibrillation, non-diabetic hyperglycaemia, type 1 or type 2 diabetes, or chronic kidney disease?

Search results and study selection

A search in MEDLINE for recent systematic reviews relating to brief advice for diet or physical activity (including search terms for MECC) obtained 415 references. Only a single article was found for full text review relating to brief interventions (Whatnall et al., 2018[73]); other articles tending to relate to much more intensive lifestyle change interventions (Table 19).

Table 19: Characteristics of the included studies: brief advice for diet and physical activity

Study	Type of Study	Intervention	Number of Studies	Total n
NICE Guidelines PH44, 2013[26]	Systematic Review & Meta-analysis	Physical activity brief advice for adults in primary care	15	NR
Whatnall et al., 2018[73]	Systematic Review	Brief nutrition interventions	45	23,327
NR = Not recorded				

The MECC and Health & Wellbeing Programme leads were recommended as contacts for further information by the steering group. They indicated that it was unlikely that further searches would be successful in identifying data around the required outcomes for this topic. They highlighted several potential sources of information and further

references; these are detailed in Table 20 together with reasons why they were not suitable for the current review.

Table 20: Studies recommended by MECC contacts with reason for not including in review

Study	Type of Study	Intervention	Reason(s) unsuitable
PHE Evidence Summary 2017294, 2017[74]	Evidence summary	10 minutes brisk walking each day	Intervention is walking itself, not brief advice about walking. No metabolic/CVD outcome data.
Aveyard et al., 2016[75]	RCT	Screening and brief intervention for obesity	Brief advice for weight management rather than diet or physical activity. Comparison is more intensive intervention rather than do nothing.
Lister et al., 2017[76] (note unpublished)	ROI Tool	Various types of MECC including diet and physical activity	None of the interventions included in the tool are based on metabolic or CVD risk reduction effectiveness data.
NICE Guideline PH49, External evidence review from Bazian (2013)[77]	Evidence review	Various types of lifestyle intervention including diet and physical activity	Lifestyle interventions reviewed are more intensive than brief advice. No metabolic/CVD outcome data.

Review evidence

The included study (Whatnall et al., 2018[73]) reported outcomes from 45 different studies including increases in fruit servings, changes in carbohydrate or fat intake or improvement in healthy diet score, but did not conduct a meta-analysis of any outcome and did not review any of the relevant outcomes for this project (data not shown). None of the data sources highlighted by the MECC team provided relevant outcomes to inform this review question.

Conclusions

No direct evidence was found relating to the CVD or metabolic benefits of brief advice for diet or physical activity. Some indirect evidence about changes in diet or physical activity does exist, but it is currently unclear how this could relate to changes in CVD risk. Note that the lack of direct evidence does not mean that these interventions are not important for reducing CVD risk.

The lack of relevant findings from this search highlights an evidence gap suggesting that this review question could benefit from further research. The lack of direct CVD evidence means that brief advice for diet and physical activity will not be included as an intervention in the CVD Prevention ROI tool at this stage.

Weight management

NICE recommendations

NICE Public Health Guideline PH53: Weight management: lifestyle services for overweight or obese adults, 2014[29] recommends that an integrated approach to preventing and managing obesity should be followed. This includes referring overweight and obese adults (BMI of ≥ 25 kg/m2 or ≥ 23 kg/m2 in Asian populations; and ≥ 30 kg/m2, respectively) to a lifestyle weight management programme that contains core components for effective weight loss and to prevent weight regain. This includes using a multi-component approach (eg dietary intake, physical activity and behaviour change), delivered by trained staff, lasting at least 3 months and including achievable goals.

Summary of evidence in the guidelines

NICE Guideline PH53, 2014[29] includes an evidence review about the effectiveness of the type of multi-component behavioural weight management programmes (BWMPs) that might be available in the UK for adults classified as overweight or obese. The BWMPs included diet, exercise or behavioural modification programmes offered in groups, individually, combined group and individual sessions, supervised, face-to-face contact or remote contact only (phone or web based), goal setting eg set daily energy intake; conducted in general practice or pharmacy settings, and delivered by a generalist (eg a GP, nurse, pharmacist, healthcare assistant, or health educator/trainer); or conducted in a commercial setting (Slimming world, Jenny Craig, Weight watchers, Rosemary Conley). A meta-analysis of 29 studies suggested a mean weight difference of -2.59kg in the intervention group compared with a no intervention control group. No subgroup analyses in individuals with high CVD risk conditions were performed and no CVD risk reduction outcomes were presented. The review therefore aimed to find more recent evidence about the effectiveness of BWMPs, to find evidence specific to individuals in high risk groups and to find a wider range of outcomes including CVD reduction outcomes and other metabolic outcomes than were presented in the Hartmann-Boyce, 2014 review.

Review question: What is the effectiveness of NICE guideline based behavioural weight management programmes for people who are overweight or obese and have 1 or more high CVD risk condition?

Search results and study selection

A search for this topic yielded a total of 435 references. After sifting, 3 reviews[78-80] met the inclusion criteria and were included in the brief review (Table 21). Brown et al., 2017[78] specifically reviewed the effectiveness of NHS Tier 3 weight management

interventions in adults in the UK. Unfortunately, it did not contain a meta-analysis of results and therefore could not be included in the summary of outcomes. Two further reviews were identified; Hartmann-Boyce et al., 2014a[79] and Hartmann-Boyce et al., 2014b[80], who conducted meta-analyses comparing BWMPs or different commercial based BWMPs to usual care. These latter 2 studies were variations on the evidence in NICE Guideline PH53, 2014[29], published by the same authors. None of the identified studies specifically investigated the effectiveness of BWMPs in high CVD risk groups.

Table 21: Characteristics of included studies: Behavioural weight management programmes

Study	Type of Study	Intervention	Number of Studies	Total n
General population overweight or obese				
Brown et al., 2017[78]	Systematic review	Specialist weight management services (Tier 3 - BWMPs) for adults in the UK.	14	NR
Hartmann-Boyce et al. 2014a[79]	Meta-analysis	BWMPs	37	16,000
Hartmann-Boyce et al. 2014b[80]	Meta-analysis	BWMPs assessed by trials in everyday contexts (eg commercial, primary care etc.)	8	3,700
BWMP = Behavioural Weight Management Programmes; NR = Not Reported				

Review evidence

Hartmann-Boyce et al., 2014a[79] found that BWMPs effectively reduce BMI by -2.84 kg within 12 months, similar to the reduction of -2.59 kg reported in NICE Guideline PH53, 2014[29] (Table 22). Hartmann-Boyce et al., 2014b[80] reported that commercial programmes achieved a weight loss of up to -6.83 kg by 12 months, but that BWMPs in primary care only achieved a weight loss of -0.45kg. Weight regain rates were reported in NICE Guideline PH53, 2014[29] as being 0.004 kg per month.

Hartmann-Boyce et al., 2014b[80] also reported the effectiveness of BWMPs in reducing LDL cholesterol and systolic blood pressure. Their results indicated that commercial or primary care BWMPs offered a non-significant reduction in systolic blood pressure at 12 months and no clear change in LDL cholesterol, but this was supported by very low quality evidence (Table 22).

Table 22: Evidence summary: Behavioural weight management programmes

Study	Intervention	Mean difference	95% CI	Time Point	Total n	Number of Studies
Outcome 1: Weight Loss						
NICE Guideline PH53, 2014[29]	BWMPs total	-2.59 kg	-2.78; -2.41	12 months	13,453	29
	BWMPs weight	-2.13 kg	-2.38; -1.87	12	6,747	28

Study	Intervention	Mean difference	95% CI	Time Point	Total n	Number of Studies
	loss programmes only			months		
Hartmann-Boyce et al. 2014a[79]	BWMPs total	-2.84 kg	-3.63; -2.07	12 months	13,453	37
Hartmann-Boyce et al. 2014b[80]	Commercial + Meal Replacement	-6.83 kg	-8.39; -5.26	12 months	442	2
	Group based Commercial	-2.21 kg	-2.89; -1.54	12 months	1,595	5
	BWMPs in Primary Care	-0.45 kg	-1.34; 0.43	12 months	944	5
Outcome 2: Weight Regain						
NICE Guideline PH53, 2014[29]	BWMPs total	0.004 kg /month	-0.065; 0.07	NA	NR	NR
Outcome 3: Systolic blood pressure						
Hartmann-Boyce et al. 2014b[80]	Commercial + Meal Replacement	−0.8 mm Hg	−2.0; 0.4	12 months	1,195	2
	BWMPs in Primary Care	−0.2 mm Hg	-2.3; 1.8	12 months	642	2
Outcome 4: LDL Cholesterol						
Hartmann-Boyce et al. 2014b[80]	Commercial + Meal Replacement	0.15 mmol/L	-0.10; 0.40	12 months	442	1
	Group based Commercial	-0.07 mmol/L	-0.14; 0.00	12 months	772	1
	BWMPs in Primary Care	0.07 mmol/L	-0.10; 0.24	12 months	261	1
BWMP = Behavioural Weight Management Programmes; NR = Not Recorded; NA = Not Applicable						

Conclusions

The data from Hartmann-Boyce et al. 2014a[79] will be used to inform the magnitude of weight loss in the tool. Systolic blood pressure and LDL cholesterol changes will not be incorporated as these were not significant. Quality assessment of this study using key domains from AMSTAR-2[37] is shown in Table 23.

Table 23: Quality assessment: Weight management

Study	Are the PICOs for the review question clear and defined?	Was the literature search compre-hensive?	Did the authors satisfactorily assess risk of bias of included studies?	How many studies were included, how large were they and of what design?	Did they discuss heterogeneity when reporting results?	Overall quality?
Hartmann-Boyce et al. 2014a[79]	YES	YES	YES	37 RCTs	YES	HIGH

Smoking cessation

NICE recommendations

Recommendations about interventions for smoking cessation are found in NICE Guideline PH10: Stop Smoking Services (2008)[28]. The guidelines recommend a range of interventions that can be offered as part of NHS Smoking Cessation Services for anyone who smokes or uses any other form of tobacco. This should include behavioural counselling, group therapy, pharmacotherapy (including Nicotine Replacement Therapy (NRT), varenicline, or buproprion) or a combination of effective treatments.

Summary of evidence in the guidelines

Evidence for the effectiveness of interventions for smoking cessation was reviewed in NICE Guideline PH10 (2008)[28]. The review identified 7 studies of English smoking cessation services that provided evidence that intensive interventions for smoking cessation provided by the NHS Stop Smoking Services are effective in the short term. Over 50% of clients who had set a quit date were self-reported as quit at 4 weeks. For long-term quit rates, 5 studies were identified that suggested 13-23% of successful quitters at 4 weeks self-reported as abstinent at 52 weeks. However, no meta-analysis was carried out and no subgroup analyses in high CVD risk individuals were reported. Searches were therefore conducted to identify more recent systematic reviews, preferentially with meta-analysed data and subgroup analysis of high CVD risk individuals.

Review question: What is the effectiveness of NICE recommended smoking cessation services in terms of long-term quit rates in individuals from high CVD risk groups or in the general population?

Search results and study selection

The searches were conducted in 2 stages. In the first stage, searches were specifically carried out to identify systematic reviews for the effectiveness of smoking cessation services in the high CVD risk groups, whilst in the second stage a wider set of searches for reviews and observational studies without population subgroup restrictions were carried out. In total, 604 search results were found of which 4 studies were selected. One of these was an observational study that specifically examined the effectiveness of the NHS Stop Smoking Programme (Dobbie et al., 2014)[81]. One review looked at the effectiveness of smoking cessation in people with type 1 or type 2 diabetes (Nagrebetsky et al., 2014[82]), whilst the other 2 reviews concerned the general smoking population (Stead et al., 2016[83] and Hartmann-Boyce et al., 2014[84]) (Table 24).

Dobbie et al, 2014[81] analysed 4 week and 52 week abstinence in 202,804 participants of the NHS Stop Smoking Programme. Nagrebetsky et al., 2014[82] included 7 RCTs of non-pharmacological and pharmacological interventions (including some combined interventions) compared with less intensive interventions eg routine doctor's advice or standard care. Hartmann-Boyce et al. (2014)[84] provided an overview of the results of various Cochrane reviews for smoking cessation interventions. The paper included a range of interventions, both non-pharmacological (eg telephone counselling; internet-based interventions; motivational interviewing) and pharmacological interventions (eg varenicline at various doses; NRT; anti-depressants). The Hartmann-Boyce review included 1 review comparing combined interventions with usual care, which was an older version of the Stead et al., 2016[83] paper. This intervention was thought to correspond most closely to the NHS Stop Smoking Programme and was therefore included in the review.

Table 24: Characteristics of included studies: Smoking cessation

Study	Type of Study	Intervention	Number of Studies	Total n
Dobbie et al., 2014[81]	Observational Study	NHS Stop Smoking Programme	NA	202,804
Hartmann-Boyce et al., 2014*[84]	Systematic Review	Interventions to combat tobacco addiction	466 RCTs	NR
Nagrebetsky et al., 2014[82]	Systematic Review	More intensive smoking interventions in people with diabetes	7	872
Stead et al., 2016[83]	Systematic Review	Combined pharmacotherapy and behavioural interventions for smoking cessation	53	>25,000
NR = Not recommended; NA = Not applicable; *A summary of new or updated Cochrane reviews since 2013.				

Review evidence

Dobbie et al., (2014)[81] presented results indicating that 8% of those recruited to the NHS Stop Smoking Programme were carbon monoxide validated as abstinent from smoking at the 52 week follow-up. This result was obtained from a prospective study that included a subset of 3,075 of the observational study participants.

For the other studies, review outcomes tended to be presented as relative risks of quitting at the specified time-point (usually 6 months) compared to a non-intervention group. Note that because this evidence comes from RCTs, this does mean that the study population is motivated to quit and therefore relative risks of quitting may not be transferable to the general population.

Results from Hartmann-Boyce et al., 2014[84] showed that a variety of different interventions were more effective in increasing quit rate than no intervention, ranging from a relative risk of 1.39 with individual counselling to 2.27 with varenicline, whilst combined behavioural and pharmacological interventions gave a relative risk of 1.82

compared to control (updated to 1.83 in the more recent Stead et al., 2016[83] review) (Table 25). Absolute quit rates for the combined intervention, reported in Stead et al., 2016[83] (not shown in Table 25) were 15% for the intervention group compared to 8.6% for the control group.

In individuals with diabetes, intensive smoking cessation interventions were found to have a relative risk of 1.32 for quitting compared to brief advice. However, it is unclear whether this lower figure reflects a genuine difference in people with diabetes, or a difference in the composition of the intervention.

Table 25: Evidence summary: Smoking cessation

Study	Intervention	Mean	95% CI	Time Point	Total n	Number of Studies
Outcome No 1: Percentage Quitting						
General Population						
Dobbie et al., 2014[81]	NHS Stop Smoking Programme	0.077	0.066; 0.09	52 weeks	3,075	NA
Outcome No 2: Relative Risk of Quitting Compared to Control						
General Population						
Hartmann-Boyce et al., 2014[84]	Telephone counselling	1.27	1.20; 1.36	>6 months	30,246	51
	Individual counselling	1.39	1.24; 1.57	>6 months	9,587	22
	Tailored and interactive internet-based intervention with telephone contact	2.05	1.42; 2.97	>6 months	686	2
	Physician advice to quit	1.76	1.58; 1.96	>6 months	22,239	26
	Self-help materials	1.45	1.27; 1.66	>6 months	15,711	14
	Motivational interviewing	1.27	1.14; 1.42	>6 months	10,538	14
	Buproprion	1.62	1.49; 1.76	>6 months	13,728	44
	NRT	1.60	1.53; 1.68	>6 months	51,265	117
	Varenicline 1.0mg 2/d	2.27	2.02; 2.55	>6 months	6,166	14
	Varenicline (low dose)	2.09	1.56; 2.78	>6 months	1,272	4
	Pharmacotherapy and behavioural interventions	1.82	1.66; 2.00	>6 months	15,021	40
Stead et al., 2016[83]	Combined pharmacotherapy and behavioural interventions	1.83	1.68; 1.98	>6 months	19,488	52
Diabetes						
Nagrebetsky et al., 2014[82]	Intensive smoking cessation interventions (mixed)	1.32	0.23; 7.43	>6 months	543	4
NRT = Nicotine Replacement Therapy						

Conclusions

The only evidence directly relating to NHS Stop Smoking Services is Dobbie et al., (2014)[81]. Furthermore, this evidence is presented using the outcome of proportion quitting at 52 weeks, which is easy to implement in the tool. Whilst the study is neither a

systematic review nor an RCT, it is part of a Health Technology Assessment and therefore likely to be of high quality.

Alcohol brief interventions

NICE recommendations

NICE Public Health Guideline PH24: Alcohol-Use Disorders: Prevention, 2010[85] includes recommendations that people who have been identified through screening as drinking a hazardous or harmful amount of alcohol are offered a session of structured brief advice (5-15 minutes) or extended brief advice (20-30 minutes) on alcohol. These sessions should cover the potential harm caused by their level of drinking, the barriers to change and outline practical strategies to help reduce alcohol consumption.

Summary of evidence in the guidelines

NICE Guideline PH24, 2010[85] reviewed evidence about the effectiveness of early identification of alcohol-use disorders and brief interventions to manage alcohol misuse among adults and adolescents. Primary and secondary outcomes reported included changes in patterns of alcohol consumption such as reduction in number of alcohol units consumed per week and abstinence. However, they did not report either CVD risk reduction outcomes or metabolic outcomes. We therefore aimed at finding reviews which reported reductions in metabolic markers (in particular for blood pressure; which is known to be correlated with alcohol consumption[86]), and cardiovascular events (stroke, myocardial infarction, and CVD mortality), specifically in a primary care setting. Whilst reviews were primarily sought for populations with CVD high risk (on the basis that intervention effectiveness might differ in people with risk conditions), it was acknowledged that most evidence would likely relate to the general population.

Review question: What is the effectiveness of NICE Guideline based adult alcohol screening and brief intervention programmes in reducing metabolic risk factors (particularly systolic blood pressure) or cardiovascular events in primary care settings, in CVD high risk groups or in the general population?

Study search, selection and quality assessment

A search for systematic reviews obtained 303 references of which 8 reviews[87-94], seemed to meet the inclusion criteria and were read at full text level. This included a review of reviews by O'Donnell et al., 2014[93]. One further review[95], which was among the reviews included in the review of reviews was also read in full. Eight of the reviews included meta-analyses but primary and secondary outcomes only included reduction in

alcohol intake (in various forms), hospitalisations, or mortality, and did not include metabolic or CVD outcomes. A further review (Timko et al., 2016[94]) carried out a search specifically for the impact of brief interventions for alcohol in individuals with hypertension. This review did summarise blood pressure outcomes from individual identified studies, but did not meta-analyse the results.

Given that the identified meta-analyses did not report metabolic outcomes, the next step was to look at the outcomes from the individual RCTs reported in Timko et al., 2016[94]. This identified 3 RCTs with systolic blood pressure outcomes[96-98], comparing brief interventions for alcohol with no intervention in individuals with hypertension. A more recent RCT with systolic blood pressure outcomes was also identified in a quick PubMed search[99]. Details of the studies identified in this review are summarised in Table 26.

Table 26: Characteristics of the included studies: Alcohol brief interventions

Study	Type of Study	Intervention	Number of Studies	Total n
O'Donnell et al., 2014[93]	Review of Reviews	Brief alcohol interventions in primary care	24 SRs (56 RCTs)	NR
Timko et al., 2016[94]	Systematic Review	Brief interventions for unhealthy substance abuse in primary care	27	NR
Keurhorst et al., 2015[92]	Meta-analysis	Brief alcohol interventions in primary care	29	NR
Donoghue et al., 2014[88]	Meta-analysis	Brief alcohol interventions in primary care	23	NR
Jonas et al., 2012[89]	Meta-analysis	Brief alcohol interventions in primary care	23	NR
Kaner et al., 2009[91]	Meta-analysis	Brief alcohol interventions in primary care	22	5,800
Kaner et al., 2007[91]	Meta-analysis	Brief alcohol interventions in primary care	21	7,286
Bertholet et al., 2005[87]	Meta-analysis	Brief alcohol interventions in primary care	19	5,639
Cuijpers et al., 2014[95]	Meta-analysis	Brief alcohol interventions in primary care	32	7,521
Wilson et al., 2014[98]	RCT	Brief alcohol interventions in hypertensive patients	1	67
Rose et al., 2008[97]	RCT	Brief alcohol interventions in hypertensive patients	1	300
Maheswaran, 1992[96]	RCT	Brief alcohol interventions in hypertensive patients	1	41
Chi et al., 2017[99]	RCT	Brief alcohol interventions in hypertensive patients	1	1,422
NR = Not Reported				

Review evidence

Only 1 of the 4 studies included in the review (Rose et al., 2008[97]) found a significant reduction in systolic blood pressure, with the other studies finding either a non-

significant reduction or a slight increase (Table 28).Table 27Table 27: Evidence summary: Alcohol brief interventions

Study	Intervention	Mean Difference	95% CI	Time Point	Total n	Setting
Outcome 1: Systolic blood pressure						
Wilson et al., 2014[98]	Brief alcohol interventions in hypertensive patients	+1.2 mm Hg (note, SBP drop in both arms but greater in control arm)	NR but not significant	6 months	67	UK
Rose et al., 2008[97]	Brief alcohol interventions in hypertensive patients	-4.2 mm Hg	-0.3; -8.1	2 years	300	US
Maheswaran, 1992[96]	Brief alcohol interventions in hypertensive patients	No change	NR but not significant	8 weeks	41	UK
Chi et al., 2017[99]	Brief alcohol interventions in hypertensive patients	-1.9 mm Hg	NR but not significant	18 months	1,422	US
NR = Not Recorded						

Conclusions

Whilst evidence suggests that harmful or hazardous alcohol consumption is correlated with high blood pressure, there is little data about the benefits of brief interventions for alcohol in reducing blood pressure or in improving CVD outcomes, and the data that does exists is inconclusive. Note that the lack of direct evidence does not mean that this intervention is not important for reducing CVD risk.

The lack of relevant findings from this search highlights an evidence gap suggesting that this review question could benefit from further research. The lack of significant and conclusive metabolic or CVD evidence means that brief advice for alcohol will not be included as an intervention in the CVD Prevention ROI tool.

Exercise referral schemes

NICE recommendations

NICE Public Health Guideline PH54: Physical Activity Exercise Referral Schemes (2014)[100] recommends that exercise referral schemes should only be funded for individuals who are sedentary or inactive, and have existing health conditions or other factors that put them at increased risk of ill health. Exercise referral schemes should incorporate core techniques of behaviour change such as agreeing goals, tailoring interventions to individual need, monitoring progress and providing feedback.

Summary of evidence in the guidelines

NICE Guideline PH54 (2014)[100] included a systematic review and meta-analysis of the effectiveness of exercise referral schemes compared to no exercise referral. Meta-analysed outcomes generally focused on improvements in level of self-reported physical activity and cardio-respiratory fitness, but metabolic outcomes for systolic blood pressure and BMI were also reported (see Table 29); although these came from only a 2 primary studies and were not significant. No CVD outcomes were reported. The review therefore focussed on finding systematic reviews of exercise referral schemes that had been carried out since the NICE review and that reviewed evidence around metabolic improvements or CVD risk reduction.

Review question: What is the effectiveness of exercise referral on metabolic or CVD outcomes in sedentary individuals with 1 or more high CVD risk conditions?

Search results and study selection

The search for systematic reviews published since the NICE PH54 (2014)[100] evidence review identified 138 papers. Only 2 relevant reviews were found, 1 of which was a slight update of the NICE evidence for health technology assessment by Campbell et al., 2015[101] and did not contain any additional metabolic data. In addition, a study by Parretti et al., 2017[102] was found, which investigated the effectiveness of exercise referrals in the UK among obese individuals. The review was aimed at exploring whether the effects of exercise referral vary by baseline BMI, and compared the results of the primary study; EMPOWER[103] carried out in an obese population, against the results of the Campbell et al., 2015 review[101]. Summary of the study characteristics is provided in Table 29.

Table 28: Characteristics of the included studies: Exercise referral schemes

Study	Type of Study	Intervention	Number of Studies	Total n
Campbell et al., 2015[101]	Meta-analysis	Exercise referral schemes in primary care	8	5,190
Parretti et al., 2017[102]	Systematic Review & comparative analysis	Exercise referral schemes in primary care for obese individuals	1	347

Review evidence

The evidence from the NICE guideline PH54[100], Campbell et al., 2015[101], and the Parretti et al., 2017[102] study found insignificant changes in systolic blood pressure and BMI; however, their findings were slightly contradictory. NICE guideline PH54[100] and Campbell et al., 2015[101] reported a slight fall in systolic blood pressure, but a slight rise in BMI for exercise referral compared to usual care at 6 to 12 months whereas Parretti et al., 2017[102] reported a slight rise in systolic blood pressure, but a slight fall in BMI among the intervention group at 6 months (Table 29). Overall, the metabolic evidence suggests that exercise referral offers no tangible benefit to either normal weight or obese patients. No study reported CVD risk outcomes.

Table 29: Evidence summary: Exercise referral schemes

Study	Mean difference	95% CI	Time point	No of studies	n
Outcome 1: Systolic blood pressure					
NICE Guideline [PH54] [100] Campbell et al., 2015[101]	-0.05 mm Hg	-1.84, 1.74	6 to 12 months	2	702
Parretti et al., 2017[102]	0.68 mm Hg	-2.04, 3.40	6 months	1	347
Outcome 2: BMI					
NICE Guideline [PH54] [100] Campbell et al., 2015[101]	0.01 kg/m^2	0.14, 0.16	6 to 12 months	3	809
Parretti et al., 2017[102]	−0.36 kg/m^2	-1.19, 0.47	6 months	1	347

Conclusions

There are few studies that have examined metabolic or CVD outcomes following exercise referral, and those that have done indicate that there is no significant benefit on BMI or systolic blood pressure for exercise referral compared to control.

The lack of relevant findings from this search highlights an evidence gap suggesting that this review question could benefit from further research. The lack of significant metabolic or CVD evidence means that exercise referral will not be included as an intervention in the CVD Prevention ROI tool.

Individualised nutritional advice

NICE recommendations

Individualised nutritional advice is recommended for individuals with FH and CKD in their respective guidelines. NICE Guideline CG71: Identification and Management of Familial Hypercholesterolaemia (2008)[19], recommends that all individuals with FH should be offered individualised nutritional advice from a healthcare professional with specific expertise in nutrition. NICE Guideline CG182: Chronic Kidney Disease (2014)[24] indicates that diet is one of the cornerstones of treatment for CKD and recommends that dietary advice should be offered about potassium, phosphate, calorie and salt intake appropriate to the severity, of CKD and in the context of detailed dietary assessment and supervision.

Summary of evidence in the guidelines

NICE Guideline CG71 (2008)[19] reviewed the effectiveness of dietary interventions to improve outcomes in adults and children with AF. The review found only very limited and short term evidence for cholesterol lowering diets, most of which was inconclusive. No specific review of individualised nutritional advice was included within the NICE CG71 Guideline.

NICE Guideline CG182 (2014)[24] includes a review of the clinical and cost-effectiveness of low protein diets for improving renal outcomes. However, the findings of the review indicated that low protein diets should not be recommended. No specific review of individualised nutritional advice was included within the NICE CG182 Guideline. This rapid review therefore aimed at identifying any evidence about the effectiveness of individualised nutritional advice for either FH or CKD.

Review question: What is the effectiveness of individualised nutritional advice in improving metabolic outcomes or CVD risk in individuals with FH or CKD?

Search results and study selection

This topic was included at a late stage following discussion with a CKD expert from within ScHARR and therefore a full search was not performed. A PubMed search using key words from the review question identified 2 Cochrane systematic reviews of dietary interventions for FH[104 105] and 1 very recent Cochrane systematic review of dietary intervention for CKD[106] (Table 30).

The 2 reviews for FH both examined the potential benefits of a cholesterol lowering diet for FH rather than individualised nutritional advice per se[104 105]. Both reviews found only

a single relevant RCT (the same study) with only 19 participants. For CKD the Palmer et al., 2017[106] review was more promising. This included data from 17 studies and 1,639 individuals, and examined a range of different dietary interventions including dietary counselling, increased fruit and vegetable intake, Mediterranean and high protein diets. Subgroup analyses for different types of intervention were included, allowing outcomes to be extracted specifically for dietary counselling, which was thought to most closely resemble the review question.

Table 30: Characteristics of included studies: Individualised nutritional advice for CKD and FH

Study	Type of Study	Intervention	Number of Studies	Total n
Familial Hypercholesterolaemia				
Malhotra et al., 2014[104]	Systematic Review	Dietary interventions for FH (cholesterol lowering diet)	1	19
Shafiq et al., 2010[105]	Systematic Review	Dietary interventions for FH (cholesterol lowering diet)	1	19
Chronic Kidney Disease				
Palmer et al., 2017[106]	Systematic Review	Dietary interventions for CKD (dietary counselling, increased fruit and veg, Mediterranean, low protein)	17	1,639

Review evidence

Outcomes from the reviews are summarised in Table 31. The reviews of dietary interventions for FH found non-significant reductions in either total cholesterol or LDL cholesterol after following a cholesterol lowering diet for 1-2 months. The Palmer et al., 2017[106] review for dietary interventions for CKD found a significant reduction in systolic blood pressure for dietary counselling compared to usual care. Non-significant reductions in weight, BMI (not shown) and CVD mortality were also observed.

Table 31: Evidence summary: Individualised nutritional advice for CKD and FH

Study	Intervention	Mean Difference	95% CI	Time Point	No of studies	n
Familial Hypercholesterolaemia						
Outcome No 1: Total Cholesterol						
Malhotra et al., 2014[104]	Dietary interventions for FH (cholesterol lowering diet)	-0.4 mmol/L	-0.95; 0.15	1-2 months	1	19
Shafiq et al., 2010[105]	Dietary interventions for FH (cholesterol lowering diet)	-0.4 mmol/L	-0.95; 0.15	1-2 months	1	19
Outcome No 2: LDL Cholesterol						

Malhotra et al., 2014[104]	Dietary interventions for FH (cholesterol lowering diet)	-0.27 mmol/L	-0.79; 0.25	1-2 months	1	19
Shafiq et al., 2010[105]	Dietary interventions for FH (cholesterol lowering diet)	-0.27 mmol/L	-0.79; 0.25	1-2 months	1	19
Chronic Kidney Disease						
Outcome No 3: Systolic Blood Pressure						
Palmer et al., 2017[106]	Dietary counselling for CKD	-11.83 mm Hg	-13.67; -9.98	NR	2	95
Outcome No 4: Weight						
Palmer et al., 2017[106]	Dietary counselling for CKD	-0.2 kg	-1.93; 1.53	NR	3	200
Outcome No 5: CVD Mortality						
Palmer et al., 2017[106]	Dietary counselling for CKD	6.58 (RR)	0.35; 122.21	NR	1	62
NR = Not Recorded: RR = Relative Risk						

Conclusions

The lack of significant outcomes from the review of nutritional advice for FH means that this intervention will not be included in the tool. Systolic blood pressure outcomes for nutritional advice for CKD will be included in the tool from Palmer et al., 2017[106]. Quality assessment of this study using key domains from AMSTAR-2[37] is shown in Table 32 (note that quality is only low-moderate as comes from just 3 RCTs).

Table 32: Quality assessment: Individualised nutritional advice

Study	Are the PICOs for the review question clear and defined?	Was the literature search compre-hensive?	Did the authors satisfactorily assess risk of bias of included studies?	How many studies were included, how large were they and of what design?	Did they discuss heterogeneity when reporting results?	Overall quality?
Palmer et al., 2017[106]	YES	YES	YES	3 RCTs	YES	LOW-Moderate

Pharmacist medicines use review

NICE recommendations

The NICE Guideline NG5: Medicines optimisation; The safe and effective use of medicines to enable the best possible outcomes, (2015)[31] outlines the medication use monitoring strategies that should be adopted so as to optimise adherence, minimise medicine related problems, reduce waste and enable possible best outcomes. The guideline recommends that medication reviews should be considered for people with chronic long term conditions (guideline No 25), or individuals taking multiple medications. The onus of determining which health professional should conduct medication review is left with individual organisations (guideline No 26). In the UK, the NHS contracts accredit pharmacists to carry-out Medicines Use Review (MUR) and Prescription Intervention Services for patients on multiple medications or with long-term conditions[107].

Summary of evidence in the guidelines

NICE Guideline NG5, (2015)[31] included a systematic review examining the effectiveness of MURs. This found 28 primary studies, but due to differences in outcomes reported in each study, only 1 meta-analysis was performed relating to mortality outcomes. This indicated that MUR had no significant impact on mortality. No CVD, metabolic or adherence outcomes were reported. This rapid review therefore aimed at identifying any evidence about the effectiveness of pharmacy led MURs in improving either metabolic risk factors or adherence to medication in individuals with high CVD risk conditions treated with lipid modifying drugs, anti-hypertensives, anticoagulants, or/and blood glucose lowering drugs.

Review question: What is the effectiveness of Pharmacist-led Medicine Use Reviews (MURs) in improving metabolic outcomes and adherence in individuals with high CVD risk conditions taking lipid modification therapy, anti-hypertensives, anticoagulants or blood glucose lowering medication?

Search results and study selection

The review was conducted in 2 stages. In stage 1, the searches focused on identifying recent systematic reviews. This search identified 349 articles of which 4 well conducted reviews were found to be relevant (Table 33) [108-111]. These all evaluated the effectiveness of pharmacist led interventions in patients with hypertension.

Since no systematic reviews assessing the effectiveness of MURs in patients taking lipid lowering drugs, anticoagulants or blood glucose lowering drugs were identified, a

second search was done to identify relevant RCTs. The RCT search identified 71 articles, of which 6[112-117] were deemed relevant and included in the brief review. Among these RCTs, Blackburn et al., 2016[113], Eussen et al., 2010[115] and Aslani et al., 2011[114] investigated effectiveness of MURs in improving adherence to statins; Elliott et al., 2016[116] investigated adherence to medication among people taking anti-hypertensives, blood glucose lowering medication or anticoagulants; Al Hamarneh et al., 2017[117] recruited CKD patients with at least 1 uncontrolled CVD risk factor, and O'Connor et al., 2014[112] studied medication adherence in people with type 2 diabetes (Table 33).

Table 33: Characteristics of included studies: Pharmacist Medicine Use Review

Study	Type of Study	Intervention	Number of Studies	Total n
Rotta et al., 2015[110]	Review of Reviews	Pharmacist-delivered MUR in adults with hypertension	49 (269)	NR
Cheema et al., 2014[109]	Meta-analysis	Pharmacist-led interventions on blood pressure control in adults with hypertension	16	3,032
Santschi et al., 2014[111]	Meta-analysis	Pharmacist-led interventions on blood pressure control in adults with hypertension	39	14,224
Morgado et al., 2011[108]	Meta-analysis	Pharmacist-delivered MUR in adults with hypertension	15	3,280
Blackburn et al., 2016[113]	RCT	Pharmacist-delivered MUR in adults at risk of CVD who were on statins	1 (30†)	1906
Aslani et al., 2011[114]	RCT	Pharmacist-delivered MUR in adults at risk of CVD who were on statins	1 (17†)	142
Eussen et al., 2010[115]	RCT	Pharmacist-delivered MUR in adults at risk of CVD newly prescribed statins	1 (26†)	899
Elliott et al., 2016[116]	RCT	Pharmacist-delivered MUR in adults with hypertension, type 2 diabetes or on anticoagulants	1 (46†)	504
Al Hamarneh et al., 2017[117]	RCT	Pharmacist-delivered MUR in adults with CKD and at least 1 uncontrolled CVD risk factor	1 (56†)	290
O'Connor et al., 2014[112]	RCT	Pharmacist-delivered MUR in adults with type 2 diabetes	1	2,378
† = number of community pharmacies in RCT				

Review evidence

Pharmacist MUR and metabolic risk factor reduction

Four systematic reviews[108-111] reported the effectiveness of pharmacist MUR in reducing systolic blood pressure. There seemed to be an agreement among all the included reviews that MUR by a pharmacist is associated with between -6 to -11 mm Hg reductions in systolic blood pressure. Individuals with CKD seemed to benefit similarly from pharmacist MUR, with a -10 mm Hg reduction in systolic blood pressure reported at 3 months of follow-up in an RCT[117] (Table 2).

A number of the included RCTs reported effectiveness of pharmacist MURs in reducing LDL cholesterol among patients taking statins with type 2 diabetes[112], CKD[117] and in general. All the studies reported that pharmacist MUR significantly reduced patients LDL cholesterol to a similar extent (between 0.09 and 0.2 mmol/L).

Two RCTs, O'Connor et al., 2014[112] and Al Hamarneh et al., 2017[117] reported reduction of HbA1c among patients with type 2 diabetes (the latter also with CKD). In CKD patients, MUR significantly improved HbA1c by 0.7%; however, in the patients with type 2 diabetes[112], there was no significant difference between the intervention and control groups.

Pharmacist MUR and adherence to medication

One systematic review Morgado et al., 2011[108], assessed the effectiveness of pharmacist MUR and adherence to anti-hypertensive medication. The evidence from this review was contradictory; 5 of the 15 studies included in the adherence analysis found that pharmacist MUR significantly increased adherence to anti-hypertensive medication, whereas 5 found no significant results and 5 found greater adherence in the control arm. We searched for RCTs to obtain the impact of pharmacist MUR in patients taking other CVD prevention medication. Three RCTs[112 113 116] reported association between pharmacist MUR and adherence to medication among patients with type 2 diabetes[112], patients with a range of conditions including hypertension, type 2 diabetes or on anticoagulants[116], and patients taking statins[113]. Only Elliott et al., 2016[116] found that pharmacist MUR significantly improved adherence to medication (Table 34). However, this was a composite result obtained from a mixed population of adults with hypertension, type 2 diabetes, asthma or taking aspirin (not recommended for AF in any case), and separate results for each group were not presented. This benefit was not observed in the other studies. The observations here should be taken with caution since this evidence is from single primary studies.

Table 34: Evidence summary: Pharmacist Medicine Use Review

Study	Mean Difference	95% CI	Time Point	No of studies	n
Outcome No 1: Mortality					
NICE Guideline NG5, (2015)[31]	0.96	0.81; 1.13	NR	10	3,081
Outcome No 2: Systolic Blood Pressure					
Hypertension taking anti-hypertensives					
Santschi et al., 2014[111]	-7.6 mm Hg	-9.0; -6.3	8.3 months	39	14,224
Cheema et al., 2014[109]	-6.13 mm Hg	-8.44; -3.81	3 to 13 months	11	2,240
Morgado et al., 2011[108]	-4.9 mm Hg	SD ± 0.9	mean 6.7 months	8	2,619
Rotta et al., 2015[110]	-8 to -11 mm Hg	NR	NR	6 (SRs)	NR
CKD taking anti-hypertensives					
Al Hamarneh et al., 2017[117] (RCT)	-10.5 mm Hg	13.5; -7.4	3 months	NA	283

Study	Mean Difference	95% CI	Time Point	No of studies	n
Outcome No 3: LDL Cholesterol					
QRISK2 ≥ 10% taking statins					
Aslani et al., 2011[114] (RCT)	-0.17 mmol/L	-0.19; -0.53	9 months	NA	97
Eussen et al., 2010[115] (RCT)	-0.2 mmol/L	-0.21; -0.19	12 months	NA	1,016
CKD taking statins					
Al Hamarneh et al., 2017[117] (RCT)	-0.2 mmol/L	-0.1; -0.4	2 months	NA	257
Type 2 Diabetes taking statins					
O'Connor et al., 2014[112] (RCT)	-0.09 mmol/L	NR	2 months	NA	663
Outcome No 4: HbA1c					
Type 2 Diabetes taking blood glucose lowering medication					
O'Connor et al., 2014[112]	-0.28%	NR	2 months	NA	1,102
CKD and type 2 diabetes taking blood glucose lowering medication					
Al Hamarneh et al., 2017[117] (RCT)	-0.7%	-0.9%; -0.4%	2 months	NA	234
Study	**% Adherence intervention**	**% Adherence Control**	**p-value**	**Time point**	**n**
Outcome No 5: Adherence					
Hypertension taking anti-hypertensives					
Morgado et al., 2011[108]	67.0% to 95.8%	50.0% to 92.0%	Varies	6.7 months	2,619
QRISK2 ≥ 10% taking statins					
Blackburn et al., 2016[113] (RCT)	71.6%	70.9%	0.64	12 months	1,906
Type 2 Diabetes					
O'Connor et al., 2014[112] to control elevated glucose (RCT)	85.9%	87.6%	0.54	2 months	1,102
O'Connor et al., 2014[112] to control hypertension (RCT)	85.8%	83.0%	0.35	2 months	791
O'Connor et al., 2014[112] to control lipid levels (RCT)	79.6%	81.9%	0.47	2 months	663
Mixed population					
Elliott et al., 2016[116] (RCT)	70.7%	60.5%	0.037	10 weeks	378
NR = Not Reported; NA = Not Applicable.					

Conclusions

This review found several useful studies for informing the effectiveness of pharmacist MUR. Given that most studies reported results for only 1 of the pharmacological treatments in the model, it was decided that the data from Elliott et al., 2016[116] would be most appropriate to use, as this reports a single measure of improvement in adherence across all medication types reviewed. Whilst this study did not include people taking statins, or taking anticoagulants (other than aspirin), it was thought a reasonable

assumption that improvements in adherence might be similar across these medication types too. Quality assessment of this study using key domains from CASP[38] is shown in Table 35.

Table 35: Quality assessment: Pharmacist Medicine Use Review

Study	Was the assignment of patients to treatments randomised (assessment of selection bias)	Were the groups similar at the start of the trial (assessment of confounding)?	Were all of the patients who entered the trial properly accounted for at its end (assessment of attrition bias)	Were researchers collecting data blinded to treatment allocation (detection bias)?	Was there a risk of selective reporting (reporting bias)?	Overall quality?
Elliott et al., 2016[116]	YES	YES	YES	MAINLY	NO	HIGH

Blood pressure self-monitoring for management of hypertension

NICE recommendations

The current version of NICE Guideline CG127: Hypertension in adults: Diagnosis and Management (2011)[17] does not have recommendations around blood pressure self-monitoring as part of hypertension management (it does have recommendations about home blood pressure monitoring to diagnose hypertension, but this is not the subject of this review). However, the steering group indicated that including this intervention in the tool would be useful.

Summary of evidence in the guidelines

This topic has not been reviewed as part of the NICE CG127 (2011) guideline[17]. Searches without date limits were therefore carried out for systematic reviews about the effectiveness of blood pressure self-monitoring for improving blood pressure control. Prevention of CVD events and improved adherence to antihypertensive medication were collected as secondary outcomes.

Review question: What is the effectiveness of blood pressure self-monitoring in improving blood pressure control in people with hypertension?

Search results and study selection

The search for systematic reviews identified 39 articles of which 5 well conducted reviews were found to be relevant (Table 36). Tucker et al., 2017[118] reviewed 36 studies around blood pressure self-monitoring and included subgroup analyses of individuals with diabetes and CKD. Duan et al., 2017[119] was the largest review, including 46 studies; however this had a slightly different focus examining the effectiveness of tele-monitoring for hypertension. The 3 other included studies were slightly smaller and older, and focussed more on improvements in adherence rather than improvements in blood pressure reduction.

Table 36: Characteristics of included studies: Blood pressure self-monitoring

Study	Type of Study	Intervention	Number of Studies	Total n
Tucker et al., 2017[118]	Meta-analysis	Blood pressure self-monitoring	36	11,175
Duan et al., 2017[119]	Meta-analysis	Blood pressure telemonitoring	46	13,875
Agarwal et al., 2011[120]	Meta-analysis	Home blood pressure monitoring	37	9,446
Fletcher et al., 2015[121]	Meta-analysis	Blood pressure self-monitoring	28	7,021
Ogedegbe et al., 2006[122]	Systematic review	Home blood pressure monitoring	11	NR
NR = Not Reported				

Review evidence

Review evidence related to either systolic blood pressure reduction or improvement in adherence to anti-hypertensive medication (Table 37). Reductions in systolic blood pressure of between -1.68 and -5.91 mm Hg were reported[118-120]. Tucker et al, 2017[118] found that blood pressure reductions with self-monitoring were greater in patients with CKD; although the uncertainty around this was high.

In general, blood pressure self-monitoring improves adherence to anti-hypertensive medication, with significant improvements reported by both Fletcher et al., 2015[121] and Agarwal et al., 2011[120] using different measures.

Table 37: Evidence summary: Blood pressure self-monitoring

Study	Intervention	Mean Difference	95% CI	Time Point	No of studies	n
Outcome No 1: Systolic Blood Pressure						
Tucker et al., 2017[118]	Self-monitoring in patients with hypertension	-3.24 mm Hg	-4.92; -1.57	12 months	15	6,300

	Self-monitoring in patients with diabetes	-3.68 mm Hg	-3.93; -2.08	12 months	15	1,545
	Self-monitoring in patients with CKD	-5.91 mm Hg	-10.42; -1.41	12 months	8	307
Duan et al., 2017[119]	Blood pressure tele-monitoring	-3.99 mm Hg	-5.06; -2.93	3-24 months	39	23,952
Agarwal et al., 2011[120]	Home blood pressure monitoring	-1.68 mm Hg	-2.58; -0.79	2 to 36 months	22	552
Outcome No 2: Medication Adherence						
Agarwal et al., 2011[120]	Home blood pressure monitoring	2.02 (RR)	1.32; 3.11	2 to 36 months	10	NR
Fletcher et al., 2015[121]	Blood pressure self-monitoring	0.21 (SMD)	0.08; 0.34	NR	13	1,809
Ogedegbe et al., 2006[122]	Home blood pressure monitoring	1.24 (RR)	NR	NR	11	NR
NR = Not Reported; RR = relative risk; SMD = standardised mean difference						

Conclusions

The evidence clearly indicates the blood pressure self-monitoring results in a significant reduction in systolic blood pressure outcomes. Evidence to inform this will be used from Tucker et al., 2017[118], as this study is very recent and the intervention corresponds to that defined by the review question. Whilst Duan et al., 2017[119] is a much larger study, it relates to tele-monitoring rather than self-monitoring which is slightly out of scope. A difference in magnitude of systolic blood pressure reduction in individuals with Diabetes or CKD will not be incorporated in the tool as this data is based on a much smaller number of individuals and it is unclear whether the difference is significant. Quality assessment of this study using key domains from AMSTAR-2[37] is shown in Table 38.

Table 38: Quality assessment: blood pressure self-monitoring

Study	Are the PICOs for the review question clear and defined?	Was the literature search compre-hensive?	Did the authors satisfactorily assess risk of bias of included studies?	How many studies were included, how large were they and of what design?	Did they discuss heterogeneity when reporting results?	Overall quality?
Tucker et al., 2017[118]	YES	Partial YES	YES	15 RCTs	YES	Moderate - HIGH

NHS Health Checks

NICE recommendations

NICE Guideline CG181: CVD Risk Assessment and the Modification of Lipids (2014)[20], indicates that for the primary prevention of CVD in primary care, a systematic strategy should be used to identify people who are likely to be at high risk. People older than 40 should have their CVD risk reviewed on an ongoing basis. NICE recommends that the QRISK2 risk assessment tool should be used to assess risk (apart from in people with type 1 diabetes, FH or CKD). In the UK this guideline has been operationalised in the NHS Health Check, which is a 5-yearly check-up offered to individuals aged between 40 and 75 without pre-existing conditions.

Summary of evidence from the guidelines

NICE Guideline CG181 (2014)[20] includes evidence around the use of the QRISK2 tool to assess risk, but does not include evidence around the effectiveness of systematic strategies to identify high risk individuals. However, since the start of the Health Check programme, many studies have been carried out evaluating the uptake and effectiveness of the programme. A largescale update of the economic evaluation underpinning the NHS Health Check programme is currently underway, but will not be completed in time to feed into this iteration of the CVD Prevention ROI Tool. However, given the importance of NHS Health Checks for detection of high risk individuals, it was necessary to include them in the tool. Searches were therefore carried out to identify useful evidence that could be used to inform the effectiveness of NHS Health Checks.

Review question: What is the effectiveness of NHS Health Checks for identifying individuals at high risk of CVD due to QRISK ≥ 10%, familial hypercholesterolemia, hypertension, atrial fibrillation, non-diabetic hyperglycaemia, type 2 diabetes, or chronic kidney disease?

Search results and study selection

Two separate searches were carried out to inform this question. The first search aimed to identify systematic reviews. This found 95 search results; however, upon sifting none of these were found to relate specifically to the NHS Health Check. A rapid evidence synthesis carried out by the University of Cambridge for PHE[123] was identified separately through the PHE working group; this incorporated evidence from 68 studies around a range of different questions, but did not include a meta-analysis.

A second search was then performed to identify RCTs or observational studies evaluating the NHS Health Check, which had been carried out in the UK and published

in the last 10 years. This found 44 studies, of which 4 of the most recent were included in the review (Table 39). This included 2 of the most recent and highest quality studies that had been found in the Cambridge review (Robson et al., 2016[124] and Chang et al., 2016[125]) and 2 that had been published since (Robson et al., 2017[126] and Forster et al., 2016[127]). Robson et al., 2017[126] used data specifically from an East London population, whereas the other 3 studies were based on national data and therefore likely to be of greater relevance. Three of the studies compared outcomes in health check attendees against matched non-attending controls, whereas 1 study (Robson et al., 2016[124]) did not have a comparator group but evaluated outcomes over the entire cohort of attendees during the first 4 years of the Health Check Programme.

Table 39: Characteristics of included studies: NHS Health Checks

Study	Type of Study	Intervention	Number of Studies	Total n
Usher-Smith et al., 2017[123]	Systematic review	NHS Health Check	68	NR
Robson et al., 2017[126]	Observational (matched non-attenders)	NHS Health Check in East London	NA	272,259
Robson et al., 2016[124]	Observational (no comparator)	NHS Health Check nationally	NA	1,679,024
Forster et al., 2016[127]	Observational (matched non-attenders)	NHS Health Check nationally	NA	257,368
Chang et al., 2016[125]	Observational (matched non-attenders)	NHS Health Check nationally	NA	138,788
NR = Not Reported; NA = Not Applicable				

Review evidence

Detection of high risk conditions

The primary outcomes for this review related to detection of high risk conditions. Three of the reviews evaluated detection outcomes for a range of high risk conditions including diabetes, hypertension, CKD, AF and FH (Table 40). Robson et al., 2017 measured detection as an odds ratio compared with detection in Health Check non-attenders, finding that Health Checks improved detection by between 1.3 and 1.8 fold depending upon high risk condition. The other 2 studies reported the percentage of attendees detected with each high risk condition. This ranged from over 4% detected with hypertension to less than 0.1% detected with AF and FH.

Other reported outcomes

A range of other outcomes were reported in the primary studies including attendance rate, the proportion of attendees who had key metabolic outcomes recorded in their notes (eg for BMI, blood pressure etc.), the proportion of attendees falling into different QRISK2 risk categories and the proportion who were prescribed statins or anti-hypertensives, or who were referred to weight management or smoking cessation

programmes in response to their NHS Health Check assessment. These are summarised in Table 40.

Table 40: Evidence summary: NHS Health Checks

Study	Detection Rate: Health Checks	Detection Rate: Controls	Detection Rate: Odds Ratio (95% CI)	Total n	Time Point
Outcome No 1: Detection of Diabetes					
Robson et al, 2017[126]	NR	NR	1.3 (1.21; 1.39)	NR	5 years
Robson et al, 2016[124]	0.9%	NA	NR	214,295	4 years
Chang et al., 2016[125]	1.62%	0.22%	NR	29,672	NR
Outcome No 2: Detection of Hypertension					
Robson et al, 2017[126]	NR	NR	1.5 (1.43; 1.57)	NR	5 years
Robson et al, 2016[124]	3.7%	NA	NR	214,295	4 years
Chang et al., 2016[125]	4.08%	0.76%	NR	29,672	NR
Outcome No 3: Detection of CKD					
Robson et al, 2017[126]	NR	NR	1.83 (1.52; 2.21)	NR	5 years
Robson et al, 2016[124]	0.4%	NA	NR	214,295	4 years
Chang et al., 2016[125]	0.34%	0.11%	NR	29,672	NR
Outcome No 4: Detection of AF					
Robson et al, 2017[126]	NR	NR	1.83 (1.52; 2.21)	NR	5 years
Chang et al., 2016[125]	0.10%	0.04%	NR	29,672	NR
Outcome No 5: Detection of FH					
Robson et al, 2017[126]	NR	NR	1.83 (1.52; 2.21)	NR	5 years
Chang et al., 2016[125]	0.10%	0.006%	NR	29,672	NR

Study	Population	Mean value	Total n	Time Point
Outcome No 6: Attendance Rate				
Robson et al, 2017[126]	Total Eligible	7.3% to 17%	272,259	5 years (2009 to 2013)
Robson et al, 2016[124]	Total Eligible	5.8% to 30.1%	1,679,024	4 years (2009 to 2012)
Chang et al., 2016[125]	Total Eligible	21.4%	138,788	NR
Outcome No 7: QRISK2 Measured				
Robson et al, 2017[126]	Total Attendees	96.2%	85,122	5 years
Robson et al, 2016[124]	Total Attendees	80%	214,295	4 years
Outcome No 8: BMI Recorded				
Robson et al, 2016	Total Attendees	98%	214,295	4 years
Outcome No 9: SBP Recorded				
Robson et al, 2016[124]	Total Attendees	99.7%	214,295	4 years
Forster et al., 2016[127]	Total Attendees	100%	75,123	NR
Outcome No 10: Cholesterol Recorded				
Robson et al, 2016[124]	Total Attendees	91.5%	214,295	4 years
Forster et al., 2016[127]	Total Attendees	91%-92%	75,123	NR
Outcome No 11: QRISK2 ≥ 10%				
Robson et al, 2017[126]	QRISK2 Measured	26.2%	81,887	5 years
Robson et al, 2016[124]	QRISK2 Measured	47%	171,441	4 years
Outcome No 12: New Statin Prescription				
Robson et al, 2017[126]	QRISK2 ≥ 20%*	37.2%	5,814	5 years
Robson et al, 2016[124]	QRISK2 ≥ 20%*	19.30%	27,624	4 years
Outcome No 13: New Anti-hypertensive Prescription				
Robson et al, 2016[124]	QRISK2 ≥ 20%*	8.8%	27,624	4 years
Outcome No 14: Referred to Weight Management				

Study	Detection Rate: Health Checks	Detection Rate: Controls	Detection Rate: Odds Ratio (95% CI)	Total n	Time Point
Robson et al, 2016[124]	Total Attendees	38.7%	214,295	4 years	
Outcome No 15: Referred to Smoking Cessation					
Robson et al, 2016[124]	Total Attendees	6.8%	214,295	4 years	
NR = Not Reported; NA = Not Applicable; CKE = Chronic Kidney Disease; AF = Atrial Fibrillation; FH = Familial Hypercholesterolaemia; SBP = Systolic Blood Pressure; BMI = Body Mass Index.* QRISK2 ≥ 20% was the former threshold for statin prescription.					

Conclusions

Some high quality evidence for the effectiveness of NHS Health Checks for detecting high risk conditions exists. It is more appropriate to use nationally representative data than local data to inform the effectiveness of NHS Health Checks and therefore the data from Chang et al., 2016[125] is the most appropriate to include in the database of interventions as this also provides data from matched non-attendees. Note that in the tool, NHS Health Checks will be simulated in real individuals and therefore detection of a condition will depend only upon whether or not they have a condition. The Chang et al., 2016[125] data will therefore be used to validate this approach rather than being directly used in the model.

Cascade testing for FH

NICE recommendations

NICE Guideline CG71: Identification and Management of Familial Hypercholesterolaemia (updated 2008)[19] recommends that cascade testing using DNA testing should be used to identify affected first, second and where possible third-degree biological relatives of people with a genetic diagnosis of FH (both current and newly detected index cases).

Summary of evidence from the guidelines

The 2017 update of NICE CG71 includes a new evidence review and economic modelling study comparing a variety of different case identification and cascade testing strategies against no testing. The systematic review identified 43 studies, of which 14 assessed cascade testing. Diagnostic yield for cascade testing with genetic diagnosis in relatives of an index FH case ranged from 32.8% to 55.9% depending upon the study. However, the value for this used both in the NICE economic model and in another recent cost-effectiveness analysis (Kerr et al., 2017[128]) was 50.89%, which came from UK FH services data. Given that these 2 cost-effectiveness analyses were both UK based and carried out within the last year, it was not thought worth investigating other review evidence and therefore no searches for this topic were performed.

Conclusions

The tool will use the same evidence as that used in the 2017 update of NICE Guideline CG71 (2008)[19] to inform the effectiveness of cascade testing.

Opportunistic detection of high CVD risk conditions

NICE recommendations

A number of guidelines have given direction regarding strategies to be used to identify new cases for various conditions which are regarded as risk factors for CVD. Hypertension and QRISK2 score ≥ 10% are normally identified opportunistically in general practice (GP) centres when high risk individuals are invited for risk assessment for CVD as set out in NICE clinical guidance CG181 (2014)[20]. However, risk assessment for CVD is covered in the NHS Health Checks review and will not be considered further in this review. For type 2 diabetes, the 2012 NICE public health guideline PH38 (2012)[23] sets out a 2-stage strategy to identify people with diabetes and non-diabetic hyperglycaemia. Firstly General Practitioners (GPs) and other health

professionals are advised to offer risk assessment to high risk individuals. Secondly, the guideline recommends that service providers including community pharmacies, dental surgeries, NHS walk-in centres and opticians; faith groups, community services such as workplaces, job centres, local authority leisure services, shops, libraries, faith centres, residential and respite care homes and day centres and voluntary organisations should offer questionnaires or validated web based tools for self-assessment for risk of type 2 diabetes. For AF, the 2013 NICE Medical Technologies Guidance MTG13[129] recommends the use of the Watch BP Home A device as it could help increase the number of people with atrial fibrillation who are diagnosed. NICE Guideline CG182 (2014)[24], lays down guidelines for early identification of CKD; and finally NICE Guideline CG71 (2008)[19], outlines the strategies for early identification of FH including cascade testing, which is covered in a separate review. Note that systematic population screening is not recommended outside of the NHS Health Check for detection of any of these high risk conditions.

Summary of evidence from the guidelines

Although many strategies are recommended for opportunistic detection of CVD risk conditions, the NICE guidelines are generally lacking in evidence for the effectiveness of these methods. NICE MTG13 (2013)[129] contains an evidence review for Watch BP Home A, in which the results of 7 different primary studies are summarised, providing some support for the recommendation for its use. However, this was the only specific piece of evidence found in the NICE guidelines. Searches were therefore carried out to find systematic reviews (in the first instance) relating to a variety of opportunistic detection mechanisms for the range of high CVD risk conditions.

Review question: What is the effectiveness of different opportunistic detection methods for identifying individuals with QRISK ≥ 10%, familial hypercholesterolemia, hypertension, atrial fibrillation, non-diabetic hyperglycaemia, type 2 diabetes, or chronic kidney disease?

Search results and study selection

Two separate searches were run to explore methods for opportunistic detection of CVD risk factors; firstly to identify systematic reviews relating to opportunistic detection of all conditions and secondly to identify randomised controlled trials (RCTs) or observation studies for opportunistic detection of conditions that had not been identified in the first search (in particular relating to diabetes, non-diabetic hyperglycaemia, CKD and QRISK ≥ 10%). Search terms included several technologies known to be in use to identify AF including Watch BP Home A, AliveCor and GRASP-AF.

The search for systematic reviews identified 182 articles whereas that for RCTs identified 85 articles. In total, 7 studies (5 systematic reviews, 1 RCT and 1

observational study) met the inclusion criteria and were included in the brief review (Table 41). A systematic review by Fleming et al., 2015[130] reported opportunistic community blood pressure testing for hypertension in 9 different scenarios; community buildings or public areas such as supermarkets (by nurses, dentists or lay persons); pharmacies; dental practices; mobile units, or at home by students or other health care professionals. The review included 72 studies from across the globe.

A well conducted and large Health Technology Assessment (Welton et al., 2017[131]) investigated the effectiveness of different AF opportunistic detection and systematic screening strategies in individuals >65 years old (note that systematic screening is not recommended by NICE). The 3 other systematic reviews[132-134] examined the sensitivity and specificity of automated blood pressure monitoring devices and a variety of other opportunistic detection mechanisms for detecting AF. An RCT[135] and an observational study[136] were found that investigated opportunistic detection of type 2 diabetes, 1 of which also reported on screening for non-diabetic hyperglycaemia[135]. We did not identify any relevant reviews that investigated the effectiveness of different opportunistic detection strategies for CKD or QRISK2 ≥ 10%.

Table 41: Characteristics of included studies: Opportunistic detection

Study	Type of Study	Intervention	Number of Studies	Total n
Hypertension Detection				
Fleming et al., 2015[130]	Systematic review	Community screening for hypertension (note no comparator)	73	NR
AF Detection				
Welton et al., 2017[131]	Systematic Review and meta-analysis	Opportunistic screening OR systematic population screening for AF	15	18,331
Kane et al., 2016[132]	Systematic Review	Automated BP monitors used for opportunistic AF detection	7	3,438
Taggar et al., 2016[133]	Meta-analysis	Multiple detection methods for AF; Blood pressure monitors, non-12-lead ECGs and Smartphone Apps compared with 12 lead ECG	21	NR
Verberk et al. 2016[134]	Meta-analysis	Automated BP monitors used for opportunistic AF detection compared with 12 lead ECG	6	2,332
Type 2 Diabetes Detection				
Khunti et al., 2016[135]	RCT	Computer based risk score (Leicester Practice Computer Risk Score [LPCRS]) compared with Patient self-assessment score [Leicester Self-Assessment Score] LSAS)	1	577
Bowen et al. 2017[136]	Cross-sectional study	Random glucose testing	1	7,161
NR = Not Reported				

Review evidence

Uptake or coverage of opportunistic screening

Two systematic reviews and an RCT reported uptake of opportunistic screening for hypertension, AF and type 2 diabetes. Fleming et al., 2015[130] covered screening for hypertension in 9 different scenarios. There was a lot of heterogeneity in the results with varying coverage rates for each screening site reported (range 3.0% to 96.7%). In the Welton et al., 2017[131] HTA, uptake of screening and opportunistic detection for AF ranged from 52.1% to 73.3% in the 4 trials included in this analysis. Lastly, Khunti et al., 2016[135] assessed response rates for 2 opportunistic tools for early detection of hyperglycaemia, and reported that 75% of those invited were screened (Table 42).

Opportunistic screening and detection of cardiovascular risk factors

Three studies reported detection rates of hypertension[130], AF[131 137] and T2DM[135] in opportunistic screening compared to routine care. Fleming et al., 2015[130] reported that hypertension was detected in 6.05% to 73.75% of those that accepted opportunistic screening in different settings. Twelve of the 73 studies also reported referral outcomes after screening. The data showed that between 26% and 43% of participants screened were referred to a primary care facility, and a further 44% of those referred had a hypertension diagnosis. Opportunistic screening was found to be more effective than usual care in detection of AF in the Welton et al., 2017[131] review. Specifically, they found that opportunistic screening identified 1.61% of AF compared to 1.03% identified through usual care. In Khunti et al., 2016[135], no difference was seen between use of the opportunistic computer risk score use and the self-assessment risk score for detecting undiagnosed type 2 diabetes or non-diabetic hyperglycaemia[135].

Sensitivity and specificity of different screening tools for AF

Four systematic reviews reported the sensitivity and specificity of opportunistic detection of AF using automated blood pressure monitors or other tools, whilst a further review reported the sensitivity and specificity of opportunistic methods to detect type 2 diabetes.

Kane et al., 2016[132], appraised the diagnostic accuracy of automated blood pressure monitors used for opportunistic AF detection. They reported a specificity of >85% and a sensitivity of >90%. The authors concluded that these devices compared favourably with manual pulse palpitation and offer a promise as screening tools for AF, subject to further validation. Taggar et al., 2016[133] compared the sensitivity and specificity of blood pressure monitors, non-12-lead electrocardiography (ECG) and smartphone apps with that of 12-lead ECG. The authors reported that blood pressure monitors and non-12-lead ECG had the greatest accuracy for detecting pulse irregularities due to AF compared with 12-lead ECG diagnosis. Similar findings were observed for smartphone apps, but evidence was of lower quality. Verberk et al. 2016[134] investigated the effectiveness of automated blood pressure monitors compared to non-12-lead ECG.

They also found that blood pressure monitors were more sensitive and specific than non-12-lead ECG. Finally, Welton et al., 2017[131] reported similar findings for blood pressure monitors, non-12-lead ECG and pulse palpation.

For type 2 diabetes, a cross-sectional study by Bowen et al., 2017[136], compared the sensitivity and specificity of American Diabetes Association (ADA), the U.S. Preventive Services Task Force (USPSTF) and the random serum blood glucose (RBG) screening guidelines in identifying T2DM. The results show that the ADA guideline had higher sensitivity (99.2%), but poor specificity. However, the 2015 USPSTF guideline was significantly better at detecting undiagnosed diabetes than the ADA screening guideline.

Table 42: Evidence summary: Opportunistic screening

Outcome No 1: Uptake/Coverage				
Study	**Intervention**	**Uptake**	**P value**	**No of studies**
Hypertension Detection				
Fleming et al., 2015[130]	Health centre	3.06% to 47.58%	NR	2
	Community building	12.09% to 88.73%	NR	5
	Public area (eg retail)	5.53% to 96.70%	NR	4
	Mobile unit	21.35% to 88.10%	NR	4
	Pharmacy	39.8% to 91.7%	NR	4
	Dentist	64.15%	NR	1
	Home	3.43% to 85.71	NR	4
	Mixed	82.04% to 98.74%	NR	2
AF Detection				
Welton et al., 2017[131]	Targeted Screening	52.1%	NR	NR
Type 2 Diabetes/Non-diabetic hyperglycaemia Detection				
Khunti et al., 2016[135] (RCT)	LPCRS	75%	0.945	1
	LSAS	75%	0.945	1
Outcome No 2: Screening Yield				
Study	**Intervention**	**Proportion Detected**	**95% CI**	**No of studies**
Hypertension Detection				
Fleming et al., 2015[130]	Health centre	20.0% to 50.0%	NR	2
	Community building	13.3% to 33.62%	NR	NR
	Public area (eg retail)	17.75% to 61.54%	NR	9
	Mobile unit	9.9% to 70%	NR	7
	Pharmacy	6.05% to 61.54%	NR	14
	Dentist	8.50% to 38.60%	NR	9
	Home	17.76% to 73.75%	NR	7
	Mixed	20.37% to 53.11%	NR	5
AF Detection				
Welton et al., 2017[131]	Targeted Screening	1.61%	1.24; 1.96	173
Type 2 Diabetes Detection				
Khunti et al., 2016[135] (RCT)	LPCRS	5.26 per 1000 patient years	NR	1
	LSAS	1.92 per 1000 patient years	NR	1

Non-Diabetic Hyperglycaemia Detection				
Khunti et al., 2016[135]	LPCRS	9.86 per 1000 patient years	NR	1
	LSAS	12.8 per 1000 patient years	NR	1
Outcome No 3: Sensitivity and Specificity of Screening Tools				
Study	**Intervention**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Number needed to treat**
AF Detection				
Welton et al., 2017[131]	Blood pressure monitor	95.5% (86.4; 99.2)	91.9% (71.7; 98.2)	NR
	Single lead ECG	96.1% (91.7; 98.6)	94.0% (88.2; 97.6)	NR
	Pulse palpation	91.6% (75.0; 98.6)	78.8% (51.0; 94.5)	NR
Taggar et al., 2016[133]	Blood pressure monitor	90.0% (90.0; 100)	92.0% (88.0; 95.0)	NR
	Single lead ECG	91.0% (86.0; 94.0)	95.0% (92.0; 97.0)	NR
	Smartphone applications	97.0% (95.0; 99.0)	95.0% (88.0; 99.0)	NR
	Pulse palpation	92.0% (85.0; 96.0)	82.0% (76.0; 88.0)	NR
Verberk et al., 2016[134]	Blood pressure monitor	98.0% (95.0; 100)	92.0% (88.0; 96.0)	NR
Kane et al., 2016[132]	Blood pressure monitor	>85% all devices	NR	NR
Type 2 Diabetes Detection				
Bowen et al., 2017[136] (cross-sectional study)	RBG	81.6% (74.9; 88.4)	78.0% (76.6; 79.5)	14
	ADA	99.2% (98.4; 100.0)	23.0% (20.9; 25.1)	35
	2008 USPSTF	41.9% (34.8; 48.9)	76.7% (75.0; 78.4)	44
	2015 USPSTF	65.2% (58.4; 71.9)	66.5% (64.4; 68.5)	32
	ADA + RBG ≥100	100% (100; 100)	20.1% (18.2; 22.0)	35
	2008 USPSTF + RBG ≥ 100	90.7% (86.2; 95.3)	61.9% (60.1; 63.7)	20
	2015 USPSTV + RBG ≥ 100	93.5% (89.6; 97.3)	53.7% (51.5; 55.9)	24
NR = Not Recorded; LPCRS = Leicester Practice Computer Risk Score; LSAS = Leicester Self-Assessment Score; RBG = Random Serum Blood Glucose Screening Guidelines; ADA = American Diabetes Association Guidelines; USPSTF = US Preventative Services Task Force Screening Guidelines.				

Conclusions

Several different methods of opportunistic detection have been identified in the review. The Welton et al., 2017[131] review will be used to inform opportunistic detection of AF, as this is the most recent study and reviews a range of relevant AF detection mechanisms including blood pressure monitors and pulse palpation. The RCT by Khunti et al., 2016[135] will be used to inform opportunistic detection of diabetes and non-diabetic hyperglycaemia as unlike Bowen et al., 2017[136] it is a UK study examining the effectiveness of commonly used diabetes risk scores. Finally, the Fleming et al., 2015[130] review was the only study that we found to inform the effectiveness of community blood pressure testing. This does not include a meta-analysis and it is unclear which individual strategies correspond to those commonly used in the UK, but it will be highlighted as a source of evidence in the database of interventions. Quality assessment of the 2 included meta-analyses using key domains from AMSTAR-2[37] and the Khunti et al., 2016[135] RCT using key domains from CASP[38] is shown in Table 43.

Table 43: Quality assessment: Opportunistic detection

Study	Are the PICOs for the review question clear and defined?	Was the literature search compre-hensive?	Did the authors satisfactorily assess risk of bias of included studies?	How many studies were included, how large were they and of what design?	Did they discuss heterogeneity when reporting results?	Overall quality?
Welton et al., 2017[131]	YES	HIGH	YES	15 (range of study designs)	YES	HIGH
Fleming et al., 2015[130]	YES	YES	Partial YES	73 (range of study designs)	YES	Moderate-HIGH
Study	**Was the assignment of patients to treatments randomised (assessment of selection bias)**	**Were the groups similar at the start of the trial (assessment of confounding)?**	**Were all of the patients who entered the trial properly accounted for at its end (assessment of attrition bias)**	**Were researchers collecting data blinded to treatment allocation (detection bias)?**	**Was there a risk of selective reporting (reporting bias)?**	**Overall quality?**
Khunti et al., 2016[135]	Partial YES	Partial YES	YES	Unclear	NO	Moderate

Annual review

NICE recommendations

For each of the high CVD risk conditions there are NICE recommendations about regular (usually annual) follow-up within primary care to review medications, give advice to help manage the condition, monitor disease progression and test for the potential presence of other high CVD risk conditions that may be comorbid with the first condition. A summary of the tests recommended for each condition upon diagnosis and annually thereafter are shown in Table 44.

Table 44: NICE recommended tests for other high risk conditions in individuals with a pre-existing high risk condition

Pre-existing High Risk Condition	Upon Diagnosis	Annual Review
Hypertension	- Assess cholesterol and CVD risk - Assessment for AF - Assess for diabetes - Assess for non-diabetic hyperglycaemia	- Assess cholesterol and CVD risk - Assess for CKD - Check blood pressure

	- Assess for CKD	
QRISK ≥ 10%	- Consider possibility of FH if cholesterol above 7.5 mmol/l. - Assess blood pressure - Assess for CKD - Assess for diabetes - Assess for non-diabetic hyperglycaemia	- Nothing mentioned
FH	- Assessment for AF	- Check cholesterol
CKD	- Assess blood pressure	- Assess blood pressure - Check eGFR
Type 1 Diabetes	- Assess blood pressure - Assess for CKD	- Assess blood pressure - Assess for CKD - Check blood glucose
Type 2 Diabetes	- Assess cholesterol and CVD risk - Assess blood pressure - Assess for CKD	- Assess cholesterol and CVD risk - Assess blood pressure - Assess for CKD - Check blood glucose
Non-diabetic hyperglycaemia	- Assess for diabetes	- Assess for diabetes
AF	- Nothing mentioned	- Nothing mentioned but stroke risk should be reviewed at age 65.

Summary of evidence from the guidelines

Whilst annual review for each condition is recommended; no evidence to support the effectiveness of annual reviews for either managing the high risk condition of interest or for detection of other high risk conditions is given in any of the NICE guidelines. Searches were therefore carried out to find systematic reviews relating to annual review for management or detection of high CVD risk conditions.

Review question: What is the effectiveness of annual review for managing individuals with QRISK ≥ 10%, familial hypercholesterolemia, hypertension, atrial fibrillation, non-diabetic hyperglycaemia, type 2 diabetes, or chronic kidney disease; or for detecting comorbid high risk conditions in individuals with a pre-existing condition?

Search results and study selection

The search found 1,102 results; however, upon sifting none of the studies were found to be relevant to the search question.

Conclusions

The lack of relevant findings from this search suggests that there is an evidence gap around the benefits of annual review for detection or management, indicating that this area may benefit from further research. Whilst no relevant data was found, some assumptions can be made to enable annual review to be modelled. The steering group considered that it was reasonable to assume that the benefit of annual review in pharmacological management of a condition might be similar to that achieved through a

pharmacist medicine use review. In terms of detection of new conditions, it may also be reasonable to assume that if an individual has an undetected comorbid high risk condition, it will be detected as part of an annual review for their pre-existing condition if NICE guidelines specify that the relevant tests for the comorbid condition are carried out.

Interventions and evidence to be included in the tool

Following intervention effectiveness reviews, it was decided that 5 topics would not be directly included in the tool due to either a lack of evidence (see evidence gaps below) or due to evidence that the intervention was not effective.

For the following 3 topics no good quality relevant outcome data could be found (note that this does not mean that these interventions are not important for CVD prevention):

- brief dietary advice (only dietary outcomes analysed)
- brief physical activity advice (only physical activity outcomes analysed)
- screening and brief advice for alcohol (only low quality/non-significant blood pressure outcome data found – good quality data relates to alcohol consumption only)

For a further 2 topics, the evidence seems to indicate that there is no significant benefit:

- exercise referral in sedentary individuals (not effective according to metabolic data)
- individualised nutritional advice in people with FH (not effective according to metabolic data albeit very little data available)

All other topics were included in the tool. The database of interventions made to accompany the tool summarises the chosen effectiveness and cost-effectiveness evidence for each topic included in the tool, together with additional intervention parameters including costs, current usage, eligibility criteria and duration of effect.

Evidence gaps

The effectiveness reviews highlighted some evidence gaps that could be used as the basis of further research. Evidence gaps are presented here together with some methods for potentially bridging these in future versions of the tool.

Evidence gap 1: direct CVD or metabolic benefits of brief advice for diet, physical activity and alcohol

Whilst evidence exists about the benefits of brief lifestyle advice to improve dietary behaviours, physical activity behaviours or drinking behaviours, and evidence exists that

links changes in such behaviours to improvements in CVD or metabolic outcomes, no or very little evidence exists to directly link brief advice to either reductions in CVD or metabolic changes.

The lack of direct evidence meant that such interventions could not be included in this iteration of the tool. However, there are several ways in which future iterations of the tool could include these interventions:

- primary studies could be commissioned to directly bridge the evidence gap and provide direct evidence to be included in future iterations of the tool
- additional model adaptations could be carried out to enable direct simulation of individual lifestyle behaviours, their changes with age and their correlation with metabolic risk factors and CVD; this would enable behavioural effectiveness outcomes from identified studies to be directly added into the model (NB: an alternative way that this could be done is through development of an update of QRISK2 which includes behavioural risk factors but this may be problematic due to a general lack of behavioural data in primary care records)
- additional searches could be carried out to bridge the gap by providing a series of evidenced steps linking brief intervention to behavioural change to metabolic or CVD change, but it is likely that this method would require a range of additional assumptions to be made and therefore quality of evidence would be lower than for the other interventions in the tool

It is important to note that the identification of this evidence gap does not mean that diet, physical activity and alcohol consumption are not areas that should be targeted for improvements in local populations. It just means that it is not currently possible to evaluate their return on investment within the same framework as the other interventions.

Evidence gap 2: Benefits of annual review for management of high risk conditions and detection of comorbid high risk conditions

The reviews were unable to find any direct evidence about the benefit of the annual review for management of high risk conditions or detection of comorbid high risk conditions in individuals that already have 1 condition. This may be because in practice an annual review may not exist as a specific entity; instead the component parts may be distributed between different primary care visits and different healthcare professionals (eg GPs, nurses, pharmacists etc.), therefore making it difficult to analyse. It is very likely that people who do not attend an annual review (or who are not invited) will have worse outcomes than those who do. This could include delays in detection of comorbid conditions, sub-optimal use (and thereby effectiveness) of prescribed medications, incorrect medication for current disease and a poor awareness of their condition and its

prognosis leading to poor lifestyle choices. It was important to include annual review in the tool; however, assumptions about its effectiveness had to be made.

Evidence gap 3: combinatorial effect of interventions

Very little data was found to inform the combinatorial effect of multiple interventions acting in 1 individual. For some of the topics reviewed, it is highly likely that intervention effectiveness is assessed in individuals who are taking another intervention for the same condition. For example; the effectiveness of blood pressure self-monitoring has been assessed in individuals who are taking anti-hypertensive therapy and therefore represents the additional benefit of the combined interventions. Equally the effectiveness of structured education for diabetes has been assessed in individuals who are almost certainly taking some level of glucose lowering treatment. However, no data was found to inform the combinatorial effects of common CVD prevention treatments that are aimed at different high risk conditions. For example; the combined CVD prevention effect of statins and anti-hypertensives in individuals eligible for both. Note that there is evidence about the combined effect of different anti-hypertensives on blood pressure, which appears to diminish with the addition of each new drug[138] (although recent evidence challenges this[139]), but this is not relevant for the tool as combination anti-hypertensive treatment was modelled as a class effect and not as separate treatments.

The lack of evidence about combinatorial effects of interventions means that some assumptions had to be made about how interventions are combined in 1 individual in the tool. Modelling of CVD risk through the QRISK2 equations[13] means that the combined risk of multiple interventions that act on different metabolic risk factors can be calculated. However, it was still necessary to decide how the risk factors themselves should be combined.

This issue was discussed with the steering group and it was decided that the most reasonable assumption was to assume that interventions have independent effects and therefore that there is no interaction between multiple interventions. The following examples illustrate this:

- if Intervention A reduces systolic blood pressure by 10 mm Hg compared with no intervention and Intervention B reduces total cholesterol by 1mmol/L compared with no intervention, someone receiving both interventions will receive both metabolic reductions
- if Intervention A reduces systolic blood pressure by 10 mm Hg compared with no intervention and Intervention B reduces systolic blood pressure by 20 mm Hg compared with no intervention, someone receiving both interventions will have a reduced systolic blood pressure of 20 + 10 = 30 mm Hg (ie additive)

- if Intervention A reduces systolic blood pressure by 10% compared with no intervention and Intervention B reduces systolic blood pressure by 20% compared with no intervention, someone receiving both interventions will have a reduced systolic blood pressure of 1-((1-0.1) x (1-0.2)) = 28% (ie applying the effectiveness of 1 intervention first, then applying the effectiveness of the second intervention to the new baseline metabolic level)
- if Intervention A has a relative risk for CVD of 0.4 compared with no intervention and Intervention B has a relative risk for CVD of 0.3 compared with no intervention, someone receiving both interventions will have a reduced CVD risk of 0.4 x 0.3 = 0.12 (note that this is only relevant for intervention effects that do not go through QRISK2 intermediate risk factors eg anti-coagulant treatment for AF combined with a user-defined intervention)

The steering group recognised that this was potentially a simplification of the real situation and that the combined effects may be either lower or higher than this in practice. This is recognised as a limitation of the model.

Additional evidence found during reviews

As a bi-product of searches for the included topics, some evidence relating to a series of other topics of potential interest was found. The steering group agreed that these should not be included in the tool as they were not directly recommended by NICE, and tend to represent interventions that improve the uptake or adherence of interventions already in the tool. The steering group was keen that CCGs and local authorities should design their own locally tailored mechanisms for improving uptake and adherence of NICE recommended interventions, rather than being told to do it a particular way. Therefore the steering group did not wish to be seen to endorse particular methods over and above other methods. However, the identification of some evidence-based mechanisms for doing this could provide useful information to provide to tool users.

The following table summarises the additional interventions and gives a brief description of evidence found and for which target population. Note that because searches were not carried out to target these interventions specifically, the evidence found is by no means a complete list of the evidence that may be available.

Table 45: Interventions with some evidence found but not included in tool

Intervention	Evidence found	Target population
Educational interventions for health professionals	One systematic review and meta-analysis: • Fahey, 2005[140]	Evidence found for individuals with hypertension.
Nurse led programmes to enhance disease management (including nurse led	One systematic review and meta-analysis: • Clark, 2010[141]	Evidence found for individuals with hypertension.

prescription, monitoring, community education and follow-up programmes).		
Integrated Care Programmes to enhance adherence to medicines (range of interventions including medication reminder systems, adherence feedback, treatment simplification, cognitive education, behavioural counselling).	Five systematic reviews and meta-analyses: • van Driel, 2016[142] • Jornten-Karlsson, 2016 • Deichmann, 2016[143] • Gallagher, 2017[144] • Viswanathan, 2015[145]	Evidence found for individuals taking lipid lowering medication; anti-coagulants for AF; and taking various medications for CKD or type 2 diabetes.
Digital solutions for medicines adherence or to improve management (including telemedicine, computer/web based programmes, mobile phone apps, automated brief messages).	Three systematic reviews and meta-analyses: • McLean, 2016[146] • Arambepola, 2016[147] • Flodgren, 2015[148]	Evidence found for individuals with hypertension and type 2 diabetes.
Integrated Lifestyle Programmes using a number of combined strategies over a 12 month or longer duration (eg counselling, exercise prescription, dietary intervention).	Four systematic reviews and meta-analyses: • Zhang, 2017[149] • Fleming, 2008[150] • Glynn, 2010[151] • Clarkesmith, 2017[152]	Evidence found for individuals with hypertension, high cardiovascular risk and with AF.
Organisational interventions to improve delivery of care (eg implementation of a hypertension detection and follow-up programme)	One systematic review and meta-analysis: • Fahey, 2005[140]	Evidence found for individuals with hypertension.
Appointment reminder systems (eg postal reminders or computer generated feedback)	One systematic review and meta-analysis: • Fahey, 2005[140]	Evidence found for individuals with hypertension.

Additional evidence reviews and data gathering

A range of additional evidence reviews and data gathering was carried out to inform other parameters required for development of the ROI tool. This included reviewing the cost-effectiveness of interventions, the cost of interventions, the current usage of interventions (including how many people are offered them, percentage uptake and discontinuation rate), duration of intervention effect, the prevalence (total and detected) of each high risk condition and the current level of good management for each high risk condition. The results of these reviews are presented in this chapter.

Cost-effectiveness of interventions

Cost-effectiveness review protocol

It is necessary to ensure that interventions included in the tool are those that have been found to be cost-effective. Therefore it was important to review economic evaluations for each topic. However, as the reviewed cost-effectiveness evidence was not itself used in the tool (instead the tool models cost-effectiveness directly through input of costs and health benefits) it was less important to find the most up-to-date evidence sources than it was for the effectiveness reviews.

It was surmised that NICE was likely to have only recommended cost-effective interventions, and therefore that good economic evidence would have been sought as part of guideline development. The first step was therefore to investigate NICE guideline documentation for evidence of cost-effectiveness. This enabled most topics to be completed. The second step was to use a number of studies that had either been carried out within ScHARR or that were known of from ScHARR's work on other projects. This included in particular, cost-effectiveness studies relating to interventions for diabetes and non-diabetic hyperglycaemia where ScHARR has particular expertise. The third step was to carry out a limited number of searches for economic evidence relating to the handful of topics that had not been completed following steps 1 and 2.

There were several criteria for inclusion of economic evidence. Studies had to be UK based, recent (within the last 10 years) and as far as possible meet NICE public health modelling guidance[153] or NICE technology appraisal reference case criteria[129] for economic modelling. This includes criteria such as using the relevant time horizon (lifetime in the case of CVD) and using Quality Adjusted Life Years (QALYs) as the measure of benefit. Outcomes were given as per person outcomes where possible. Outcomes extracted were incremental costs (£), incremental QALYs and 2 measures of

cost-effectiveness: Incremental Cost-effectiveness Ratio (ICER) and Incremental Net Monetary Benefit (NMB) defined as follows:

ICER = incremental costs/incremental QALYs
NMB = (incremental QALYs * willingness to pay threshold) – incremental costs

Whilst ICERs are more commonly used, with interventions with an ICER below £20,000 per QALY considered to be cost-effective by NICE; they are not a useful outcome when interventions are cost saving, as this produces negative ICERs that are not comparable. NMB is an alternative measure, which converts the QALY gain into a monetary value using the willingness to pay threshold (here assumed to be £20,000), thus allowing all cost-effectiveness measures to be somewhat comparable. For NMB, any value over zero is cost-effective and any value less than zero is not cost-effective.

Note that full comparability is not possible when comparing cost-effectiveness results produced in different models, each with different assumptions and parameter inputs. One advantage of the CVD Prevention ROI tool is that it can compare the cost-effectiveness across the range of included interventions within a single framework; something that has previously never been done.

Cost-effectiveness search results

Cost-effectiveness data was not identified through NICE guidance or ScHARR based work for the following topics and therefore full searches were necessary:

- anti-hypertensive combination therapy and ACE/ARB anti-hypertensive therapy for CKD
- brief advice for diet
- blood pressure self-monitoring
- opportunistic detection

Anti-hypertensive therapy
The searches found 5 studies relating to the high risk conditions and 15 not specific for high risk conditions. Of these only 1 was a cost-effectiveness study (Zhang et al, 2010[154]), however this relates to effectiveness of Eplerenone in patients with heart failure after acute myocardial infarction who were taking both ACE inhibitors and beta-blockers. Therefore, it was not appropriate as study participants are post-acute MI heart failure patients.

Brief advice for diet
The searches found 24 studies relating to the high risk conditions and 34 not specific for high risk conditions. Of these only 1 (Gulliford et al, 2014[155]) was a cost effectiveness

study which related to a universal strategy of brief dietary intervention for primary prevention in primary care.

BP self-monitoring

The searches found 23 studies of which 4 were cost-effective studies of interest. After reviewing abstracts it was found that all but 1 related to the wrong patient subgroup, didn't report QALYs or related to diagnosis rather than condition management. Cost effectiveness data was therefore extracted from Kaambwa, B., et al. (2014)[156] which analysed telemonitoring and self-management in the control of hypertension based on the TASMINH2 trial in the UK.

Opportunistic detection

The searches found 18 studies relating to the high risk conditions and 137 not specific for high risk conditions. Only 2 related to cost effectiveness of opportunistic detection of CVD risk factors or high risk conditions. One of these was for opportunistic detection of diabetes (Pereira Gray et al 2012[157]), for which cost-effectiveness information was already available from the effectiveness review[135]. The remaining study (Crossan, C., et al. 2017[158]), analysed the cost-effectiveness of case-finding strategies for primary prevention of CVD and was considered too similar to NHS Health Checks to be considered a novel opportunistic detection intervention.

Cost-effectiveness review summary

The following table summarises the cost-effectiveness studies found for each topic and the cost-effectiveness results within those studies. Note that for some topics it was either not possible to find any cost-effectiveness data at all (eg individualised nutritional advice for CKD), or not possible to find data that reported QALYs (eg opportunistic detection of diabetes). In the latter case an alternative measure of cost-effectiveness has been reported where available (eg cost per case detected).

Several interventions were found to not be cost-effective. This includes brief advice for diet, insulin pump and exercise referral. Brief advice for diet and exercise referral was excluded in any case from the tool due to lack of relevant effectiveness evidence. Insulin pump was retained in the tool on the advice of the steering group as it is beneficial for certain groups of people with type 1 diabetes.

Table 46: Summary of cost-effectiveness data for each topic

Intervention	Population	Study Details	Incremental per person costs (£)	Incremental per person QALYs	Cost-effectiveness (NMB*) (£)
Anti-hypertensive combination therapy	Hypertension	NICE Guideline CG127 (2011)[17]	Range from -£140 to -£920 depending on drug and gender (cost-saving)	Range from 0.32 to 0.75 depending on drug and gender	Ranges from £6,540 to £15,920. All drugs dominate no treatment
Anti-hypertensive ACE/ARB therapy	CKD	Adarkwah et al., 2013[159]	-£29,073	1.79	£64,873
Lipid modification drugs (Atorvastatin 20mg)	QRISK ≥ 10%	NICE Guideline CG181 (2014)[20]	£250 to £1,700 depending upon baseline QRISK and gender	0.215 to 0.580 depending upon baseline QRISK and gender	£2,620 to £11,121 depending upon baseline QRISK and gender
Anticoagulants	AF	NICE Guideline CG180 (2014)[18]	£25,591	5.149	£77,386
Blood glucose lowering medication	Type 1 Diabetes	Insulin is necessary for survival. No CE analysis exists.	NA	NA	NA
	Type 2 Diabetes	NICE Guideline NG28 (2015)[22]	Ranges according to treatment eg = -£794 for Metformin compared to placebo	Ranges according to treatment eg = = 0.121 for Metformin compared to placebo	Ranges according to treatment eg = £3,214 for Metformin compared to placebo
NHS Diabetes Prevention Programme	Non-diabetic hyperglycaemia	NICE Guideline PH38 (2017)[23]	Ranges from £24 to -£533 depending upon whether optimistic, conservative or pessimistic scenario	Ranges from 0.013 to 0.049 depending upon whether optimistic, conservative or pessimistic scenario	Ranges from £244 to £1,520 depending upon whether optimistic, conservative or pessimistic scenario
Brief advice/ recommendations for diet	All high risk groups	Gulliford et al., (2014)[155]	£139.76	0.004	-£59.76 NB. Unlikely to be cost effective (47.9%) even at low unit costs.
Brief advice/ recommendations for physical activity	All high risk groups	NICE Guideline PH44 (2013)[26]	£8.07	0.00466	£85.13
Structured, evidence based education programmes for diabetes	Type 1 Diabetes	Kruger et al., (2013)[160]	£426	0.0294	£163
	Type 2 Diabetes	Gillett et al., (2010)[161]	£82	0.0392	£702
Insulin Pump	Type 1 Diabetes	Cummins et al., (2010)[162]	£22,677	0.601	-£10,677
Weight management programmes (tier	Overweight/ obese in all high risk	NICE Guideline PH53 (2014)[29]	No costs stated	No QALYs stated	No NMB stated, but ICER ranges between

2-3)	groups				£2,897/QALY and dominating depending upon baseline BMI, gender and age
Alcohol brief intervention or extended brief intervention	Heavy drinkers in all high risk groups	Purshouse et al., (2013)[163]	£58m (note country wide costs only reported)	84,000 (note country wide QALYs only reported)	£1,622m (note country wide NMB calculated)
Smoking cessation programme	Smokers in all high risk groups	NICE Guideline PH10 (2017 update)[28]	-£895 to £138 depending upon intervention	-0.05 to 0.40 depending upon intervention	£877 to £8,895 depending upon intervention
Exercise referral programmes	Sedentary people in all high risk groups	NICE Guideline PH54 (2014)[27]	£226 (no specified condition); £224 (hypertension)	0.003 (no specified condition); 0.004 (hypertension)	-£166 (no specified condition); -£144 (hypertension)
Individualised nutritional advice for CKD	CKD	No cost effectiveness studies found and no health economic data submitted to NICE	NA	NA	NA
Annual review for management	All high risk groups	No effectiveness studies found on this topic, so not searched for cost-effectiveness.	NA	NA	NA
Pharmacy Based Interventions	People taking anti-hypertensives	Elliott et al., (2017)[164]	-£144	0.05	£1,144
Blood pressure self- monitoring to optimise treatment	Hypertension	Kaambwa (2012)[156]	Men £383, Women £576	Men 0.24, Women 0.12	Men £4,417, Women £1,824
NHS Health Checks	Detects all high risk groups	Department of Health (2008)[165]	£27.33	0.01	£173
Opportunistic Detection of AF	Detects AF	Welton et al., (2017)[166]	BP monitors = £7,459 Single lead ECG = £10,326 (GP) Pulse palpation = £8,129 per screen for opportunistic detection	BP monitors = 0.85 Single lead ECG = 0.83 (GP) Pulse palpation = 0.81 per screen for opportunistic detection	BP monitors = £9,541 Single lead ECG = £6,274 Pulse palpation = £8,071 per screen for opportunistic detection
Opportunistic Detection of hypertension	Detects Hypertension	No cost effectiveness studies found	NA	NA	NA
Opportunistic Detection of type 2 diabetes	Detects Type 2 diabetes	Khunti et al., 2016[135]	£7.47 per attendee	No QALYs included	£170 per diabetes diagnosis
Opportunistic Detection of Non-Diabetic Hyperglycaemia	Detects Non-diabetic hyperglycaemia	Khunti et al., 2016[135]	£7.47 per attendee	No QALYs included	£59 per identification of NDH OR diabetes
Cascade testing	Detects FH	NICE Guideline	£89.39	0.055	£1,011

for FH		CG71 (2017 update)[19]			
Annual review for detection	Detects all high risk groups	No searches performed.	NA	NA	NA
QALY = Quality Adjusted Life Year; *NMB = Incremental Net Monetary Benefit (incremental QALYs * willingness to pay threshold [£20,000]) – incremental costs; NA = Not Applicable.					

Intervention costs

Interventions were costed primarily through the studies identified from the cost-effectiveness literature review. Where possible, resource use was extracted from the identified studies and costed using the most recent (2016/17) costs using PSSRU unit costs[167] for staff time or from prescribing data for drug costs[168]. In some cases, the intervention cost was directly extracted and inflated. Costs were inflated to 2016/17 values using retail price index (excluding mortgage interest)[169]. Expert advice from the steering group was used to choose between options where more than 1 cost was found.

Table 47: Summary of cost data for each topic

Intervention	Cost	Data Source
Antihypertensive Therapy	ACE Inhibitor daily dose (3.8p); Calcium Channel blocker daily dose (5.2p); Thiazide Diuretic daily dose (3.7p). Average annual cost combination therapy (all 3 medications) per patient = **£46.36**	NHS Digital: Prescription cost analysis 2016[168].
Lipid Modification Therapy: Statins	Atorvastatin 20mg daily dose = 4.2p Annual lipid test = £1 Total annual Cost = **£16.33**	NHS Digital: Prescription cost analysis 2016[168].
Lipid Modification Therapy: Ezetimibe (for FH only)	Ezetimibe 10mg 28 tabs = £26.31 Taken by 46% of patients. Average annual cost per patient spread over all patients with FH = **£159.24**	Costs from BNF 2018[170]; Proportion taking Ezetimibe from NICE Guideline CG71 (2017)[19]
Anticoagulants	NOACs (£1.85 average daily cost) Warfarin (£0.029 average daily cost) Proportion taking Warfarin = 71% Weighted mean average annual cost = **£391.68**	NHS Digital: Prescription cost analysis 2016[168]. Pink et al. 2011[171] for monitoring costs.
Blood Glucose Lowering Medication for Type 2 Diabetes	Three step treatment regimen: 1st line Metformin = **£79.59** Additional costs year 1 = **£64.00** 2nd line Metformin + Sitagliptin = **£513.16** 3rd line Insulin = **£1,1103.12** Annual costs include drugs, blood glucose monitoring, staff time, eye screening.	SPHR Diabetes model[58]. Drug costs from BNF 2018[170]. Staff time costs from PSSRU 2017[167]. Laboratory Tests from National Schedule of Reference Costs 2016/17[172].
Insulin Pump	Annual Cost pp Insulin Pump = **£2,939.91** Annual Cost pp Multiple Daily Injections = **£969.45** Includes costs of insulin, blood glucose monitoring, device (annualised assuming 5 year life on average), needles etc.	Cummins et al., 2010[162]
NHS DPP	**£223** per person (one-off cost)	NICE PH38 2017 update[23]

Structured Educational Programmes for Diabetes	DAFNE (Type 1 Diabetes) = **£456.57** per person. DESMOND (Type 2 Diabetes) = **£89** per person (real world cost)	Dan Pollard (update for Sheffield T1D model)[173] Gillett et al., 2010[161]
Weight Management	**£53** per commercial group-based £70 for GP group-based £91 for GP individual-based Per person costs	NICE PH53 Costing report 2014: Managing overweight and obesity in adults: lifestyle weight management services[29]
Smoking Cessation	NHS Stop Smoking Programme per person setting a quit date = **£148.16**	NHS Digital: Statistics on NHS Stop Smoking Services 2016/17[174]
Individualised Nutritional Advice for CKD	Individualised programme = **£108** Group programme (of 6): £18 Using band 5 dietician or PN every 2 weeks for 30 mins over 3 months.	PSSRU, 2017[167]
Blood Pressure Self-Monitoring	**£57.35** annual cost Includes costs of equipment (annuitised over 5 years) and training to use device.	Kaambwa et al., 2014[156]
Pharmacy New Medicines Service	**£28** per person (one-off cost) Actual Contractual Payment	Community Pharmacy Contractual Framework[175]
NHS Health Checks	**£30.90** per Health Check (including inflation). Note that this does vary by local authority.	Economic Modelling for Vascular Checks (2008) Department of Health.[165]
FH Diagnosis and Cascade Testing	Genetic Testing Index Case = **£364.08** Extra Cost +ve Result = **£382.65** Extra Cost -ve Result = **£179.46** Genetic Testing Relatives = **£123.77** Extra Cost +ve Result = **£265.07** Extra Cost -ve Result = **£184.62**	Kerr et al., 2017[128]
Opportunistic Detection of AF	Blood pressure monitor AF = **£0.60** ECG = **£5.00** Pulse Palpation = **£0.60** Costs per person include staff time and ECG costs.	Welton et al., 2017 HTA[166]

Duration of intervention effect

The identified effectiveness evidence reviews provided little data about the duration of effect of interventions used to manage CVD in high risk populations, so a set of assumptions were made, informed through expert clinical opinion from the steering group about how long intervention effects would endure:

- for pharmacological treatments, blood pressure self-monitoring and insulin pump it was assumed that the intervention effects would endure for as long as an individual was taking the intervention
- for smoking cessation, it was assumed that individuals who quit for 12 months would not start smoking again
- for medicine use review, it was assumed that the benefit of the review would last 1 year
- for one-off lifestyle interventions (DPP; diabetes education, nutritional advice for CKD and weight management) it was assumed that the intervention effect would

decline linearly over 5 years, in line with the default assumptions for duration of effect of the NHS DPP in the DPP ROI tool[10]

Current care usage of interventions

In addition to data about effectiveness and cost evidence for each topic included in the tool, it was necessary to find evidence about the current care usage of interventions, ideally at a local level, so that the potential gain of improving usage or efficiency of interventions could be assessed. Unlike the parameters discussed previously, this data is presented as the default within the tool user interface, which tool users can over-ride if they have better information. Initially, 4 different types of parameter were considered:

- offer rate: The proportion of eligible people offered an intervention
- uptake: The proportion of those offered an intervention who take it up
- discontinuation: The proportion of those taking an intervention who discontinue
- adherence: The proportion taking an intervention as it is intended to be taken (eg timing, dosage, number of sessions etc.)

Due to problems in finding data to inform all of these parameters, and a need to simplify the tool user interface to make it more user-friendly, the first 3 parameters were condensed into a single user-modifiable measure defined as the proportion of eligible people using or undergoing the intervention (referred to as intervention 'usage'). For adherence, it was assumed that the effectiveness estimates already incorporated a level of adherence that was close to the adherence in the general population, and that users would not be able to directly modify adherence to interventions (although indirect modification of adherence through medicines use review, blood pressure self-monitoring or the user-defined intervention would be possible).

The first step was to find sources of local data that could be used to populate these parameters. A variety of different sources were identified; some with the help of PHE and others through the NICE Guideline 'How Well Are We Doing?' assessments, which links to both national and local data that helps answer the question of how well the country is doing in following different aspects of the NICE guidelines. A summary of the identified data sources is as follows:

- the Quality and Outcomes Framework (QOF)[176] is an annual voluntary reward and incentive programme for GP practices to promote quality of care particularly in management of chronic conditions, public health concerns and implementing preventative measures; data about how well GPs are achieving QOF targets is publicly available by practice and aggregated to CCG level
- GP Contract Services Indicators no longer in QOF (INLIQ)[177] provide information from most CCGs about how they are currently performing on indicators that used to be in QOF but have now been retired

- the National Diabetes Audit[178] records local data at CCG level about achievement of NICE recommended diabetes care pathway indicators
- the National Cardiovascular Intelligence Network (NCVIN) has a set of models that provide prevalence estimates for conditions including Diabetes, Hypertension, AF and CKD at CCG level[179-182]
- NHS Digital Stop Smoking Services Statistics provides information about the delivery of Stop Smoking Services at the local authority level[174]
- NHS Digital provides information about local delivery of the NHS Health Check at the local authority level[183]
- the Pharmaceutical Services Negotiating Committee contains data about the proportion of pharmacies offering medicine reviews in each local authority[175]
- the National Chronic Kidney Disease Audit[184] provides national data on a range of CKD diagnosis and treatment targets
- the National Diabetes Prevention Programme is a pilot study for the collection of data from GP practices in England contains some data around the first wave rollout of the NHS DPP[185]

The second step was to carry out a set of searches to find observational studies from the UK and published within the last 10 years to inform usage of those interventions for which local data had not been found. A single search was done covering all topics; which found 1,685 studies in total. These were sifted to extract any useful information. If more than 1 study was found to inform usage of an intervention, a choice was made based primarily on size of study population (large studies using national primary care databases favoured over small local studies) and date of data collection (with newer sources preferred over older ones).

In 3 cases (proportion getting antihypertensive therapy; proportion getting individualised nutritional advice for CKD; proportion getting annual review), no data sources were found through either of the 2 methods described above. For antihypertensive therapy, it was decided in consultation with the steering group that information about the proportion of people with high blood pressure who are treated to target (available from GP Contract Services: Indicators no longer in QOF[177]) would be used as a proxy to represent the proportion of people taking antihypertensive therapy. The proportion of people getting NHS Health Check was used as a proxy to represent the proportion getting annual review. For nutritional advice, no such proxy could be found and clinical experts were unsure what proportion of eligible patients was referred. Given that a value needs to be included in the tool inputs, 20% was chosen on the basis that tool users can modify this if they have better data from their local area.
For 2 of the interventions; statins and diabetes education, usage differs significantly by high risk condition. In this case the weighted average usage was calculated (based on proportions of eligible people with each condition at baseline in the HSE 2014) and used as the input value in the tool. However, the difference in usage between conditions is recalculated in the model, as not including this would impact upon the estimates of

benefit from the interventions. The data sources used to inform usage for each of the interventions are shown below, together with the national average.

Table 48: Summary of data used to inform current care intervention usage

Intervention	Current Usage as Proportion of Eligible (England Average)	Data Source
Antihypertensive Therapy	**57%**	No data found. As a proxy using percentage of hypertensives with blood pressure <140/90 mm Hg GP Contract Services England 2016/17: Indicators no longer in QOF (INLIQ)[177] HYP003, including exceptions. (local data)
Lipid Modification Therapy	- CKD or T1D or T2D = 64.2%; - FH = 86.3% - QRISK ≥ 10% only = 20.8% Weighted average (1.3% FH; 46% CKD/T1d/T2D; 52.7% QRISK ≥ 10% only) = **42%**	- Steen et al. 2017[186] (THIN database). - NICE Guidelines CG71 (2017 update)[19]. - Finnikin et al. 2017 (THIN database)[187]. (All national data) - Proportions eligible with each condition from HSE 2014[11].
Anticoagulants	**76%**	QOF AF006 (% assessed for stroke risk) multiplied by Q0F AF007 (% high stroke risk patients taking anticoagulants)[176] including exceptions. (local data)
Blood Glucose Lowering Medication for Type 2 Diabetes	**71%**	McGovern et al. 2018[188] (national data)
NHS DPP	**35%**	NHS DPP Pilot Study for the Collection of Data: Proportion offered and not declined intervention[185] (national data)
Structured Educational Programmes for Diabetes	- Type 1 diabetes = 8% - Type 2 diabetes = 7% Weighted average = **7%**	National Diabetes Audit[178]: Attended within 12 months diagnosis (local data)
Insulin Pump	6% of all type 1 diabetes **15%** eligible type 1 diabetes (assuming 40% eligible)	White et al. 2013[189] (national data)
Weight Management	**13%**	Booth et al. 2015[190] (national data)
Smoking Cessation	**3%**	NHS Digital: NHS Stop Smoking Services[174] Proportion of smokers setting a quit date (April-September 2017). Doubled to account for annual rate. (local data)
Individualised Nutritional Advice for CKD	**20%**	No data found and expert opinion unclear. Assumption.
Blood Pressure Self-Monitoring	**31%**	Baral-Grant et al. 2012[191] (national data)
Pharmacy New Medicines Service	**65%**	Pharmaceutical Services Negotiating Committee NMS Statistics 2016/17[175]: Pharmacies offering NMS (local data)
NHS Health Checks	**44%**	NHS Health Check Data 2013-2018[183]: Proportion appointments received per population eligible (local data).
Annual Review	**44%**	Assumption that is similar to NHS Health Check.
FH Diagnosis and Cascade Testing	- Proportion adults with total cholesterol > 7.5mmol/l given	- Green et al. 2016[192] (national data) - NICE Guidelines CG71 (2017 update)[19]

	testing for FH = 28% - Proportion index cases taking up genetic testing = 84.1% Combined = **24%**	(national data)

Current care detection and management of high risk conditions

In addition to information about the interventions, it was also necessary to fill the tool inputs with information about the current proportions that are detected with the condition (of all those with the condition) and well-managed with the condition (of all those that are detected).

For detection, it was necessary to know both the total prevalence for each of the high risk conditions, and the detected prevalence each of the high risk conditions. The current proportion detected with a condition was then obtained using the following equation:

% Detected = Total Prevalence/Detected Prevalence

Local estimates of total prevalence are available from the National Cardiovascular Intelligence Network for Diabetes, Hypertension CKD & AF[179-182]. For other conditions, national estimates were used, taken directly from the Health Survey for England 2014 baseline characteristics[11]. There was information about detected prevalence at a local level for most of the conditions from QOF, whilst national data sources were identified where QOF data did not exist.

For QRISK ≥ 10%, no data source was identified to inform detected prevalence. However, a study by Finnikin et al., (2017)[187] indicates that 10.7% of people have a QRISK score recorded. If it can be assumed that recording of a score is independent of the value of that score, this would imply that 10.7% of people with QRISK ≥ 10% have been detected. The data sources used to inform prevalence and proportion detected for each condition is shown below, together with the national average.

Table 49: Summary of data used to inform prevalence and proportion detected for high-risk conditions

Condition	Prevalence (national average)	Data source
Hypertension	Estimated Prevalence = 28%	NCVIN Hypertension Expected Cases 2014[181] (local data)
	Detected Prevalence = 17%	QOF HYP001 hypertension prevalence[176] (local data)
	Proportion Detected = 60%	Calculation*
QRISK ≥ 10%	Estimated Prevalence = 34%	HSE 2014[11] data based on QRISK2 parameters.

	Proportion with a QRISK score recorded = 11%	Finnikin et al., 2017[187] THIN database (national data)
	Proportion Detected = 11%	As above
Familial hypercholesterolaemia	Estimated Prevalence = 0.4%	Steering group recommendation. (national data)
	Detected Prevalence = 0.028%	NICE Guidelines CG71, 2017 update[19] (national data)
	Proportion Detected = 7%	Calculation*
Diabetes	Estimated Prevalence = 8.4% Prevalence Type 1 = 0.6% Prevalence Type 2 = 7.8%	NCVIN Diabetes Prevalence model 2018 projected values[179] (local). HSE 2014[11] for Type 1 Diabetes.
	Detected Prevalence = 6.6% Prevalence Type 1 = 0.6% Prevalence Type 2 = 6%	QOF DM017 Diabetes Register[176] (local data) Note for type 1, all assumed to be detected.
	Proportion Detected = 78% Detected Type 1 = 100% Detected Type 2 = 78%	Calculation*
Non-diabetic hyperglycaemia	Estimated Prevalence = 11.2%	HSE 2014[11] data based on HbA1c.
	Detected Prevalence = 1.2%	NHS DPP Pilot Study for the Collection of Data[185]: Recorded diagnosis (national data)
	Proportion Detected = 10.7%	Calculation*
Chronic Kidney Disease	Estimated Prevalence = 6% (CKD stages 3a-5)	NCVIN CKD Prevalence Model Estimates 2015[180] (local data).
	Detected Prevalence = 4%	QOF CKD005 CKD Register[176] (local data)
	Proportion Detected = 65%	Calculation*
Atrial Fibrillation	Estimated Prevalence = 3.0%	NCVIN AF Prevalence Estimates 2017[182] (local data)
	Detected Prevalence = 2.3%	QOF AF001 AF Register[176] (local data)
	Proportion Detected = 76%	Calculation*
*Proportion Detected = Detected Prevalence/Estimated Prevalence		

To represent the proportion currently well-managed for each condition within the tool, a single key indicator was chosen corresponding either to usage of the most clinically important intervention for that condition, or to target metabolic control. Again, where possible local data was chosen, but national data was used where local data was not available. Note that whilst these indicators are used to represent the proportion currently well managed within the tool, improvements in management in the model actually work through improving usage of all relevant interventions for that condition.

Table 50: Summary of data used to inform proportion well-managed for high-risk conditions

Condition	Current proportion Well managed (national average)	Data source

Hypertension	57%	Percentage of hypertensives with blood pressure <140/90 mm Hg GP Contract Services England 2016/17: Indicators no longer in QOF (INLIQ)[177] HYP003. (local data)
QRISK ≥ 10%	21%	Finnikin et al. 2017[187] (THIN database; national data)
Familial hypercholesterolaemia	86%	NICE Guidelines CG71 (2017 update)[19]: Proportion of those with FH taking statins (national data)
Diabetes	40%	National Diabetes Audit 2016/17[178]: Percentage of people with Diabetes meeting all 3 treatment targets (HbA1c, Blood Pressure and Cholesterol) (local data). Weighted average for type 1 and type 2 diabetes.
Non-diabetic hyperglycaemia	35%	NHS DPP Pilot Study for the Collection of Data[185]: Proportion offered and not declined intervention (national data)
Chronic Kidney Disease	55%	CKD Audit report[184]: Proportion of people with CKD stage 3-5 meeting NICE blood pressure targets (national data)
Atrial Fibrillation	76%	QOF AF006 (% assessed for stroke risk) multiplied by Q0F AF007 (% high stroke risk patients taking anticoagulants)[176] (local data)

Conceptual tool development

Setting up the tool user group workshop

Tool user group recruitment

Attendees for the workshop were targeted for invitation on the basis of being the target users for the future tool. It was considered by the steering group that this should primarily be CCG and local authority public health representatives with responsibilities around CVD, as well as regional, national and charitable sector representation. Steering group members supported the identification of GPs with CVD as a special interest, charitable organisation contacts, PHE regional leads with responsibility for CVD or health checks, and the use of NHS England delivery partners to distribute invitations to all CCGs with circulation highlighted as an opportunity within their Right Care CVD pack. Local stakeholders with a known interest in CVD were also contacted directly by the Public Health Registrar on the ScHARR project team. This method ensured wide reach to relevant stakeholders and representation on the day from NHS England, PHE, British Heart Foundation, allied health professions from secondary care trusts, and 7 CCGs from across the country.

Developing the Tool User Group workshop agenda

The project team aimed to ensure that from the workshop they would understand in sufficient detail what users wanted from a user tool to facilitate decisions about investment in CVD prevention. This was not trivial, because the workshop needed to allow sufficient open discussions so that the tool users were not constrained by a predisposed idea of what the tool would do, whilst ensuring that discussions were not so open that by the end of the workshop the team would not have sufficient information to be able to develop the tool. The team also needed to ensure that sufficient time was spent on discussion of analyses that could feasibly be undertaken using the existing health economic model within the timescales of the project, whilst allowing participants some dialogue beyond this in order to understand what may be desirable within future research.

As such, the decision was made at an early stage to hold a morning session asking open questions about the tool users' current priorities and what they would ideally want from such a tool (whole group discussion), and then an afternoon session asking more specific questions which were led by key information needed by the project team and more constrained by what our health economic model could do within the timescales of this project (small group discussions).

Methods for obtaining and recording participant input

21 participants agreed to attend the workshop and these were divided into 4 groups of 5 or 6 people so that in each group there were participants from different geographical locations, with different roles, both representing CCGs and LAs. Notes from the workshop were collated. There were 9 people who wanted to be involved in the user group but could not attend the workshop, so were instead sent the questions for the workshop to answer electronically. Three replies were received and these were also incorporated into the summary of the workshop.

Summary of findings

Tool user strategy and vision relating to CVD prevention

- focus on finding undiagnosed hypertension and increasing treatment for AF noted
- more effective to consider all risk conditions together
- lifestyle interventions are of particular interest (eg tackling smoking, physical activity and sugar)
- current issues due to a lack of application, not a lack of knowledge in primary care. Needs to be easier to action

Questions that could be answered by a ROI tool

- other ROI tools focus mostly on health outcomes, but for LAs outcomes of interest are in relation to local economy and societal context, such as unemployment, social care, economic productivity lost
- issues of where costs and savings occur and whether these are ‘cashable’ or efficiencies in the system that are transferable elsewhere are complex due to block contracts, social care funding etc
- costs of detection should not be missed and it could be important to consider the cost of ‘doing nothing’ for a baseline case. It is also important to be able to phase the interventions and not expect to able to do everything at once in a year
- some concern about how lifestyle approaches are captured, rather than pushing medicalisation and drugs. For example consider social prescribing as an intervention
- consistency between the RightCare logical model template and the tool would support its use

Information requirements required to support the case for CVD prevention

- consensus that default values would be useful, but with the option to modify with local information eg costs of health checks vary from £12 to £64 pp in NW region. However, users need to be able to understand where default values have come from and how calculations have been made
- a need for outputs at multiple geographies and small enough to make a local difference, possibly even below LA where LA are large or mixed demographically
- NICE costing templates are very comprehensive but can be onerous to locally populate
- number needed to treat might be a useful output as easily understood and transferable in terms of clarity on value of an intervention
- each element of NICE guidance should be accounted for separately, as becomes a point of diminishing return, and also need to avoid inappropriate incentivisation, such as in QOF of reducing easy wins to below thresholds, rather than those most likely to benefit. Total patient risk is not helpful, it is the 'risk amenable to intervention', so resource can be best targeted at those where largest benefit can be gained
- need a sense of what is needed for the intervention eg extra investment in staff or clinic time and medication costs, and the resulting change in appointments, hospital admissions, ROI released

Information that is currently used to inform how well local areas are doing

- some areas have local tools, such as 'healthier futures' in West Yorkshire, which directly drill local GP patient records
- national audits provide some data, as do locally performed audits where done
- Nottingham are doing a PHE/BHF project on national CVD prevention audit
- could Bradford Healthy Hearts work be retrospectively fitted to determine real world transferability?

Tool inputs

- consensus agreement that there is a need for all 3 local levels: CCG, STP and LA, due to considerable difference in geographies in some areas. For very large local authorities, it might be useful to break results down by sub-local authority, or lower tier LA (district as well as upper tier county). Also useful for national and regional
- the STP level was generally felt most important as expect more work to be done at this level in the future. Many STPs have a prevention work-stream; however, variation across areas is often masked by larger geographies
- consensus agreement that a condition focussed approach (rather than an intervention focussed approach) was the most valuable, strategically and with respect to business cases

- however, also thought the intervention focussed approach might be more valuable to those actually commissioning services. Prefer a shorter list of interventions, perhaps through hiding those of low priority to the user, or somehow prioritising them by strength of evidence/effectiveness using colour or star ratings. Nearly all interventions were ranked as useful or very useful (those that were not were due to some local areas already prioritising them or decommissioning them, and varied by group).
- would like to see the value of the national average, or quartile ranges, so that they know how much they would need to improve to meet it
- there were conversations about whether numbers of people would be more compelling than % of population etc.
- in reality, local areas want to know which interventions or changes offer them the best ROI without trying every possible combination. Whilst this is not possible, having some pre-run data available would help
- need to focus as much as possible on outcomes rather than process measures and to look at precursors amenable to an intervention (eg checking BMI of all adults regularly might encourage younger people to take care of their weight and then not need a DPP in the future).
- would like to have ability to overwrite default input estimates with own data (but also useful to have a default value there)

Tool outputs

- the general consensus was that users would like to be presented with the potential cost-savings so that they can decide how much they might like to spend following generation of model outputs. This would mean no need to input costs at the start (however, want to be able to see cost data to give some rough indications of what expected costs might look like for incentivising interventions)
- generally, clinical events avoided is the most important output (but needs to potentially separate out by type, eg diabetes cases, strokes, MIs, CKD diagnosis etc.), together with deaths avoided
- QALYs are of less interest to commissioners and providers. Life years is important, but would be better if it was healthy life, or related to ability to be economically active
- cost outcomes were considered very important and should include the cost of delivering interventions, savings/net costs in different settings (primary care, secondary care, social care). Tensions between primary and secondary care particularly important and relate to what is required for the business case. Investment is almost certainly to be reinvestment of an opportunity cost in an alternative way
- cost-effectiveness outcomes were thought to be of less importance and potentially confusing

- additional costs of interest were drugs and staff time splits, intermediate care (stroke), bed days (would help in working with provider to reduce), length of hospital stay (useful incentive for provider), acute admissions
- wider societal benefits were considered useful to LAs, such as similar to what has been included in the MSK tool
- stratification of results would be useful for the high risk conditions, deprivation quintiles, ethnicity, age, mental illness and learning disability. Particularly useful to see the impacts on health inequalities
- time periods should include short (1 year), medium (2-5ys) and long (10y and over), although it would be useful if the user could define this. There was acknowledgement that CCGs needed to see a very fast short timeframe return and yet some of the ROI of these interventions would be unlikely to occur within these timeframes
- it should be able to generate a brief report if possible or something that can be exported into a document

Conceptual tool

A conceptual tool was developed in Excel showing the proposed layout of the ROI tool, based upon tool user comments and modelling feasibility. This underwent several iterations of development following feedback from the steering group and tool user group, the latter who were sent the conceptual tool together with a Google questionnaire to direct feedback.

Conceptual tool inputs

Whilst the tool users were generally fairly happy with the way the tool was laid out, based upon the comments received it was clear that the tool needed to be as simple as possible with very clear explanations of what it could do and of each element of the tool, with examples. The majority of users wished information about the tool to be included within the tool itself as far as possible, rather than in a separate user guide (although this changed following final tool development). The tool layout was therefore adapted to include a front-sheet with a full explanation of how to use the tool.

On the second sheet, users can enter their email address, a name for their model run and their locality, then can decide which type of question they would like the tool to answer:

- I want to improve detection or management of key CVD risk factors
- I want to improve usage of the key interventions for people at risk of CVD

This reflects the findings of the tool user group workshop that whilst most tool users found the first question more useful, some tool users would find the second type of question useful when actually commissioning interventions.

It became clear that management could be defined in several different ways and the first iteration of the conceptual tool gave users the choice to choose between these different definitions (eg based on metabolic targets vs interventions). However, user comments suggested that this was very confusing and that they didn't really know which of the options to choose. Later versions of the conceptual tool therefore simplified this by removing these additional questions.

Depending upon the choice between the 2 questions outlined above, the second input page differs in layout, showing either each of the CVD risk factors, with estimates of current detection and management; or each of the interventions, with estimates of current intervention usage. Users are able to modify these proportions if they have better local estimates than the tool can provide. Users can input 1 or more hypothetical improvement of choice for detection/management/intervention usage. Information about targets that could be aimed for is available next to each target proportion box as a pop-up information bubble when hovered over using the mouse. In both options, users can decide whether or not they want to phase in changes over more than 1 year. If they select yes, an additional set of boxes will appear below to enable phasing in of changes over up to 3 subsequent years.

An additional feature of the 'intervention focussed' input page is that there is the capability for users to enter their own intervention (perhaps something that they are doing specifically in their local area), either on its own or in combination with any of the other interventions. In order to do this, users need to know certain information about the intervention including the CVD risk factor that it is aimed at, the effectiveness of the intervention in reducing CVD risk, the cost of the intervention, the duration of intervention effect (ie the number of years over which the intervention effect should be applied) and the current proportion of people undergoing the intervention. Responses from the tool user group suggested that they would be unlikely to use this function of the tool. However, the steering group (who had suggested this initially) were keen that it was kept in the tool as it was likely to be useful for national modelling purposes.

Conceptual tool outputs

The tool user group was presented with a range of figures and tables and asked to choose those that would be of most use to them. They were particularly interested in the number of clinical events avoided and costs saved, and how these changed over time. All users agreed that for summary results, the most useful mortality outcome is premature deaths, and most users agreed that the most useful cost outcome is total cost savings. Local tool users were not particularly interested in seeing cost-

effectiveness results; however these were retained in the tool due to their utility at national level (local tool users can opt to not see these if they wish). Amongst the range of cost-effectiveness outcomes available, most users chose the incremental-cost effectiveness ratio (ICER) as being the most useful cost-effectiveness outcome. However, net monetary benefit was chosen instead as this is more meaningful over time, particularly if the target improvement is cost-saving, as the ICER is not meaningful in this scenario. However, a need to clearly explain net monetary benefit within the tool was identified.

Model reviews

Search and review strategy

The original SPHR Diabetes Prevention Model did not enable modelling of AF, FH or CKD (apart from end stage diabetic CKD). As there was not significant expertise within ScHARR for modelling these conditions, a rapid review of published health economic models from these 3 disease areas was carried out with the aim of identifying useful model structures, methodology and parameter values that could be used for model adaptation. Searches were carried out in Medline using terms for each condition, for economic modelling studies and with a date limit of 2007. Search terms can be found in Appendix A.

The review protocol differed from that for the effectiveness and cost-effectiveness reviews, as the aim was to identify any useful information rather than a single high quality study. Firstly; a title and abstract search was carried out to discard irrelevant studies (eg effectiveness studies), duplicates and anything without available full text. Note that any identified costing studies (if UK based) or health-related quality of life studies were retained at this point as they may contain useful data. Secondly; the full text of each study was rapidly scanned to identify anything of interest. Studies were discarded at this stage if they used the same model as a previously reviewed study (eg an adaptation of the same model for a different country), as this was unlikely to provide any additional useful information. For each retained full-text reviewed study, information was gathered about the setting (eg country); the model structure (eg cohort Markov model or discrete event simulation – see Brennan et al 2006 for more information about model structures[193]); the included health states if relevant; the model intervention focus (eg screening or treatment); and the method used for modelling CVD risk (if any). In addition, any particularly useful model methodology or parameter values were also collected. This might refer to modelling disease prevalence, characteristics of individuals with disease, disease progression, treatment parameters, costs, utilities and more detailed information about modelling CVD risk.

Model review: atrial fibrillation

Search question

What model structures, methodology and parameters relating to the cost-effectiveness modelling of interventions aimed at the detection and management of atrial fibrillation have been published over the past 10 years?

Results summary

The search for AF modelling studies found 298 results. This was reduced to 118 studies after sifting of titles and abstracts and 43 studies following full-text review. Six of the studies retained at full text review did not include models; 3 of these were costing studies, 1 was a health-related quality of life analysis and 2 studies were comparative analyses of AF cost-effectiveness models (Table 51).

It was found that most models were designed using a cohort Markov structure with cycles ranging from 2 weeks to annual. In some cases a short-term decision tree was also used first. The models that did not use a cohort Markov structure used discrete event simulation in 3 cases, individual patient level Markov simulation in 2 cases and 1 model was a budget impact tool. In 1 further study there was insufficient description to know what model structure had been used.

Whilst most models had been developed for analysing treatment decisions, 4 models focussed on screening/early detection of AF and 1 was a full system model designed to be able to evaluate interventions throughout the entire NICE recommended detection and treatment pathway[194] (albeit excluding population screening). Models tended to assess stroke/CVD risk using transition probabilities derived from published trial data, often based on the CHA2DS2-VASc score[195], although in 1 case based upon Warfarin therapeutic range and in another case modelled directly from Clinical Practice Research Datalink (CPRD) primary practice data[196]. None of the models; even those which simulated individual patient characteristics, used QRISK2[13] or QStroke[197] algorithms to take account of modifiable risk factors.

Table 51: Characteristics of reviewed models for AF

Study (first author and year)	Setting	Focus	Model type	Included health states	Stroke/CVD risk
Ademi, 2015[198]	Australia	Treatment	Cohort Markov model (annual cycles)	5 health states - well; post stroke/systemic embolism; post major bleeding; post-major bleeding and stroke; dead	Modelled using transition probabilities from the warfarin arm of ARISTOTLE study
Akerborg, 2012[199]	Canada, Italy, Sweden & Switzer-land	Treatment	Cohort Markov model (monthly cycles)	11 health states including stroke and congestive heart failure (yr1 and post); AF (nonsymptomatic, symptomatic); acute	Modelled from survival data from the ATHENA trial

Study (first author and year)	Setting	Focus	Model type	Included health states	Stroke/CVD risk
				coronory syndrome with or without treatment.	
Ali, 2015[200]	UK	Treatment	No model - costing study	NA	NA
Aronsson, 2015[201]	Sweden	Screening & Treatment	Cohort Markov model (annual cycles)	Health states include no AF, detected AF, non-detected AF plus a range of bleeding and CVD events	Modelled using CHA2DS2-VASc score[195]
Aronsson, 2015[202]	Denmark, Finland, Germany & Sweden	Treatment	Cohort Markov model (monthly cycles)	Health states include symptomatic and non symptomatic AF, CVD & bleeding events	Modelled using CHA2DS2-VASc score[195]
Bruggen-jurgen, 2007[203]	Germany	Treatment	No model - costing study	NA	NA
Canestaro, 2013[204]	US	Treatment	Cohort Markov model (monthly cycles)	Health states include CVD events and bleeds, different levels of deficit following stroke & post event stages	Modelled using transition probabilities from literature
Coleman, 2012[205]	US	Treatment	Cohort Markov model (monthly cycles)	Health states include CVD and bleeding events and severity of deficit following stroke	Modelled using transition probabilities mainly derived from the ACTIVE-A trial
Coyle, 2013[206]	Canada	Treatment	Cohort Markov model (3 monthly cycles)	Health states include range of CVD and bleeding events	Modelled using transition probabilities derived from a network meta-analysis
Dorian, 2014[207]	UK	Treatment	Cohort Markov model	Health states include CVD events and bleeding events	Modelled using CHA2DS2-VASc score[195]
Eckman, 2009[208]	US	Treatment	Cohort Markov model (monthly cycles)	28 health states including long and short term symptoms of stroke and	Modelled using transition probabilities

Study (first author and year)	Setting	Focus	Model type	Included health states	Stroke/CVD risk
				bleeding	derived from a network meta-analysis
Hernandez, 2017[209]	US	Treatment	Cohort Markov model (annual cycles)	6 health states including stroke and bleeding.	Modelled using transition probabilities derived from the RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI trials
Kansal, 2012[210]	UK	Treatment	Cohort Markov model (3 monthly cycles)	Health states include various CVD and bleeding events	Modelled using transition probabilities derived from the RE-LY trial
Lamotte, 2007[211]	UK	Treatment	Cohort Markov model (3 monthly cycles)	4 health states including no AF, AF, Stroke and Death	Modelled using transition probabilities derived from literature
Lee, 2012[212]	US	Treatment	Cohort Markov model (2 weekly cycles)	8 health states including stroke, MI & bleed	Modelled using transition probabilities derived from literature including the ARISTOTLE trial
Limone, 2014[213]	NA	NA	No model comparative analysis	NA	NA
Liu, 2017[214]	Taiwan	Treatment	Cohort Markov model (6 weekly cycles)	Health states including stroke, systemic embolism and bleed	Modelled using transition probabilities derived from literature
Lord, 2013[194]	UK	All aspects of disease pathway	DES model (Simul8)	Not relevant	Modelled by CHA2DS2-VASc score[195]

Study (first author and year)	Setting	Focus	Model type	Included health states	Stroke/CVD risk
		including detection, treatment and monitoring (not population screening)			using a Swedish AF cohort study to get event risk.
Lorenzoni, 2014[215]	Italy	Early detection	Insufficient description to know	Insufficient description to know	Insufficient description to know
Lowres, 2014[216]	Australia	Screening	Cohort model (annual cycles)	Health states not stated	Stroke risk modelled from CPRD data analysis[196].
Magnuson, 2015[217]	US	Treatment	Cohort Markov model (3 monthly cycles)	Health states include stable AF; stroke, systemic embolism, MI, haemorrhage in various levels of severity	Modelled using transition probabilities from ENGAGE AF–TIMI trial.
Marvig, 2015[218]	Europe	NA	No model - QoL study	NA	NA
McKenna, 2009[219]	UK	Treatment	Cohort short-term decision tree and long-term Markov model (annual cycles)	5 health states including AF, normal sinus rhythm, stroke and post stroke	Modelled using CHA2DS2-VASc score[195]
Micieli, 2016[220]	Canada	Treatment	Cohort Markov model (annual cycles)	5 health states including well, stroke, bleed, MI & death	Modelled using CHA2DS2-VASc score[195]
Moran, 2016[221]	Ireland	Screening	Cohort Markov model (annual cycles)	6 health states - no AF; undiagnosed AF; diagnosed AF, ischaemic stroke, haemorrhagic stroke & death	Modelled using transition probabilities derived from literature
Patrick, 2009[222]	US	Treatment	Cohort Markov model (3 monthly cycles)	Health states include stroke and haemorrhage	Modelled as a function of INR (therapeutic range for warfarin)
Pink, 2011[171]	UK	Treatment	DES model (R)	Not relevant	Modelled using

Study (first author and year)	Setting	Focus	Model type	Included health states	Stroke/CVD risk
					CHA2DS2-VASc score[195]
Rognoni, 2014[223]	Italy	Treatment	Cohort Markov model (3 monthly cycles)	10 health states including stroke and bleeding	Modelled using CHA2DS2-VASc score[195]
Saborido, 2010[224]	UK	Treatment	Cohort Markov model (annual cycles)	5 health states including normal sinus rhythm; chronic AF; post stroke (mild or severe) and death. Bleeding modelled separately.	Modelled using transition probabilities derived from literature mainly Alboni study
Salata, 2016[225]	US	Treatment	Cohort Markov model (monthly cycles)	Health states include stroke, haemorrhage and MI	Modelled using transition probabilities from RE-LY trials
Shah, 2011[226]	US	Treatment	Cohort Markov model (monthly cycles)	Health states include stroke, haemorrhage, bleed & dydpepsia	Modelled using transition probabilities from RE-LY trials
Shields, 2015[227]	UK	Treatment	Budget impact model in Excel (planning tool)	Not relevant	Modelled from literature
Shiffman, 2015[228]	US	Treatment	Cohort Markov model (annual cycles)	Health states include AF, stroke and bleed	Modelled from literature
Simpson, 2013[229]	UK	Treatment	DES model	Not relevant	Modelled using CHA2DS2-VASc score[195]
Singh, 2013[230]	Canada	Treatment	Patient level Markov micro-simulation model (monthly cycles)	Health states include bleed, MI and stroke	Modelled using CHA2DS2-VASc score[195]
Sorensen, 2009[231]	US	Treatment	Cohort semi Markov model (3 monthly cycle)	Health states include stroke and haemorrhage	Modelled using CHA2DS2-VASc score[195]
Sorensen,	NA	NA	No model -	NA	NA

Study (first author and year)	Setting	Focus	Model type	Included health states	Stroke/CVD risk
2013[232]			comparative analysis		
Sussman, 2013[233]	US	Treatment	No model - costing study	NA	NA
Vester-gaard, 2015[234]	Denmark	Treatment	Cohort Markov model (3 monthly cycles)	Health states include AF, stroke and bleed	Modelled using CHA2DS2-VASc score[195]
Wisloff, 2014[235]	Norway	Treatment	Cohort Markov model (annual cycles)	Health states including AF, stroke, MI and bleed	Modelled using CHA2DS2-VASc score[195] from Scandinavian registry data
Wu, 2014[236]	China	Treatment	Individual level state transition model in R (monthly cycles)	Health states include stroke, MI and bleeding	Modelled using CHA2DS2-VASc score[195]
You, 2012[237]	US	Treatment	Cohort semi Markov model (monthly cycle)	Health states include AF, stroke, MI, dyspepsia and bleed	Modelled from literature
Zhao, 2016[238]	Singa-pore	Treatment	Cohort semi Markov model (monthly cycle)	Health states include AF, stroke, MI and bleed	Modelled from literature
NA = Not Applicable					

Useful data extracted

A range of different types of useful data were extracted as follows:

AF prevalence and incidence

Four studies included potentially useful prevalence and incidence parameters, including information about the proportion detected/annual detection rate. AF prevalence and

incidence varies widely by age, indicating the importance of including age as a parameter within any prevalence estimates.

Table 52: Summary of AF prevalence and incidence data found in the model review

Study	Population studied	Total AF prevalence	Diagnosed AF prevalence	Annual AF incidence	Baseline annual AF detection rate
Aronsson, 2015[201] (Sweden)	75 year olds	12%	9%	NR	5% of undiagnosed AF
Lowres, 2014[216] (Australia)	65-84 year olds	5.8%	4.4%	NR	NR
Moran, 2016[221] (Ireland)	65+ year olds	NR	NR	Age Dependent	62% of incident cases
Sheilds, 2015[227] (UK)	Representative population of a CCG.	1.0%	Not separately measured	0.2%	Assumed all cases are detected.
NR = Not Recorded; CCG = Clinical Commissioning Group					

Characteristics of AF patients

One study (Lord, 2013[194]) supplied a table indicating the population characteristics of a newly diagnosed AF patient population in the UK that they had derived from analysis of the THIN primary care dataset:

Table 53: Population characteristics of a newly diagnosed AF patient population in the UK from the THIN primary care dataset from the Lord, 2013[194] model

Number of patients in dataset	12,776
Average age	73.6 years
Proportion female	47%
Proportion with a family history of congestive heart failure	5%
Average blood pressure	137/78 mm Hg
Average BMI	28.5 kg/m^2
Proportion current smokers	12%
Proportion on lipid lowering or anti-platelet medication	40%
Proportion on anti-hypertensive medication	65%
Proportion with history of haemorrhage	21%

AF Treatment Parameters

A variety of parameters around treatment eligibility, adherence to treatment and discontinuation were obtained from 3 studies.

- Sheilds, 2015[227] (UK) calculated that 84% of patients with AF were eligible for anti-coagulant treatment according to CHA2DS2-VASc score
- Sheilds, 2015[227] assumed that 41% of those eligible for treatment were adhering to treatment, whilst Lowres, 2014 (Australia) used an adherence to treatment of 55%
- Sheilds, 2015[227] included data suggesting that 14.2% of anti-coagulant treatment prescriptions were for novel oral anti-coagulants (NOACs), with the remaining for Warfarin
- Pink, 2011 (UK)[171] incorporated information about discontinuation from a primary study (Connolly et al, 2009[239]) as shown in Table 54

Table 54: Summary of data about discontinuation of anti-coagulant treatment used in Pink, 2011 model[171]

Drug	Probability major bleed leads to discontinuation	Probability adverse event leads to discontinuation	Probability discontinue Yr1 (other reasons)	Probability discontinue Yr2+ (other reasons)
Warfarin	0.1425	0.0194	0.0832	0.0459
Dabigatran 110mg	0.1801	0.0298	0.1160	0.0475
Dabigatran 150mg	0.2133	0.0292	0.1226	0.0432

Stroke risk in AF

Most models based stroke risk on CHA2DS2-VASc score[195]. The stroke risks associated with each level of CHA2DS2-VASc score, from 3 different models, are presented below:

Table 55: Modelled stroke risk in AF using CHA2DS2-VASc score[195]

	Aronsson, 2015[201] (Sweden)	Lord, 2013[194] (UK)	McKenna, 2009[219] (UK)
CHA_2DS_2-VASc 0	NR	0.3%	1.9%
CHA_2DS_2-VASc 1	NR	1.0%	2.8%
CHA_2DS_2-VASc 2	NR	3.3%	4.0%
CHA_2DS_2-VASc 3	3.6%	5.3%	5.9%
CHA_2DS_2-VASc 4	5.4%	7.8%	NR
CHA_2DS_2-VASc 5	8.3%	11.7%	NR
CHA_2DS_2-VASc 6	11.3%	15.9%	NR
CHA_2DS_2-VASc 7-9	NR	18.4%	NR
NR = Not Recorded			

Stroke outcomes in AF

Some information about the proportion of total CVD or bleeding events which were fatal was used in 3 different models as follows:

Table 56: A summary of data about AF stroke outcomes included in models

	Coyle, 2013[206] (Canada)	**McKenna, 2009[219] (UK)**	**Moran, 2016[221] (Ireland)**
Proportion strokes that are fatal	23.7%	7.4%	Age and AF dependent
Proportion non-fatal strokes that are major	33.3%	NR	NR
Proportion major bleeds that are fatal	8.4%	NR	NR
Proportion myocardial infarctions that are fatal	12.1%	NR	NR
Proportion pulmonary embolisms that are fatal	33.3%	NR	NR
NR = Not Recorded			

AF utilities

A wide range of different utility decrements were used to distinguish between well health states and those with AF, symptomatic AF, treated AF (various drugs), AF with various types of bleeding or CVD event. These are summarised in Table 57.

Table 57: A summary of different utilities and utility decrements used in AF modelling

Ademi 2015 [198]	Akerborg 2012 [199]	Aronsson 2015 [201]	Coyle 2013 [206]	Dorian 2014 [207]	Hernandez 2017 [209]	Lee 2012 [212]	Marvig 2015 [218]	Moran 2016 [221]
Utility for AF								
0.81	Varies by age & gender.	NR	0.81	0.727	0.81	NR	0.75 (newly diagnosed)	0.81 (newly diagnosed) 0.94 (un-diagnosed)
Utility for symptomatic AF								
NR	0.084 decrement	0.13 decre-ment	NR	NR	NR	NR	NR	NR
Utility with Warfarin treatment								
NR	NR	NR	NR	0.012 decre-ment	0.989	0.987	NR	NR
Utility with NOAC treatment								
NR	NR	NR	NR	0.002 decre-ment	0.989	0.994	NR	NR
Utility for AF with prior stroke								

0.67	0.295 lifetime decrement	NR	NR	NR	NR	NR	NR	NR
Utility for AF with haemorrhagic stroke								
NR	NR	0.30 decre-ment	NR	NR	NR	NR	NR	0.57
Utility for AF with ischaemic stroke								
NR	NR	0.15 decre-ment	NR	NR	NR	NR	NR	Varies by severity
NR = Not Recorded								

AF costs

Whilst all models included costs in some form, 1 of the most important findings from the 3 costing studies found in the review was that the cost of stroke appears to be higher in people with AF than people without AF (ranges from about 1.2 fold higher to 1.6 fold higher):

Table 58: Sources of evidence for cost of stroke with and without AF

Study	Acute Stroke Care without AF	Acute Stroke Care with AF	Ratio	Date costed	Setting	Costs
Ali, 2015[200]	£5,729	£9,083	1.59	2011/12	Rotherham hospital, UK	Healthcare only
Bruggen-jurgen, 2007[203]	Euros 8,817	Euros 11,799	1.34	2005	Germany	Health and some social care (including nursing home, home modifications and transport)
Sussman, 2013[233]	NR	NR	1.20 (stroke); 1.18 (TIA)	2011	US	Healthcare only
NR = Not Recorded						

Model review: familial hypercholesterolaemia

Search question

What model structures, methodology and parameters relating to the cost-effectiveness modelling of interventions aimed at the detection and management of familial hypercholesterolaemia have been published over the past 10 years?

Results summary

The search for FH modelling studies found 59 results. This was reduced to 11 studies after sifting of titles and abstracts and 7 studies following full-text review. An additional study was added on the recommendation of the steering group. This related to the update of NICE guideline CG71 for FH[19], published whilst this project was underway, which included a comprehensive model of the FH cascade testing pathway. One of the studies retained at full text review did not include a model as it was a trial based economic analysis (Table 59).

It was found that most models were designed using an initial decision tree, followed by a cohort Markov structure. One model used a decision tree only and another used individual patient level simulation. Most of the models were developed to analyse decision problems around screening of FH, with only 1 (the simulation model) evaluating just treatment, and another evaluating both screening and treatment.
A range of different methods were used to assess CVD risk. Of particular interest, 2 UK models based modelling of CVD risk upon QRISK2[13], modified by an additional FH-dependent relative risk for CVD based upon Simon Broome criteria[240]. Two US models based CVD risk upon the US Framingham risk equations[241], although it was unclear whether there was any adjustment of risk for FH in these models. Other models based CVD risk on absolute cardiac risk from various published sources.

Table 59: Characteristics of Reviewed Models for FH

Study (first author and year)	Setting	Focus	Model Type	Included health states	Stroke/CVD risk
NICE, 2017[19]	UK	Screening	Decision tree followed by cohort Markov model (annual cycles)	Health states include CVD events following low, medium or high statin treatment	Based on Lipid modification model from CG181[20] (QRISK2[13] based)
Ademi, 2014[242]	Australia	Screening	Decision tree followed by cohort	Health states include CHD,	Based only on annual incidence

Study (first author and year)	Setting	Focus	Model Type	Included health states	Stroke/CVD risk
			Markov model (annual cycles)	death and alive without CHD	of CHD
Broek-huizen, 2015[243]	Nether-lands	Treatment	No model - within trial economic analysis	NA	NA
Chen, 2015[244]	US	Screening & Treatment	Decision tree followed by cohort Markov model (annual cycles)	3 health states corresponding to pre-CVD, CVD and death	Based on Framingham risk equation[241] by age group. No extra risk due to FH included.
Kazi, 2016[245]	US	Treatment	Simulation model based on US population (CVD Policy Model)	NA	Based on Framingham study[241]. No extra risk due to FH included.
Kerr, 2017[128]	UK	Screening	Decision tree followed by cohort Markov model (annual cycles)	Health states include various first CVD events and subsequent CVD events	Based on QRISK[13] by 5 year age band and gender, followed by RR for CHD from Simon Broome register for FH[240]
Lazaro, 2017[246]	Spain	Screening	Decision tree	NA	10 year risk of cardiac event directly taken from Spanish Registry of people with FH
Nherera, 2011[247]	UK	Screening	Decision tree followed by cohort Markov model	Not clear from article	Age dependent CVD risk taken from Simon Broome Study[240]
NA = Not Applicable					

Useful data extracted

A range of different types of useful data were extracted as follows:

FH prevalence
Only 1 study reported useful FH prevalence data (NICE, 2017[19]). For this study it was assumed that the prevalence of monogenic FH in the UK population was 0.2%. This was related to high cholesterol by assuming that 28% of individuals with the top 0.51% of total cholesterol for their age group would have monogenic FH.

Cascade testing for FH
A series of useful parameters to inform cascade testing in the UK were found in the NICE, 2017[19] modelling study. This included the take-up of a genetic test in index FH cases (84.1%), the number of relatives of the index case who are offered the cascade test (2.22), the take-up of the cascade test in relatives (59.89%) and the probability that tested relatives have monogenic FH (50.89%). The model assumed that genetic testing has perfect sensitivity and specificity and that none of the relatives already know their FH status.

CVD risk in FH
Two models (NICE, 2017[19] and Kerr, 2017[128]) base the risk of CVD upon QRISK2 10 year risk equations[13], followed by FH-specific relative risks for CVD events from Simon Broome[240]. The following table shows the relative risks used to adjust QRISK2 in the NICE model. These relative risks are against general population QRISK2 values, not against a population with high cholesterol, which would be more appropriate but is not available. Note that there is no increase in stroke risk with FH:

Table 60: Relative risks used to adjust QRISK2 10 year risk for FH (from NICE, 2017[19])

RR coronary heart disease males < 60	4.0028
RR coronary heart disease males > 60	1.6199
RR coronary heart disease females < 60	5.1330
RR coronary heart disease females > 60	2.2827
RR coronary heart disease < 60 next event	4.1790
RR coronary heart disease > 60 next event	1.8842
RR stroke	1 (assumed no difference)
RR = Relative Risk	

Other models used absolute cardiac risk from various published sources. For example, Ademi, 2014[242] fixed the annual incidence of coronary heart disease in people with FH at 11.9%, and assumed that 34.2% of those would suffer a fatal event.

Lipid lowering in FH
Parameters about the adherence to lipid lowering therapy for FH and the type of medication people were taking were used in 2 studies:

- Chen, 2015[244] (US) assumed that adherence to statins was 56% in the first 9 years and 42% in year 10 or more of treatment
- Kerr, 2017[128] (UK) assumed that 86.25% of people with FH were taking statins, that 46.43% were taking Ezetimibe in addition, and that the type of statins taken were in the following ratio: Atorvastatin = 72%; Simvastatin = 20%; Rosuvastatin = 8%

FH costs
The NICE, 2017[19] and Kerr, 2017[128] studies contain detailed description of costs incurred in FH testing, both from a UK perspective. These will be considered further in the cost review carried out as part of Phase 2 of this project.

FH utilities
No model used utility values or decrements specifically for FH prior to any CVD event.

Model review: chronic kidney disease

Search question

What model structures, methodology and parameters relating to the cost-effectiveness modelling of interventions aimed at the detection and management of chronic kidney disease have been published over the past 10 years?

Results summary

The search for CKD modelling studies found 87 results. This was reduced to 23 studies after sifting of titles and abstracts and 15 studies following full-text review. Three studies retained at the full text review did not have models; 1 was a quality of life study, 1 was a review of economic models and 1 was a trial based analysis. A further study contained only a costing model rather than a cost-effectiveness model.

It was found that most models were designed as cohort Markov models, 2 of which were preceded by decision trees. Two models were Markov patient level simulation models and a further model was a continuous time cohort state transition model. Most of the models were developed to analyse decision problems around CKD treatment, but 2 evaluated screening and 1 modelled early referral to specialist strategies.

The majority of models (6) did not include any modelling of CVD, but instead based primary outputs on modelling of CKD progression. In those that did model CVD, a

variety of methods were used. Interestingly 1 UK model (Black, 2010[248]) simulated CVD risk through QRISK2[13] (ignoring the CKD input), then adjusted CVD risk using a hazard ratio specific for CKD stage. Two US models used a similar approach, but based on the US Framingham risk equations[241]. Another model used CVD risk estimates directly from primary analysis of a kidney and CVD population dataset, whilst the final model (focussed on treatment for anaemia in people with CKD) used population estimates of CVD risk multiplied by hazard ratios for haemoglobin reduction.

Table 61: Characteristics of Reviewed Models for CKD

Study (first author and year)	Setting	Focus	Model type	Included health states	Stroke/CVD risk
Adarkwah, 2011[249]	Nether-lands	Treatment	Cohort Markov model (annual cycles)	5 health states including type 2 diabetes with normo, micro or macro-albuminuria, end stage renal disease (ESRD) and death.	Not modelled
Black, 2010[248]	UK	Early Referral to Specialist Strategies	Cohort Markov model (annual cycles)	Health states including CKD stages with or without micro-albuminurea, proteinurea and CVD. Non-diabetic CKD only	Based on QRISK2[13] without CKD then multiplied by RR or HR for CVD events based on reduced ACR, eGFR or prior CVD.
Dale, 2008[250]	UK	NA	No model - review of utility data	NA	N/A
Erickson, 2013[251]	US	Treatment	Cohort Markov model (3 month cycles)	Health states including CKD stages	Based on Framingham Risk Score[241] without CKD then multiplied by HR for CVD events based on CKD stages
Hoerger, 2010[252]	US	Screening	Patient level microsimulation model (annual cycles)	7 health states including no CKD, stages 1-5 CKD and death, plus additional detail	Based on Framingham Risk Score[241] without CKD then multiplied

Study (first author and year)	Setting	Focus	Model type	Included health states	Stroke/CVD risk
				about risk factors like hypertension, diabetes, kidney damage	by HR for CVD events based on CKD stages.
Kerr, 2012[253]	UK	Treatment	Costing model - no details	Not clear from article	Based on population estimates of Stroke/MI multiplied by HR for CKD patients
Mennini, 2014[254]	Italy	Treatment	Cohort Markov model (annual cycles)	3 health states including chronic renal disease, dialysis and death	Not modelled
Ruggeri, 2014[255]	Italy	Treatment	No model - trial based analysis	NA	NA
Schlackow, 2017[256]	UK	Treatment	Patient level microsimulation model (annual cycles)	Health states included in CKD sub-model (stage 3B,4,5, dialysis, transplant) and CVD sub-model (MI, stroke, CVD death), plus patient characteristics taken into account	Based on data from SHARP (Study of Heart and Renal Protection)
Sutton, A. 2015[257]	NA	Testing	No model - review of models	NA	NA
Nguyen, 2016[258]	Singa-pore	Treatment	Cohort Markov model (annual cycles)	3 health states including pre-dialysis CKD, end stage CKD and death.	Not modelled
de Vries, 2016[259]	7 Euro-pean countries inc. UK	Treatment	Continuous time cohort state-transition model with fixed age dependent state durations	Health states include CKD stage 4, ESRD dialysis, ESRD transplantation and death	Not modelled
Wang, 2017[260]	China	Screening	Decision tree followed by Markov model	4 health states including negative test result, screen detected CKD, Symptomatically detected CKD and	Not modelled

Study (first author and year)	Setting	Focus	Model type	Included health states	Stroke/CVD risk
				death	
Wong, 2013[261]	Australia	Treatment	Decision tree followed by Markov model for mortality	Only 2 health states, not dead and dead.	Not modelled
Yarnoff, 2016[262]	US	Treatment	Cohort Markov model (annual cycles)	7 health states including no CKD, CKD stage 1-5 and death.	Modelled on the basis of a hazard ratio per 1g/dl increase in Hb concentration
NA = Not Applicable					

Useful data extracted

A range of different types of useful data were extracted as follows:

CKD prevalence

Only 1 model from the US (Hoerger, 2010[252]) had useful information about total prevalence of CKD by age and CKD stage. This data was generated through model calibration. The prevalence table generated in the model is reproduced below:

Table 62: The estimated age-specific prevalence of CKD generated by the Hoerger, 2010[252] model

	Age 40	Age 50	Age 60	Age 70	Age 80
No CKD	94.75%	88.81%	81.67%	76.53%	79.64%
Stage 1	1.28%	2.00%	2.20%	1.76%	0.94%
Stage 2	0.78%	2.17%	3.81%	4.86%	3.93%
Stage 3	3.14%	6.56%	10.98%	14.37%	13.17%
Stage 4	0.05%	0.37%	0.96%	1.84%	1.80%
Stage 5	0.00%	0.09%	0.39%	0.64%	0.52%

CKD is defined not only by stage (estimated Glomerular Filtration Rate = eGFR), but also by albumin/creatinine ratio (ACR). The prevalence of different categories of micro-albuminuria (classified as ACR 30-299mg/g) used in the Hoerger, 2010 model [252] was as follows:

Table 63: Prevalence of micro-albuminuria used in the Hoerger, 2010[252] model

Microalbuminuria	With diabetes	2%
	With hypertension	1.4% (males); 3.5% (females)
	With neither	0.5% (males); 1.4% (females)

CKD progression

Most of the models incorporated some measure of CKD progression using eGFR (CKD stage), ACR or both. The Black, 2010[248] model derived a table of transition probabilities by CKD stage, based on Scottish primary care data and calibrated to match published data on end stage renal disease (ESRD).

Table 64: CKD state transition probabilities from Black, 2010[248]

	CKD 1 & 2	CKD 3a	CKD 3b	CKD 4	CKD 5
Reduced GFR alone					
CKD 1 & 2	0	0	0	0	0
CKD 3a	0	0.927	0.073	0	0
CKD 3b	0	0	0.952	0.048	0
CKD 4	0	0	0	0.966	0.034
Reduced GFR with ACR 30-299 mg/g					
CKD 1 and 2	0.930	0.070	0	0	0
CKD 3a	0	0.895	0.105	0	0
CKD 3b	0	0	0.931	0.069	0
CKD 4	0	0	0	0.950	0.050
Reduced GFR with ACR ≥ 300 mg/g					
CKD 1 and 2	0.880	0.120	0	0	0
CKD 3a	0	0.833	0.167	0	0
CKD 3b	0	0	0.882	0.118	0
CKD 4	0	0	0	0.911	0.089

ACR = Albumin/Creatinine Ratio; GFR = Glomerular Filtration Rate; CKD = Chronic Kidney Disease

Hoerger, 2010[252] used a different approach for modelling GFR transition based on an annual decline in eGFR which differs depending upon comorbid diabetes, hypertension or macro-albuminuria (ACR > 300 mg/g). This study models GFR values rather than categorising by stage. The transitions come from US National Health and Nutrition Examination Survey (NHANES) data[263].

Table 65: Annual decline in eGFR used in Hoerger, 2010[252]

	No macro-albuminuria	With macro-albuminuria
No Diabetes or Hypertension	0.65	0.72 (age ≤ 60) 4.2 (age > 60)

Diabetes	1.1 (age ≤ 60) 2.8 (age > 60)	4.1 (age ≤ 60) 5.2 (age > 60)
Hypertension	0.72 (age ≤ 60) 1.4 (age > 60)	0.78 (age ≤ 60) 3.9 (age > 60)

ACR transitions are modelled separately. The Black, 2010[248] model does not incorporate differences in progression between individuals with and without comorbid hypertension or diabetes, unlike the Adarkwah, 2011[249] and Hoerger, 2010[252] models, but does use data about diabetic CKD to model all ACR transitions (note that it is the same as the Hoerger diabetes data). The Hoerger study also uses information about the benefit of ACR anti-hypertensive treatment in preventing these transitions. This is all summarised in Table 66.

Table 66: Summary of different ACR transition probabilities used in different CKD models

TRANSITION	Black, 2010[248]	Adarkwah, 2011[249]	Hoerger, 2010[252]
No Comorbid Conditions			
ACR < 30 to ACR 30-299	2%	NA	0.2-0.5%
ACR 30-299 to ACR > 300	2.8%	NA	0.1-5%
ACR > 300 to ESRD	NA	NA	NA
Diabetes			
ACR < 30 to ACR 30-299	NA	5.6%	2%
ACR 30-299 to ACR > 300	NA	9.4%	2.8%
ACR > 300 to ESRD	NA	5.6%	NA
Hypertension			
ACR < 30 to ACR 30-299	NA	NA	0.2-1%
ACR 30-299 to ACR ≥ 300	NA	NA	1.47%
ACR > 300 to ESRD	NA	NA	NA
ACE Inhibitor Treatment (Relative Risk)			
ACR < 30 to ACR 30-299	NA	NA	0.60
ACR 30-299 to ACR > 300	NA	NA	0.45
ACR > 300 to ESRD	NA	NA	0.61
NA = Not Applicable; ESRD = End Stage Rental Disease; ACR = Albumin/creatinine ratio			

The Shlackow, 2017[256] study used a complex series of multivariate risk equations in their model (known as the SHARP model) to calculate CKD events including stage transitions, transition to dialysis and transition to renal transplant (not shown). This used a large number of covariates including age, sex, ethnicity, educational level, diabetes, cholesterol, albumin, haemoglobin and ACR.

CVD risk in CKD

The Black, 2010[248] model bases the risk of CVD upon QRISK2 10 year risk equations[12] (not using the coefficients for CKD already within QRISK2), then multiplies this by published CKD-specific relative risks for CVD events[264]. These are shown in the following table:

Table 67: Adjusted relative risks used to estimate risks of CVD events in the Black, 2010 model[248]

	Relative risk
CKD 1 and 2 (ACR 30-299 mg/g)	2.19
CKD 1 and 2 (ACR ≥ 300 mg/g)	3.40
CKD 3 and 4 (ACR <30 mg/g)	2.36
CKD 3 and 4 (ACR 30-299 mg/g)	3.01
CKD 3 and 4 (ACR ≥ 300 mg/g)	4.35
ACR = Albumin/creatinine ratio; CKD = Chronic Kidney Disease	

The SHARP model used a complex series of multivariate risk equations to calculate CVD events including vascular death, major atherosclerotic event and major vascular event (not shown). This used a large number of covariates including age, sex, ethnicity, smoking, diabetes, systolic blood pressure, albumin, haemoglobin and ACR.

CKD utilities

No model used utility values or decrements specifically for CKD without other complications. Models did use utility decrements for end stage renal disease; however these are already incorporated within the SPHR Diabetes Model so were not reviewed in detail at this stage.

Modelling methods

Model structure

The CVD Prevention ROI tool is based on an adaptation of the School for Public Health Research (SPHR) Diabetes Prevention Model developed by the School for Health and Related Research at the University of Sheffield. The SPHR Diabetes Prevention Model was developed to forecast long-term health and health care costs under alternative scenarios for diabetes prevention. A wide range of stakeholders were involved in its development including clinicians, public health commissioners and patients. A detailed description of the methodology and assumptions used in the original model can be found elsewhere[58].

The model is an individual patient simulation model based upon the evolution of personalised trajectories for metabolic factors including body mass index (BMI), systolic blood pressure (SBP), cholesterol and blood glucose (HbA1c). The evolution of these individual level trajectories is based upon statistical analyses of the Whitehall II cohort, a longitudinal dataset of civil servants[265 266]. The baseline population consists of a representative sample of the English population obtained from the Health Survey for England (HSE), an annual survey that is designed to provide a snapshot of the nation's health[11]. Individuals aged <16 are excluded from the model. Missing anthropometric or metabolic data is imputed using ordinary least squares (OLS) linear regression models (see [58] for more details).

Schematics showing the process of setting up the baseline population, and what happens to the population in each year thereafter are shown in Figure 3 and Figure 4. Data sources are shown in burgundy and processes in turquoise. The model setup (Figure 3) starts with the baseline characteristics of individuals from the Health Survey for England 2014, which enables the total prevalence of hypertension, diabetes, non-diabetic hyperglycaemia, QRISK ≥10% and FH to be calculated following imputation of missing data. AF and CKD prevalence are taken from external data sources; risk equations are used to determine which individuals in the HSE 2014 are most likely to suffer from these conditions. The population is then reweighted to resemble the local area chosen by the tool user. The estimates of total population prevalence of each high risk condition provided in the tool outputs are calculated at this point.

The next step is to decide which individuals are diagnosed with each condition. Diagnosed prevalence is taken from local and national data sources that feed into the tool inputs relating to proportion detected with each high risk condition. These may be modified by tool users if they have selected to 'improve detection and management of CVD risk factors'. Individuals are chosen to be diagnosed through a random process, although information from HSE 2014 about who is diagnosed with conditions is used

where available. A similar process is used to decide who is currently managed/treated with particular interventions, with information about the proportions managed/treated taken from local and national data and modifiable by tool users.

Figure 3: Schematic showing the data sources and processes used to set up the model baseline population

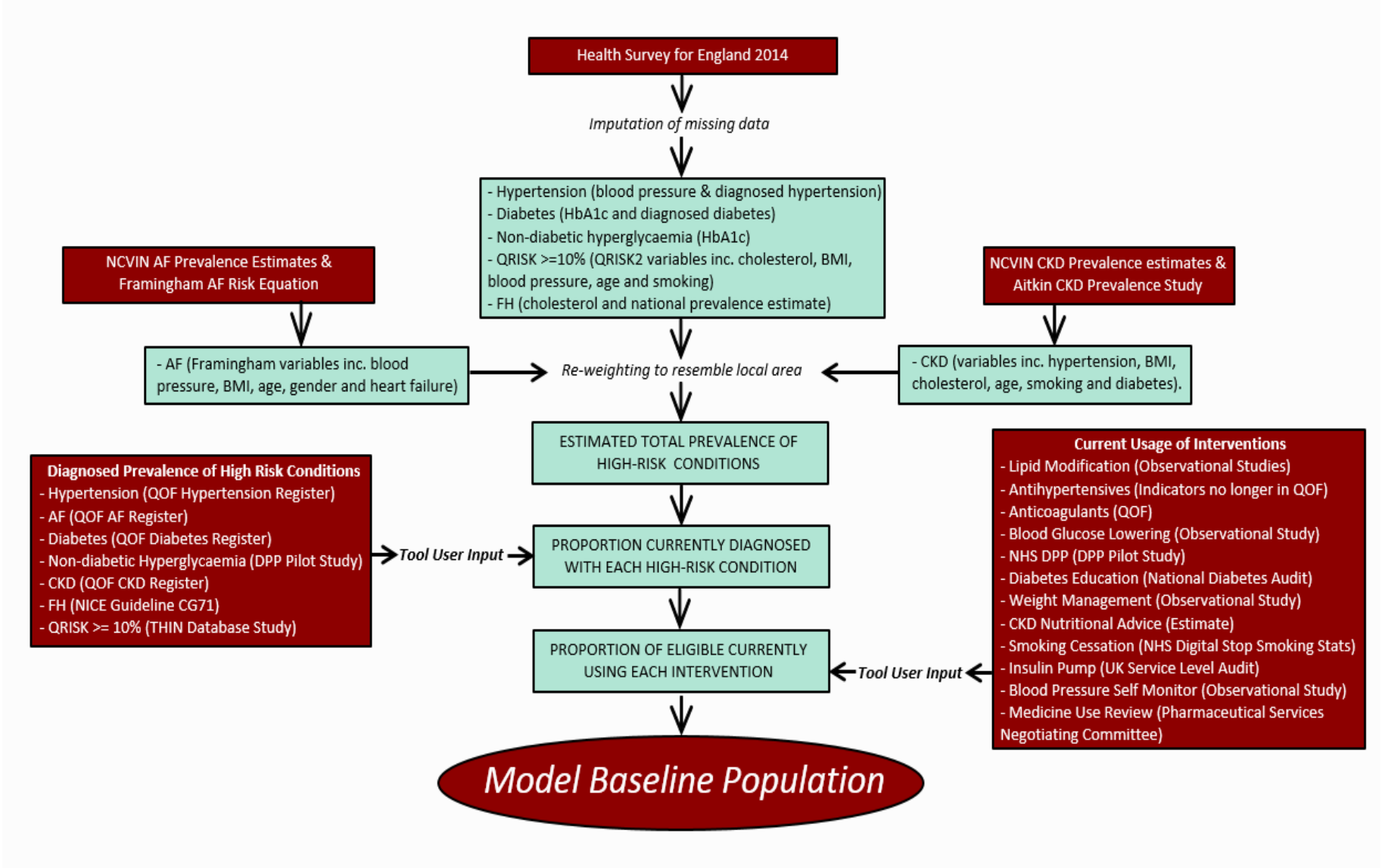
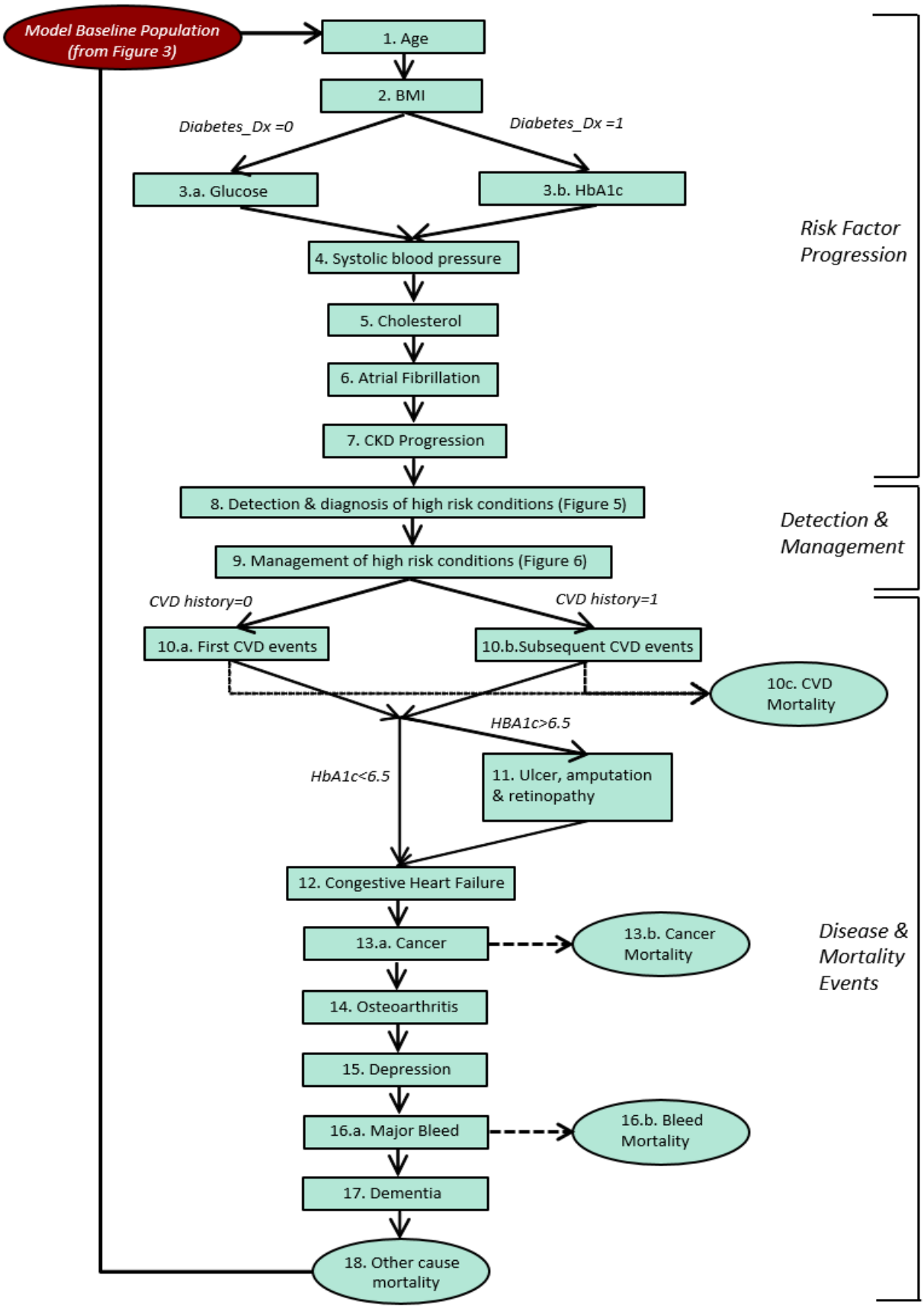


Figure 4: Model schematic showing the order in which updating of population characteristics takes place in each year of the simulation



Following setup of the model baseline population, the population is simulated over the course of the next 20 years. In each year, a series of events takes place in a specific order, with each event applied to each eligible individual in the population (Figure 4). The initial steps involve updating the age and metabolic trajectories of each individual to simulate them aging by 1 year. After this, detection and diagnosis of the CVD risk factors is applied (Figure 5). Those eligible for NHS Health Checks or annual review are randomly selected to receive these interventions according to the proportions taken from NHS Health Check appointments data, which may be overwritten by tool users if they have selected to 'improve the usage of key interventions for people at risk of CVD'. If an individual is selected to get 1 of these interventions they will undergo the series of diagnostic tests prescribed in the guidelines and be diagnosed if they have the underlying high risk factor. It is assumed that any individuals who have a health check or annual review, and who also have total cholesterol ≥7.5 mmol/L, will be eligible for FH testing, together with anyone who has had CVD in the previous year aged under 65. Finally, a process of random opportunistic testing, not associated with any particular detection mechanism, is simulated in the whole population, to ensure that the proportion diagnosed with each high risk factor remains similar to either the current proportion (based on local and national data) or the user-defined target proportion.

Following diagnosis, the management module of the model runs through each of the management interventions in turn, shown in more detail in Figure 6. As with diagnosis, the proportions of eligible people getting each intervention are prescribed by local and national data, which may be overridden by tool user inputs. Tool user inputs act in 2 ways, depending upon which of the questions the tool user has chosen to answer. Users that choose to 'improve the usage of key interventions for people at risk of CVD', can directly override the local and national data to determine the proportions getting each intervention. Users that choose to 'improve detection and management of CVD risk factors', do so through indirectly changing the usage of the key interventions recommended by NICE for each CVD risk factor (coloured differently to the right of the diagram). So for example, if a user chooses to improve management of non-diabetic hyperglycaemia to 100%, this will move usage of the NHS DPP to 100%, smoking cessation to 100% and weight management to 100% in eligible people within that high risk group.

Following management, the model simulation runs through the series of disease events that happen as a consequence of the changes in risk factors that occur through aging, diagnosis and treatment (Figure 4). For each event, every individual has a risk of its occurrence; recalculated annually (for example QRISK for CVD risk). Whether or not the event happens is random. When all events have been simulated, costs and QALYs for each individuals' new disease state are gathered, and the process recommences. Individuals that die during the year are removed from simulation in subsequent years.

Figure 5: Schematic of the data sources and processes that comprise the detection and diagnosis module of the model (expansion of box 8 from Figure 4)

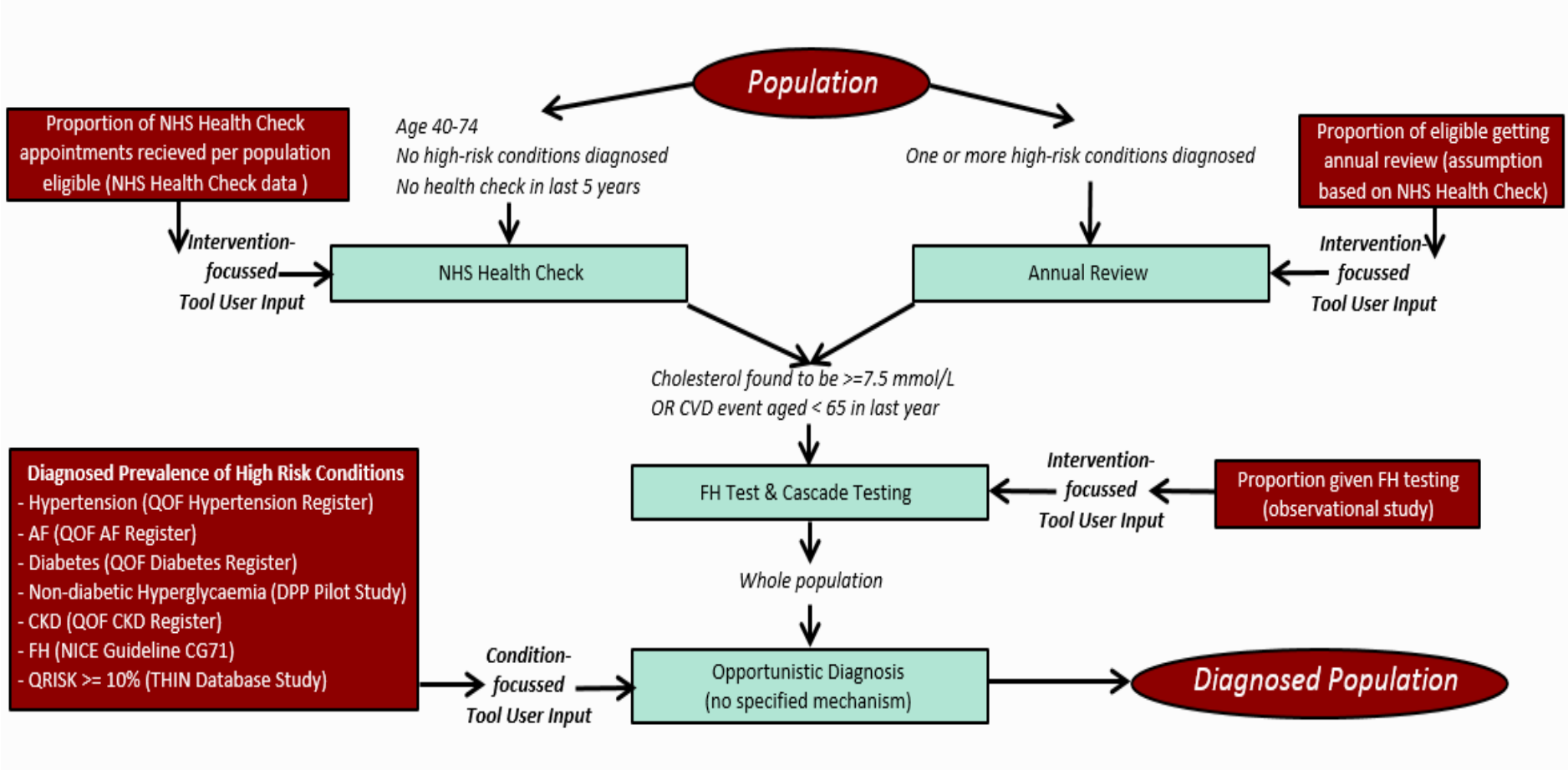
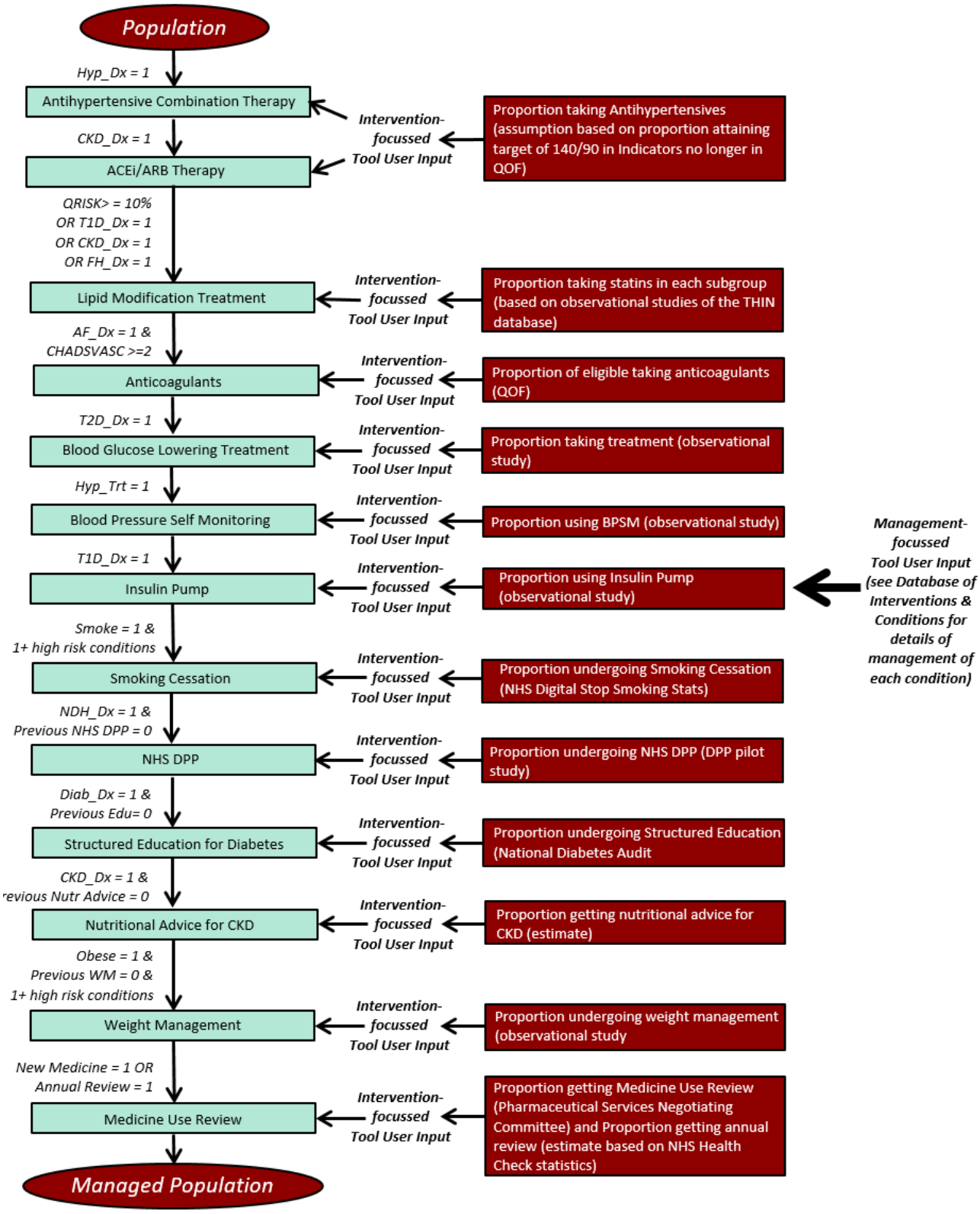


Figure 6: Schematic of the data sources and processes that comprise the management module of the model (expansion of box 9 from Figure 4). Note that management of each high risk condition is defined through optimisation of a subset of interventions, so if users choose to improve management of a condition, this will impact on the proportion of individuals using certain interventions



In the ROI tool, each model run simulates the population twice; firstly under the assumption of current care and secondly under the assumption of target care (inputted by the tool user), with the difference between these simulations then calculated to produce incremental results. In order to account for stochastic uncertainty in the model, 500 runs are performed and results from each are averaged.

This report describes in detail the model adaptations undertaken to convert the SPHR Diabetes Prevention model into the SPHR CVD Prevention model. The new model includes an expanded range of events that an individual is subject to every year. This includes development of AF; development and progression of CKD; risk of major bleeding due to anticoagulant use; detection of CVD high risk factors through NHS Health Check, annual review, cascade testing and opportunistic testing; and application of interventions to manage CVD risk in each high risk condition. In addition, major changes have been made to the way first CVD event is modelled and costs have been updated.

Model baseline population

The SPHR CVD Prevention Model uses baseline characteristics from the Health Survey for England. HSE 2014[11] was chosen for its CVD and diabetes focus, which meant it has collected most of the parameters required to carry out the model analyses and use QRISK2 and UKPDS risk equations[13, 59, 267]. Individuals aged under 16 were excluded from the model, resulting in a total of 8,077 individuals for simulation.

Some initial analyses of the baseline characteristics from HSE 2014 were carried out and are shown in Table 68. This indicates that the average individual in the HSE 2014 is overweight (BMI >25 kg/m2) and has a total cholesterol level above 5 mmol/L (the threshold that the NHS recommends healthy adults should be below[268]).

Table 68: Baseline characteristics from HSE 2014 (N=8077)[11]

Variable name (description)	Mean	Standard Deviation
Age (years)	50.02	18.63
BMI (kg/m^2)	27.52	5.48
Total Cholesterol (mmol/L)	5.194	1.104
HDL Cholesterol (mmol/L)	1.545	0.452
HbA1c (%)	5.615	0.785
Systolic Blood Pressure (mm Hg)	126.2	17.22
Diastolic Blood Pressure (mm Hg)	72.75	11.07
EQ-5D (quality of life measure)	0.877	0.189

The estimated proportion of the population in each of the high CVD risk groups was ascertained using the model (Table 69). The weighted percentage of the adult population and thereby the estimated number of individuals this should represent in

England, has been calculated using the national weights available within HSE 2014 and the most recent data from ONS on population size. Note that HSE 2014 does not contain information about diagnosis of AF, FH or CKD, so these were estimated following application of the risk equations described in later sections. Note that estimates of prevalence differ slightly from other published estimates due to the different methodology used to calculate them (in this case based on HSE 2014), and also may differ slightly from those given by any single run of the CVD prevention tool due to the stochastic nature of the model.

Table 69: Proportion of individuals from HSE 2014 in each high risk group

High Risk Group	No. Individuals (HSE 2014)	Weighted Prevalence in Adult Population (age 16+)	Estimated No. Individuals (England)
QRISK2 ≥10%	3,103	34%	15,149,093
Hypertension	2,622	30%	13,459,209
Familial hypercholesterolaemia	28	0.04%	191,833
Non-diabetic hyperglycaemia	1,186	14%	6,267,794
Diabetes	829	9.5%	4,273,364
of which type 1 diabetes	*50*	*0.6%*	*281,183*
of which type 2 diabetes	*779*	*8.9%*	*4,003,378*
Atrial Fibrillation	280	3.0%	1,354,311
Chronic Kidney Disease (stages 3-5)	577	6.0%	2,706,185
At least 1 high risk condition	4,334	49%	22,363,307
TOTAL POPULATION*	8,077	100%	45,340,600*
*Total population aged >15 in England according to ONS (2017)			

The data from HSE 2014 suggests that almost half the adults in England may suffer from at least 1 high risk condition and that about 34% may have a 10 year QRISK2 ≥ 10% and therefore should be eligible for statin treatment.

The tables below indicate how many individuals are estimated to suffer from 2 or more comorbid high risk conditions. This data indicates that in total there are likely to be over 13 million people in England with at least 2 high risk conditions of which almost 10 million have both hypertension and QRISK ≥ 10% and are thereby eligible for both statins and anti-hypertensives; about 3.5 million with both diabetes and QRISK ≥ 10%, and almost 3 million with both diabetes and hypertension. The vast majority of individuals with AF or with CKD also have QRISK ≥ 10%, and most also have hypertension.

Table 70: The estimated number of individuals in England with 2 high risk conditions

	QRISK2 ≥10%	Hyper-tension	AF	CKD	Pre-diabetes	Diabetes
QRISK2 ≥10%	15,149,093					
Hypertension	9,717,660	13,459,209				
AF	1,243,777	880,066	1,354,311			
CKD	2,491,019	1,705,808	318,318	2,706,185		
Pre-diabetes	2,928,954	2,626,741	238,025	632,693	6,267,794	
Diabetes	3,568,452	2,802,838	281,483	608,391	NA	4,273,364

Table 71: The estimated number of individuals with any 2 or more high risk conditions in HSE 2014

High Risk Groups	No. Individuals (HSE 2014)	Weighted Percentage of Adult Population	Estimated No. Individuals (England)
Any 2 conditions	2784	30%	13,733,332
Any 3 conditions	1485	16%	7,154,980
Any 4 conditions	264	2.7%	1,234,058
Any 5 conditions	26	0.27%	120,576

Local population weightings

The HSE 2014 contains survey weights, which enable the sample to represent the population of England by either increasing (weight > 1) or reducing (weight < 1) the importance of each individual[11]. This works well for a national tool, but needs adaptation to make a locally useful tool. Two local elements were included in the tool; firstly using a different set of tool inputs relating to current care detection/management of high risk conditions and usage of interventions for each local area (discussed in Section 5); and secondly using a different set of weights for each locality (CCG, LA and STP), reflecting local demographics. This second approach was similar to that used previously for the NHS DPP ROI Tool[10], but is also described briefly below.

The local weights were generated through a calibration weighting approach using iterative proportional fitting,[269] using local data about age, sex, ethnic group and deprivation quintile. To adjust these survey weights to local level, 2 datasets were used (

Table 72).

Table 72: Local population demographic data used

Population characteristic	Data source
Age/Sex profile	2011 Census[270]
Ethnic group	2011 Census[270]
Deprivation quintile	2015 English Indices of Deprivation[271]

The greatest possible number of population demographic characteristic breakdowns was used to give the best possible fit to CCG/LA populations. The 2011 census provided population data at lower super output area (LSOA) level with breakdowns for age and ethnicity (table LC2109EWLS), and at LA level by age groups, sex and ethnicity (table DC2101EW)[270]. Data was processed in order to obtain the size of each local population for each age group (16 groups: 16-17, 18-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84 and 85+), ethnic group (3 groups: White, Asian and other) and sex (males and females), cross referencing between the characteristics.

For the CCG areas, it was only possible to obtain population by sex and ethnicity (all categories) and 4 age categories (0-24, 25-49, 50-64, 65+). This loses a lot of the granularity around age groups (and prevents the exclusion of under 16s). Data was also available for LSOA by ethnicity and 16 age-groups, but not by sex, so the following approach was used. LSOA data by age and ethnic groups was combined into CCG areas. Sex breakdown was then calculated based on available data by CCG and sex at 16 age groups, assuming the same percentage female across all ethnicities.

The Index of Multiple Deprivation 2015 (IMD 2015) was obtained from the English Indices of Deprivation 2015[271], which contains the ranks and quintiles for the IMD at Lower-layer Super Output Area (LSOA) level. This was first processed to align deprivation quintiles with the HSE 2014 (1 = least deprived and 5 = most deprived)[11]. Modelling simply age/sex/ethnicity versus IMD assumes no relationship between ethnicity and deprivation. This was thought to be a weak assumption and to overcome it, data by age and ethnicity were obtained at LSOA level and combined with LSOA-level IMD to generate individual IMD target cross-tabs for each ethnic group. This allowed a CCG/LA-level variation in patterns of deprivation across ethnic groups.

Given that the estimated population of each locality has grown since 2011 to 2015, all data was normalised to reflect the current total population estimates. To do this, it was assumed that the population had grown in the same proportion across all demographics.

Inputs to the IPF algorithm were column (age/sex/ethnicity) and row (IMD/ethnicity) totals for local data (as described above) and HSE 2014 data[11]. There was a maximum of 96 possible columns (age, sex, ethnic characteristics: 16 x 2 x 3). However, where a given column contained no individuals in the HSE 2014 (1 column only: females,

ethnicity 'Asian', aged 80-85) this was combined with neighbouring columns (ages 85+) which contained at least 1 respondent, giving a total of 95 columns. There was a maximum of 15 possible rows (ethnicity/IMD: 3 x 5). There was at least 1 individual in each of these rows in the HSE 2014, meaning no rows had to be combined and a total of 15 were included. Equally, in some local areas, there were no individuals in a given cell (this was true particularly for the y variables as there were some local areas where only 2 or 3 quintiles of deprivation were represented). Where this was the case, these cells were set to a very small number rather than zero, as zeros cause problems with IPF.

Two dimensional IPF was used to estimate cross-tab data between the population demographics and the IMD for each local area. This produced a matrix for each local area showing the numbers of people with each of the demographic characteristics. HSE 2014 data was used to produce a similar matrix. Survey weights for each local area were then calculated as follows:

$$Wij = (1/nijs) \times nijp$$

Where wij is the weight applying to an individual in group ij (row i, column j), nijs is the number of people group ij in the sample (HSE 2014) and nijp is the number of people in group ij in the population (given CCG/LA).

Survey weights for all HSE 2014 individuals in a given CCG/LA add up to the total population of that CCG/LA, and can be used as a multiplier for per-person model outputs to develop CCG/LA-level outputs. STP weights were calculated by simply summing the weights for the constituent CCGs.

Modelling high risk groups

Hypertension

Baseline

Hypertension is already modelled adequately in the existing SPHR Diabetes Prevention Model. The HSE 2014 has information about individuals' systolic and diastolic blood pressure at baseline, in addition to information about which individuals are taking antihypertensives[11]. Individuals are therefore defined as having hypertension at baseline either if they exceed blood pressure thresholds (140/90 mm Hg OR 140/80 mm Hg with diabetes OR 130/80 mm Hg with diabetes plus CKD/retinopathy), or if they are known to be taking antihypertensives. Those taking antihypertensives but with very low systolic blood pressure at baseline (<110 mm Hg) are not included as it was thought that these people might be taking them for other reasons.

A proportion of those with hypertension are assumed to be diagnosed at baseline according to data about current levels of diagnosis, and a proportion of those diagnosed are assumed to be treated with antihypertensives according to data about current usage of treatment. Diagnosed and treated individuals are preferentially selected from those known to be treated with antihypertensives in the HSE 2014, in order to preserve as far as possible the correlations between diagnosis/treatment and other personal characteristics.

Over time

Systolic blood pressure changes over time are modelled through individualised trajectories that are estimated from statistical analysis of the Whitehall II cohort[265, 266]. These are dependent upon age, sex, ethnicity, smoking, BMI and family history of CVD, and correlated with changes in other metabolic trajectories (HbA1c and cholesterol). Diastolic blood pressure trajectories are not modelled as diastolic blood pressure is not included in any of the disease risk equations used in the model.

As the model progresses, individuals who did not have hypertension at baseline can become hypertensive and therefore eligible for diagnosis and treatment. It is assumed that once an individual is diagnosed as hypertensive, they remain flagged as hypertensive for their lifetime, even if their blood pressure is reduced through intervention. However, individuals with hypertension who are not diagnosed may lose the hypertension flag if their blood pressure is reduced through interventions aimed at other high risk groups, or naturally through their trajectories.

Atrial fibrillation

Baseline

Atrial Fibrillation is only modelled in a very basic way in the pre-existing SPHR Diabetes Prevention model. It is required as an input into the QRISK2 algorithm[13], but there is no information in HSE 2014 about who has AF, apart from a marker for ‘other heart condition’ (ie not coronary heart disease). In the pre-existing model individuals were therefore randomly selected as having AF from within this ‘other heart condition’ category. Given the importance of correlating AF with the other risk conditions in the model, a new way of determining who has AF at baseline based upon personal characteristics available in HSE 2014 and who develops it throughout the model simulation was required.

The Framingham AF risk equation was used to model the risk of AF in the baseline population[272]. This is based on a US population and does include 2 variables that are not available from HSE 2014 (pulse rate interval and significant murmur); however, no other risk equations were identified for AF. For the 2 variables not available in HSE 2014, it was assumed that the population average value applied to all individuals, and so the intercept was adjusted to take account of this, allowing them to be removed from

the risk equation. Equally, the age variable was adjusted to take account of average values being used in the Age * significant murmur variable. The coefficients are presented in Table 73.

Table 73: Coefficients from the Framingham AF risk equation[272]

Variables	Coefficients	Population average	Used in final risk equation
Intercept (unadjusted)	-10.785528582	N/A	No
Intercept (adjusted for pulse rate interval and significant murmur)	-9.520904351	N/A	Yes
Age (years - unadjusted)	0.15052	60.9	No
Age (adjusted for Age * murmur)	0.14933	60.9	Yes
Age squared	-0.00038	3807	Yes
Male sex	1.99406	0.45	Yes
BMI (kg/m^2)	0.0193	26.3	Yes
Systolic blood pressure (mm Hg)	0.00615	136.2	Yes
Hypertension Treatment	0.4241	0.24	Yes
Pulse Rate Interval	0.07065	16.4	No
Significant Murmur	3.79586	0.028	No
Prevalent heart failure	9.42833	0.0087	Yes
Male sex * age squared	-0.00028	1655	Yes
Age * significant murmur	-0.04238	1.9	No
Age * prevalent heart failure	-0.12307	0.61	Yes
Baseline 10 year risk	0.96337	N/A	Yes

The predicted probability of AF is calculated using the following equation:

$$P = 1 - (surv^{\exp(xbeta)})$$

Where surv = baseline risk and xbeta = Sum (of regression coefficient*value of risk factor)

This risk equation is designed to estimate the 10 year risk of AF in a population without AF. To enable estimation of baseline levels of AF in the population, the risk equation is used to give all individuals a risk score. The risk scores are then adjusted using a multiplier to ensure that overall AF risk corresponds to the known prevalence of AF in the population from local data.

A proportion of those with AF are assumed to be diagnosed at baseline according to data about current levels of diagnosis, and a proportion of those diagnosed are assumed to be treated with anticoagulants according to data about current usage of treatment. Diagnosed individuals are preferentially selected from those known to be diagnosed with ‘other heart condition’ in the HSE 2014, in order to preserve as far as possible the correlations between diagnosis and other personal characteristics.

For treatment with anticoagulants, individuals first have their eligibility assessed using the CHA2DS2-VASc score[195]. The score is calculated by simply adding up the points relating to each of the included variables. Some conditions (eg peripheral arterial disease) are not modelled and therefore the modelled CHA2DS2-VASc score does not include these. Individuals are assessed as eligible if they had a CHA2DS2-VASc score of 2 or more. Treated individuals are selected randomly at baseline from amongst those with diagnosed AF and a CHA2DS2-VASc score of 2 or more, as there is no other information in HSE 2014 on which to base the selection.

Table 74: Modelling the CHA2DS2-VASc score

Variable	Points	Model inclusion
Age	Age < 65 = 0; Age 65-74 = 1; Age 75+ = 2	Yes
Sex	Female = 1; Male = 0	Yes
CHF history	Yes = 1	Yes
Hypertension history	Yes = 1	Yes
Stroke/TIA/Thromboembolism history	Yes = 2	Stroke & TIA but not Thromboembolism
Vascular Disease history	Yes = 1	MI & Angina but not PAD
Diabetes history	Yes = 1	Yes

Over time

Development of new AF cases over time is modelled using the adapted Framingham risk equation presented in Table 73, by converting 10 year risk into 1 year risk, making the assumption that risk is constant over time. AF risk scores are updated in every year of the model to reflect changes in age, modifiable risk factors (trajectories of systolic blood pressure and BMI), development of CHF and hypertension treatment. This means that as the model progresses, individuals who did not have AF at baseline can develop it and therefore become eligible for diagnosis and treatment with anticoagulants. It is assumed that once an individual develops AF they have it for their lifetime. AF is not assumed to progress over time, nor are different types of AF (eg valvular versus non-valvular) modelled.

Chronic Kidney Disease

Baseline

In the pre-existing SPHR Diabetes Prevention model, CKD is modelled through the UKPDS risk equations as a consequence of diabetes[59], but is not modelled in the general population. The HSE 2014 does not include information specifically about CKD,

but does have a marker for renal disease in general. In the pre-existing SPHR Diabetes Prevention model, individuals were therefore randomly selected as having end stage renal disease from within this 'renal disease' category. Given the importance of correlating CKD with the other risk conditions in the model, a new way of determining who has CKD at baseline based upon personal characteristics available in HSE 2014 was required.

No risk equation was found for CKD, however; an observational study by Aitkin et al., (2014)[273] looked at the changing prevalence of CKD over time in England using blood samples from the HSE 2003 and HSE 2009/10. They assayed serum creatinine in each individual and from this estimated glomerular filtration rate (eGFR), using both the MDRD (Modified Diet in Renal Disease) or CKDEPI (CKD Epidemiology Collaboration) equations. They estimated the prevalence of CKD stages 3 to 5 adjusting for different sociodemographic and clinical factors including age, sex, ethnicity, smoking status, BMI, cholesterol, diabetes and hypertension. The presented odds ratios using the CKDEPI equation (which has better risk prediction) were used to estimate coefficients for a risk equation. The intercept was calculated as the prevalence of CKD stages 3 to 5 in people with the reference characteristics. Variables relating to tenure and education were also included in the Aitkin analysis, but given that these were not present in the model, they were not included in the risk equation.

Table 75: Estimated coefficients for a CKD risk equation based on odds ratios from Aitkin et al, (2014)[273]

Variable	Odds ratio	Coefficient	Reference
Intercept	0.001	-6.907755279	Prevalence of CKD stage 3-5 in people aged 16-34
Age 35-54	13.5	2.602689685	Reference age < 35
Age 55-64	52	3.951243719	Reference age < 35
Age65-74	151	5.017279837	Reference age < 35
Age75+	693	6.541029999	Reference age < 35
Female	1.28	0.246860078	Reference male
South Asian	0.85	-0.162518929	Reference white
Black	0.53	-0.634878272	Reference white
Other	1.13	0.122217633	Reference white
Ex-smoker	1.07	0.067658648	Reference non-smoker
Current smoker	0.79	-0.235722334	Reference non-smoker
Overweight (BMI 25-29.99)	1.12	0.113328685	Reference BMI <25 kg/m^2
Obese (BMI >=30)	1.25	0.223143551	Reference BMI <25 kg/m^2
HDL cholesterol	0.4	-0.916290732	Reference 1.5 mmol/L
Total cholesterol	0.94	-0.061875404	Reference 5.4 mmol/L

Diabetes	1.46	0.378436436	Reference no diabetes
Hypertension	1.33	0.285178942	Reference no hypertension

A CKD risk score for each individual in the model is calculated using the following equation:

$$P = \frac{1}{1 + \exp(-xbeta)}$$

Where xbeta = Sum (of regression coefficient*value of risk factor)

The risk scores are then adjusted using a multiplier to ensure that overall CKD risk corresponds to the known prevalence of CKD in the population. It is important to note that whilst CKD prevalence in the model is defined as stages 3 to 5, it is also necessary to model individuals with stages 1 to 2 at baseline as these people will later progress. The prevalence of CKD stages 1 to 2 (estimated at 6.3%) was taken from a US study of NHANES (National Health and Nutrition Examination Survey) data[274], as no UK data source for this was found. This means that the CKD risk score is adjusted to take into account the prevalence of CKD stages 1 to 5, by combining the NHANES prevalence for stages 1 to 2 with the local estimates of prevalence for stages 3 to 5.

In addition to determining which individuals have CKD at baseline, it is also necessary to partition them by stage (eGFR) and albumin creatinine ratio (ACR) in order to accurately model CKD risk and progression to end stage renal failure. The US NHANES study provided information about the prevalence and hence proportions in CKD stage 1 to 2, CKD stage 3, 4 and 5 (Table 76)[274]. The study did not separate stage 3 into stage 3a and 3b, so it was assumed that there were equal proportions of CKD cases in these 2 stages. Stages were randomly assigned amongst those with CKD.

Table 76: Prevalence of CKD stages 1 to 5 from NHANES data[274]

CKD stage	Estimated Prevalence (NHANES)	Proportion of all CKD
CKD Stage 1 to 2	0.063	57%
CKD Stage 3	0.043	39%
CKD Stage 4	0.002	1.8%
CKD Stage 5	0.002	1.8%

For ACR category, data from another US study (National Kidney Foundation's Kidney Early Evaluation Programme (KEEP)) about the proportion of people in each ACR category by CKD stage was used (

Table 77)[275]. Note that this data relates to patients with diabetes, but is used here to represent all patients with CKD given the lack of other data. ACR category was assigned randomly in the relevant proportions to people in each CKD stage.

Table 77: Proportion of people in each ACR category by eGFR (KEEP study)[275]. The remainder in each row are in category ACR < 30 (normal ACR).

CKD Stage	ACR 30 to 299	ACR > 300
No CKD	0.148	0.012
CKD stage 1 to 2	0.1245	0.0125
CKD stage 3a	0.147	0.019
CKD stage 3b	0.202	0.036
CKD stage 4	0.281	0.081
CKD stage 5	0.354	0.287

A proportion of those with CKD are assumed to be diagnosed at baseline according to data about current levels of diagnosis, and a proportion of those diagnosed are assumed to be treated with ACE inhibitors according to data about current usage of treatment. It is assumed that all individuals with end stage renal failure (stage 5) will be diagnosed. For CKD stages 3 to 4, diagnosed individuals are preferentially selected from those with 'kidney disease' in the HSE 2014, in order to preserve as far as possible the correlations between diagnosis and other personal characteristics. Whilst diagnosis at CKD stages 1 to 2 is possible, this is not explicitly modelled given the lack of information about proportions diagnosed in this subgroup. Treated individuals are preferentially selected from those already determined to be treated with antihypertensives (those with hypertension and CKD stage 3 to 5), with additional treated individuals selected randomly from amongst those with diagnosed CKD stage 3 to 5. Treatment at CKD stages 1 to 2 is not modelled.

Over time

CKD is assumed to progress over time, and in addition new cases of CKD arise from the general population. This means that as the model progresses, individuals who did not have CKD at baseline can develop it and therefore become eligible for diagnosis and treatment with ACE inhibitors. It is assumed that once an individual develops CKD they have it for their lifetime.

The model review identified several useful sources of transition probabilities to model both transitions for CKD stages and transitions for ACR. Transitions between CKD stages were taken from a UK Health Technology Assessment for early referral to specialist strategies by Black et al. (2010)[248]. In this study, transition probabilities are dependent upon ACR and current stage only. In the absence of data about the annual development of CKD stages 1 to 2, it was assumed that transitions to CKD stages 1 to 2 from no CKD will be the same as transitions from CKD stages 1 to 2 to CKD stage 3a.

Table 78: CKD state transition probabilities from Black, 2010[248]

	CKD 1 & 2	CKD 3a	CKD 3b	CKD 4	CKD 5
Reduced GFR alone					
CKD 1 & 2	0	0	0	0	0
CKD 3a	0	0.927	0.073	0	0
CKD 3b	0	0	0.952	0.048	0
CKD 4	0	0	0	0.966	0.034
Reduced GFR with ACR 30-299 mg/g					
CKD 1 & 2	0.930	0.070	0	0	0
CKD 3a	0	0.895	0.105	0	0
CKD 3b	0	0	0.931	0.069	0
CKD 4	0	0	0	0.950	0.050
Reduced GFR with ACR ≥ 300 mg/g					
CKD 1 & 2	0.880	0.120	0	0	0
CKD 3a	0	0.833	0.167	0	0
CKD 3b	0	0	0.882	0.118	0
CKD 4	0	0	0	0.911	0.089

ACR = Albumin/Creatinine Ratio; GFR = Glomerular Filtration Rate; CKD = Chronic Kidney Disease

ACR transitions are available from several data sources, of which those from a US screening model (Hoerger et al., 2010[252]) were chosen as transition probabilities are given dependent upon hypertension, diabetes, age and gender (Table 79). It is assumed that if an individual has both diabetes and hypertension, the diabetes transitions will be used as these are faster.

Table 79: Transition probabilities for ACR implemented in the model from Hoerger, 2010[252]

State Transition	Transition Probability
ACR < 30 to ACR 30-299: no comorbid conditions intercept	0.000956
ACR < 30 to ACR 30-299: no comorbid conditions male annual incidence increase	0.000073
ACR < 30 to ACR 30-299: no comorbid conditions female annual incidence increase	0.000036
ACR 30-299 to ACR > 300: no comorbid conditions, male	0.003392
ACR 30-299 to ACR > 300: no comorbid conditions, female	0.0035
ACR < 30 to ACR 30-299: hypertension	0.00203
ACR < 30 to ACR 30-299: hypertension male annual incidence increase	0.000138
ACR < 30 to ACR 30-299: hypertension female annual incidence increase	0.000075
ACR 30-299 to ACR > 300: hypertension	0.0147
ACR < 30 to ACR 30-299: diabetes	0.02
ACR 30-299 to ACR > 300: diabetes	0.0284

Evidence also suggests that ACR transitions can be slowed by the use of ACE inhibitors[249]. The probability of ACR transitions is assumed to be lower in people undergoing treatment with either ACE inhibitors or combination antihypertensive therapy (which includes an ACE inhibitor). This relative risk is applied to all treated individuals, no matter whether they have diabetes, hypertension or no comorbid conditions.

Table 80: Treatment effect of ACE inhibitors on CKD progression (Adarkwah, 2011[249])

State Transition	Relative Risk of Transition with Treatment
RR ACR < 30 to ACR 30-299	0.6
RR ACR 30-299 to ACR > 300	0.45

Type 2 diabetes

Baseline

Type 2 diabetes is already modelled adequately in the existing SPHR Diabetes Prevention Model. The HSE 2014 has information about individuals' HbA1c at baseline and also about which individuals are already diagnosed with type 2 diabetes. Individuals are therefore defined as having type 2 diabetes at baseline either if their HbA1c is above or equal to 6.5%, or if they are already diagnosed with the condition.

A proportion of those with type 2 diabetes are assumed to be diagnosed at baseline according to data about current levels of diagnosis, and a proportion of those diagnosed are assumed to be treated with glucose lowering medication according to data about current usage of treatment. Diagnosed individuals are preferentially selected from those known to be diagnosed with type 2 diabetes in the HSE 2014, whilst treated individuals are preferentially selected from those known to be treated with glucose lowering medication in the HSE 2014 in order to preserve as far as possible the correlations between diagnosis/treatment and other personal characteristics.

Over time

Development of type 2 diabetes over time is modelled through individualised trajectories of glycaemia (which includes HbA1c) that are estimated from statistical analysis of the Whitehall II cohort[265, 266]. These are dependent upon age, sex, ethnicity, BMI and family history of diabetes, and correlated with changes in other metabolic trajectories (systolic blood pressure and cholesterol).

As the model progresses, individuals who did not have type 2 diabetes at baseline can develop it and therefore become eligible for diagnosis and treatment. To be diagnosed with type 2 diabetes, individuals must have 2 separate HbA1c tests of which both must be ≥ 6.5%. This is simulated in the model by calculating a second HbA1c score, differing from the initial score by a random error term. Individuals are flagged as having type 2 diabetes if both HbA1c values rise to 6.5% or above. Once they develop

diabetes, their individualised trajectory of HbA1c is no longer estimated through Whitehall II, instead using the UKPDS outcomes model[59], which is taken from a newly diagnosed diabetic population and is dependent upon HbA1c at diagnosis and time since diagnosis, but which is not correlated with other metabolic risk factors. The UKPDS trial found that individuals have an initial drop in HbA1c due to treatment and lifestyle changes. This initial drop is only implemented in the model if an individual is flagged to start treatment.

It is assumed that once an individual is diagnosed with type 2 diabetes, they have type 2 diabetes for their lifetime, even if their HbA1c is reduced through intervention. However, individuals with type 2 diabetes who are not diagnosed may lose the type 2 diabetes flag if 1 or both of their HbA1c values is reduced through interventions aimed at other high risk groups, or naturally through changes in their trajectories.

Type 1 diabetes

Baseline
Type 1 diabetes is not modelled in the pre-existing SPHR Diabetes Prevention model. However, baseline data about which individuals have type 1 diabetes is available in the HSE 2014. Individuals are therefore defined as having type 1 diabetes at baseline if they are already diagnosed with the condition. It is assumed that all individuals with type 1 diabetes will be diagnosed (ie 100% are detected at baseline) and that all individuals will be undergoing insulin treatment.

Over time
It is assumed that no new cases of type 1 diabetes develop over time in the modelled population. However, type 1 diabetes progression is modelled. The HbA1c trajectory in individuals with type 1 diabetes is assumed to increase linearly each year by 0.045%. This value has been used previously to model progression in the Sheffield type 1 diabetes model[173], and is taken from the Diabetes Control and Complication Trial[276].

Non-diabetic hyperglycaemia

Baseline
Non-diabetic hyperglycaemia is already modelled adequately in the existing SPHR Diabetes Prevention Model. The HSE 2014 has information about individuals' HbA1c at baseline, with non-diabetic hyperglycaemia being defined as having HbA1c from 6% up to 6.5%.

A proportion of those with non-diabetic hyperglycaemia are assumed to be diagnosed at baseline according to data about current levels of diagnosis. Diagnosed individuals are selected randomly at baseline from amongst those with non-diabetic hyperglycaemia as there is no other information in HSE 2014 on which to base the selection. It is assumed

that no individuals have been treated with relevant treatments (eg the NHS DPP) prior to the model starting.

Over time

Development and progression of non-diabetic hyperglycaemia over time is modelled through individualised trajectories of glycaemia (which includes HbA1c) that are estimated from statistical analysis of the Whitehall II cohort[265, 266]. These are dependent upon age, sex, ethnicity, BMI and family history of diabetes, and correlated with changes in other metabolic trajectories (systolic blood pressure and cholesterol).
As the model progresses, individuals who did not have non-diabetic hyperglycaemia at baseline can fall into this category and therefore eligible for diagnosis and treatment. Unlike the other high risk conditions in the model, non-diabetic hyperglycaemia is a transient state that individuals may pass into and out again when they develop diabetes. It is assumed that once an individual is diagnosed with non-diabetic hyperglycaemia, they remain flagged with non-diabetic hyperglycaemia up until development of diabetes or death; even if their HbA1c is reduced below 6% through intervention. However, individuals with non-diabetic hyperglycaemia who are not diagnosed may lose the non-diabetic hyperglycaemia flag if their HbA1c value is reduced through interventions aimed at other high risk groups, or naturally through changes in their trajectories.

Familial Hypercholesterolaemia

Baseline

FH is not modelled in the pre-existing SPHR Diabetes Prevention model and no information about FH is included in the HSE 2014. Definitive diagnosis of FH is through genetic testing; however in the absence of this, FH is defined clinically through the Simon Broome criteria[240]. This includes having total cholesterol above 7.5 mmol/l or LDL cholesterol above 4.9 mmol/l plus tendon xanthomas in the patient or a first or second degree relative. People are considered at high risk if they have high cholesterol themselves plus a family history of either early CVD or raised cholesterol. Of these criteria, HSE 2014 only contains information about cholesterol. It was decided that in line with data from the model developed for the NICE CG71 2017 update[19], individuals assigned to have FH would be randomly selected from within the top 1.43% of total cholesterol values for each age band, of which 28% would be assumed to have FH. Cholesterol cut-off points for each age band are shown in Table 81.

Table 81: Cut-off points representing the top 1.43% values for total cholesterol in each population age band

Age band	Cholesterol cut-off
Age < 40	7.06 mmol/L
Age 40-74	7.88 mmol/L
Age 75+	7.29 mmol/L

A proportion of those with FH are assumed to be diagnosed at baseline according to data about current levels of diagnosis, and a proportion of those diagnosed are assumed to be treated with statins and Ezetimibe according to data about current usage of lipid modification treatment. Note that Ezetimibe treatment is modelled only for cost purposes in people also taking statins. Diagnosed and treated individuals are selected randomly at baseline from amongst those with FH as there is no other information in HSE 2014 on which to base the selection.

Over time

As FH is a genetic condition, no new cases of FH are assumed to develop over time, nor is the condition assumed to progress or undergo remission, although changes in cholesterol trajectories over time are modelled in the same way as for the general population through statistical analysis of the Whitehall II cohort[265, 266].

QRISK ≥10%

Baseline

Ten year QRISK ≥ 10% is already modelled adequately in the existing SPHR Diabetes Prevention Model. The QRISK2 risk equation requires information about age; sex; ethnicity; deprivation (Townsend score); smoking status; diabetes status; family history of CVD; atrial fibrillation; taking antihypertensives; rheumatoid arthritis; cholesterol/HDL ratio; systolic blood pressure and BMI[13]. All of these characteristics are either available from the HSE 2014 or have been imputed. Townsend score is not available in HSE 2014, but deprivation quintile is measured using the indices of multiple deprivation (IMD). A Townsend score is randomly estimated within each IMD quintile for each individual to enable a QRISK2 score to be calculated. AF is not available in HSE 2014 but is calculated as described above. The other QRISK2 input that is not available from HSE 2014 is family history of CVD before age 60. It is known that people with a family history of CVD before age 60 have a higher prevalence of FH (1.3% as opposed to 0.4% for the general population)[277]; so this information was used to estimate different rates of family history in the population with FH (36%) and without FH (11%); based on the general population average from the QRISK2 derivation and validation paper[13]. All this information is used to generate a 10 year QRISK2 score for each individual aged over 24 (note that QRISK2 is not valid for individuals younger than 24). Individuals are therefore defined as having QRISK ≥ 10% at baseline either if their QRISK2 score is greater than 10% or if they are known to be taking statins already (but are not diagnosed with type 1 diabetes or with CKD, for which statins are recommended even if individuals do not have a high QRISK2 score).

A proportion of those with QRISK ≥ 10% are assumed to be diagnosed at baseline according to data about current levels of diagnosis, and a proportion of those diagnosed are assumed to be treated with statins according to data about current usage of treatment. Diagnosed and treated individuals are preferentially selected from those

known to be treated with statins in the HSE 2014, in order to preserve as far as possible the correlations between diagnosis/treatment and other personal characteristics.

Over time
QRISK2 scores are updated in every year of the model to reflect changes in age, modifiable risk factors (trajectories of systolic blood pressure, cholesterol and BMI, plus smoking status), development of high risk conditions (diabetes and AF) and hypertension treatment. This means that as the model progresses, individuals who did not have QRISK ≥ 10% at baseline can develop it and therefore become eligible for diagnosis and treatment with statins. It is assumed that once an individual is diagnosed with QRISK ≥ 10%, they remain flagged as having QRISK ≥ 10% for their lifetime, even if their cardiovascular risk is reduced through intervention. However, individuals with QRISK ≥ 10% who are not diagnosed may lose the QRISK ≥ 10% flag if their QRISK2 score is reduced through interventions aimed at other high risk groups, or naturally through their trajectories.

There was some discussion within the steering group about using an alternative score to partition CVD risk: QRISK Lifetime[278]. Ten year QRISK has a strong age component, which means that young people at high lifetime risk but low ten year risk may not receive adequate intervention. However, currently there exists no defined cut-off for lifetime risk over which people would be considered high risk, nor a set of recommended interventions for people with high lifetime risk, and QRISK Lifetime is not routinely used in primary care practice, meaning that it was more appropriate to use QRISK ≥ 10%.

Cardiovascular events

First cardiovascular event

QRISK2 and QStroke
The SPHR Diabetes Prevention Model uses the QRISK2 algorithms to model both 10 year CVD risk (to assess who is eligible for statin treatment) and CVD event probabilities (in the form of annual risk rather than 10 year risk) for first CVD events in each individual[13]. Events include myocardial infarction (MI), angina, stroke and transient ischaemic attack (TIA), but not congestive heart failure (modelled separately) or peripheral arterial disease (not modelled). In those suffering a first event, the type of event that occurs is then assigned using age and sex dependent probabilities from a statins HTA[279]. The advantages of using the QRISK2 equations is that they are valid for a general UK population and they calculate CVD risk based upon a range of personal characteristics that are available from HSE 2014, including modifiable risk factors such as BMI, systolic blood pressure and cholesterol, and high risk conditions such as diabetes and atrial fibrillation. This means that CVD risk can be estimated not only in

individuals with single high risk conditions undergoing 1 intervention (as in the majority of primary studies), but also in individuals with multiple comorbid high risk conditions, undergoing combinations of interventions. This enables real world situations for which little or no data exists to be modelled.

Several modifications to this method were made for the SPHR CVD Prevention Model in order to more accurately model the range of conditions and interventions included in the tool. Firstly, the most recent version of the QRISK2 code was implemented (2015). Not only is this more recent than the version used in the original SPHR Diabetes Prevention Model, but it also separates type 1 diabetes and type 2 diabetes into different conditions, which was useful for this analysis. One problem with using the more recent version of the code was that only 10 year risk is published and not 1 year risk (as is required to estimate annual probability of events). Given the strong age dependence of CVD, it is unlikely that risk is linear over the 10 years; 1 year risk was therefore estimated assuming the same ratio between 1 and 10 year risk as seen in the 2011 version of the code implemented in previous versions of the SPHR Diabetes Prevention model (
Table **82**).

Table 82: Baseline risk of first cardiovascular event from QRISK2. Estimated risk in italics

Baseline Risk	QRISK2 2011	QRISK2 2015
One Year Risk Females	0.998272598	*0.99921157*
One Year Risk Males	0.996994317	*0.998320007*
Ten Year Risk Females	0.977537572	0.989747584
Ten Year Risk Males	0.96206063	0.978794217

The second modification involved implementing an additional QResearch algorithm called QStroke[197], to specifically estimate the risk of stroke and TIA. This was necessary because some of the new conditions in the model increase the risk of only cardiac events (such as FH), or only stroke events (such as AF). The algorithm is very similar to the QRISK2 algorithm, with 2 additional variables including congestive heart failure and valvular heart disease, both of which are already modelled to sufficient extent to be used as QStroke inputs (although note that valvular heart disease is assigned randomly at baseline according to known population prevalence and therefore is not correlated with other personal characteristics).

For both risk scores, the equation for the probability of an event in the next period is calculated as:

$$p(Y = 1) = 1 - S(1)^{\theta}$$

$$\theta = \sum \beta X$$

Where S is the survival function at 1 year and θ is the sum product of the coefficients multiplied by the individual's characteristics.

The method for implementing the 2 risk equations is as follows. Where 10 year risk is required (to flag individuals at high risk following screening), only QRISK2 is used. However, for calculation of CVD first event probabilities, both risk equations are run to produce individualised 1 year risk scores for both QRISK2 and QStroke. Individuals with pre-existing CVD and those aged under 25, are not given a QRISK2/QStroke score, as the algorithms are not valid in these populations. A hypothetical score for probability of cardiac disease (called pqcardiac) is then calculated as the difference between the 2 risk scores as follows:

$$pqcardiac = 1 - \exp\big(\log(1 - pqrisk) - long(1 - pqstroke)\big)$$

Whilst on average QStroke scores are about half the magnitude of QRISK2 scores, a small proportion of individuals (calculated in model validation tests as about 1.5%) receive a higher QStroke score than QRISK2 score. In this case, pqcardiac is assumed to be very small (assigned a value of 0.0001).

Modifying QRISK and QStroke

Following calculation of pqcardiac and pqstroke, a range of modifications are applied to the calculated risks (pqstroke and pqcardiac) to enable them to take account of additional high risk conditions and interventions. Similar approaches have been used in previous models for FH and CKD identified through the model review[248].

QRISK2 is not recommended by NICE for estimating CVD risk in individuals with CKD, type 1 diabetes, FH, or those taking statins. Furthermore, an additional range of adjustments are required in order to model increased CVD risk with HbA1c, and reduced CVD risk with treatments such as anticoagulants and antihypertensives. Coefficients corresponding to these modifications are shown in Table 83. Coefficients were calculated by taking the natural log of relative risks/hazard ratios.

Table 83: Variables and coefficients corresponding to QRISK2 and QStroke modifications

Variable	Hazard ratio/ Relative risk for CVD	Coefficient	Source
Non-diabetic per HbA1c unit above 5.2%	1.25	0.22314355	Khaw et al., 2001 (EPIC Cohort)[280]
Diabetic men per HbA1c	1.11	0.10093057	UKPDS

unit above 6.5%			outcomes model[59]
Diabetic women per HbA1c unit above 6.5%	1.09	0.08632524	UKPDS outcomes model[59]
FH men aged < 65	4.0028 (cardiac only)	1.38699412	Simon Broome register[240]
FH men aged 65+	1.6199 (cardiac only)	0.48236442	Simon Broome register[240]
FH women aged < 65	5.133 (cardiac only)	1.63569028	Simon Broome register[240]
FH women aged 65+	2.2827 (cardiac only)	0.82535895	Simon Broome register[240]
CKD stages 1 and 2 (ACR 30-299)	2.19	0.78390154	Black et al., 2010[248]
CKD stages 1 and 2 (ACR ≥ 300)	3.4	1.22377543	Black et al., 2010[248]
CKD stages 3 and 4 (ACR <30)	2.36	0.85866162	Black et al., 2010[248]
CKD stages 3 and 4 (ACR 30-299)	3.01	1.10194008	Black et al., 2010[248]
CKD stages 3 and 4 (ACR ≥ 300)	4.35	1.47017584	Black et al., 2010[248]
AF uncoagulated	4.8 (stroke only)	1.60943791	Framingham study[281]
Anticoagulation	0.632 (stroke only)	-0.4591612	Guo et al., 2017[55]
Statin treatment additional CVD effect per 1mmol/L Chol reduction	0.88	-0.1325645	Collins et al., 2016[39]
Antihypertensive treatment additional CVD effect per 10 mm Hg SBP reduction	0.89	-0.1119	Ettehad et al., 2016[52]
Cardiac event modifier	0.6211 (cardiac only)	-0.4762515	Imputed using HES data[282]
Stroke event modifier	0.4257 (stroke only)	-0.8541272	Imputed using HES data[282]

Type 1 diabetes: QRISK2 is not recommended by NICE for estimating CVD risk in individuals with type 1 diabetes as they are considered to be at such high risk that statins are recommended for all adults aged over 40, or those who are younger and who have been diagnosed for 10 years or more[21]. Alternative models for CVD risk in

people with type 1 diabetes do exist, which emphasize increasing risk in people over time since diagnosis (eg in the Sheffield type 1 diabetes model). However, for consistency, we wished to use the QRISK2 framework for modelling CVD event rate in all conditions and interventions. Given the small proportion of people with type 1 diabetes in the model, it was therefore decided that the type 1 diabetes coefficient already in QRISK2 would be sufficient.

HbA1c: The original SPHR Diabetes Prevention Model already calculates modifications to QRISK2 as a function of HbA1c in people with and without diabetes. These are necessary to enable the benefit of interventions that reduce HbA1c to be reflected in CVD risk reductions. CVD risk is assumed to increase with HbA1c for test results greater than 6.5 to reflect observations from the UKPDS that HbA1c increases the risk of MI and Stroke[59]. In addition, a study from the EPIC Cohort has found that in people without diabetes, a unit increase in HbA1c increases the risk of coronary heart disease by a hazard ratio of 1.25, after adjustment for other risk factors[280]. This risk ratio is applied to linearly increase risk above the mean HBA1c observed in the baseline population without type 2 diabetes, whilst a linear risk reduction is applied at HbA1c levels below the HSE mean. These coefficients are assumed to impact upon both pqrisk and pqcardiac equally.

FH: The cost-effectiveness modelling included in the recent update to NICE Guideline CG7119, incorporates relative risks of coronary heart disease in men and women with FH (compared to those without FH), which are applied on top of QRISK2 calculations to determine absolute CVD risk. These relative risks are taken from the Simon Broome register[240]. It is important to note (as did the NICE study) that this could overestimate absolute cardiac risk as the comparator group are likely to have had much lower LDL cholesterol than the FH group, and cholesterol ratio is already included as a coefficient in the QRISK2 equations. There is no evidence to suggest that FH increases risk of stroke, so these coefficients are applied to pqcardiac only.

CKD: The QRISK2 algorithm already includes a coefficient for CKD stages 4 to 5. However, it was important to model CKD risk in a wider range of CKD stages and ACR levels in order to fully incorporate the risk of CKD and the benefit of treatments. A UK Health Technology Assessment for early referral to specialist strategies by Black et al. (2010)[248] included incorporation of a QRISK2 based CVD risk estimation, with modification by CKD stage and ACR. These relative risks were used to produce coefficients that replace the pre-existing CKD coefficient in QRISK2. The coefficients are assumed to impact upon both pqrisk and pqcardiac equally.

AF and anticoagulants: The QStroke algorithm already includes a coefficient for AF; however this does not distinguish between those treated with anticoagulants or untreated, a distinction which is necessary to enable the differences in stroke risk due to anticoagulant treatment to be modelled. A 2 step process was therefore implemented to

modify QStroke. Firstly, the AF coefficient is modified to increase stroke risk from the hazard ratios reported in the QStroke publication197 (1.6 in men, 3.08 in women), to 4.8, as reported in a widely cited Framingham Study[281]. Secondly, a treatment effect based on the effectiveness evidence reviews is applied in individuals who are treated with anticoagulants. The treatment effect is calculated as a weighted average of each of the types of anticoagulant prescribed in England[283] and applied equally to all individuals assumed to be treated with anticoagulants.

Statin treatment: QRISK2 scores are used to determine which people are eligible for statins and therefore are not valid in people taking statins already. It is thought that the benefit of statins in reducing CVD is not solely produced through reducing LDL cholesterol, and therefore it is not sufficient to implement the cholesterol reductions and let these act through QRISK on their own. It was calculated that the QRISK cholesterol ratio coefficients imply a hazard ratio of only 0.9 per 1mmol/L reduction in LDL cholesterol on average, whereas the actual relative risk per 1 mmol/L LDL reduction found in the effectiveness evidence reviews is 0.79[39]. An additional coefficient has therefore been added to the model in treated individuals to enable this increased risk reduction to be incorporated. The coefficients are assumed to impact upon both pqrisk and pqcardiac equally. A similar treatment effect has been added to QRISK (both 10 year and lifetime models) to calculate the benefits of treatment with statins in the JBS3 tool[284].

Antihypertensive treatment/ACE inhibitor treatment: QRISK and QStroke incorporate both systolic blood pressure and use of antihypertensives as variables in the risk equations. However, use of antihypertensives increases risk in these models, which makes sense when comparing 2 people who have the same blood pressure, as it would be expected that having artificially lowered blood pressure would confer higher risk than natural level of blood pressure; but counteracts the known benefits of these drugs in reducing CVD. Two changes have therefore been made to the models. Firstly, the models have been adjusted to apply the additional risk to all individuals with hypertension, not just those who are using antihypertensives. Secondly, the benefits of intervention have been modelled in a similar way to statin treatment above. Unlike with statins, it is thought that most of the benefit of antihypertensives does act through blood pressure reduction. However, it is not sufficient to implement the systolic blood pressure reductions and let these act through QRISK on their own. It was calculated that the QRISK SBP coefficients imply a hazard ratio of only 0.89 per 10 mm Hg reduction in SBP on average, whereas the actual relative risk per 10 mm Hg reduction found in the effectiveness evidence reviews is 0.8[52]. As with statins therefore, an additional coefficient has been added to the model in treated individuals to enable the estimated risk reduction from the effectiveness evidence to be applied. The coefficients are assumed to impact upon both pqrisk and pqcardiac equally. An equivalent effect per 10 mm Hg reduction is assumed for ACE inhibitor treatment as for antihypertensive combination therapy. A similar treatment effect has been added to QRISK (both 10 year

and lifetime models) to calculate the benefits of treatment with antihypertensives in the JBS3 tool[284].

User-defined intervention: Tool users can input their own intervention if they know its relative risk for CVD. If the user-defined intervention option is being used, the relative risk is transformed into a regression coefficient which is assumed to impact upon both pqrisk and pqcardiac equally.

Normalisation to current care: Including the modifications described above results in an increase in CVD risk at the population level, which leads to the model overestimating the total number of events in the current care population. Hospital episode statistics indicate that in 2016/17 there were 81,393 acute or subsequent MI events requiring hospital admission (ICD 10 codes I21 & I22), and 88,245 strokes[282] (defined by the Sentinel Stroke National Audit Programme[285] through ICD 10 codes I61; I63 & I64). No good data exists for the current number of TIAs or angina, which may not require hospital admission. Using current care estimates of intervention usage, the model was estimating 131,045 MIs and 207,316 strokes in the first year. To adjust absolute event levels down to the recorded level, adjustment coefficients were calculated for each condition, which are applied to the pqcardiac and pqstroke probabilities in all individuals. Model validation indicated that this corrected the overall number of MI and stroke events occurring within the first year of the model to within 10% of the expected number for current care.

All modification coefficients described above are applied to pqcardiac and pqstroke using the same equation outlined above for initial calculation of risk, but replacing the 1 year survival function with the individualised 1-pqcardiac or 1-pqstroke score respectively.

Assigning CVD event types

Following modification of pqcardiac and pqstroke, the scores are recombined to reconstitute pqrisk, which is then compared against a random number draw to determine who gets a first CVD event. If the random number is lower than pqstroke risk, the individual will get a first stroke event, whereas if the number is below pqrisk but above pqstroke, the individual will get a first cardiac event. Within these categories, the type of event that occurs is then assigned using age and sex dependent probabilities from the statin HTA[279].

Modelling subsequent CVD events

QRISK2 and QStroke are only valid for individuals without pre-existing CVD[13]. Risk and nature of subsequent CVD event is assessed dependent upon previous CVD event, age and gender according to the statins HTA[279]. This means that there is no direct mechanism for reducing subsequent CVD events through interventions on modifiable

risk factors (although there will be an indirect impact if first CVD event is delayed). This means that the model could potentially underestimate the benefits of interventions in preventing subsequent CVD. Individuals may have further subsequent events in subsequent years, with a maximum of 1 additional event per year until death.

Other conditions and mortality

Conditions pre-existing in the model

The SPHR Diabetes Prevention Model simulates a range of additional conditions which arise as a consequence of diabetes or whose prevalence is affected by the modifiable metabolic risk factors in the model. Although some of these are not directly related to CVD, they were retained in the model to enable an estimate to be calculated of indirect cost savings that could be produced as a consequence of intervention. The assumptions and data sources for modelling these conditions have been described in full elsewhere[58], but are summarised briefly here. No changes were made to the way these conditions were modelled for this project.

Congestive heart failure is modelled through the Framingham risk equations[286], which include age, diabetes diagnosis, BMI and systolic blood pressure to adjust risk. Microvascular retinopathy, ulcer and amputation in people with diabetes are modelled through the UKPDS risk equations[59], which include age, systolic blood pressure, HbA1c and AF to adjust risk. These are assumed to apply to people with type 1 diabetes equally as those with type 2 diabetes. Two types of cancer are modelled; breast cancer and colon cancer, as incidence of these is related to BMI. Osteoarthritis is modelled as a function of BMI and diabetes as independent risk factors. Depression is modelled as a continuous chronic condition dependent upon diabetes and stroke diagnosis. Dementia was modelled using risk equations developed from the THIN database[287]. Dementia risk was calculated as a function of risk factors including age, BMI, blood pressure, cholesterol, diabetes, stroke, AF, antihypertensive usage and smoking.

Bleeding events

Major bleeding events were simulated in the SPHR CVD Prevention Model as they represent an important adverse effect of anticoagulation that should be accounted for in cost-effectiveness estimates. It was suggested that bleeding risk could be modelled through the QBleed risk equations[288], which are similar to the QRISK2 and QStroke already implemented in the model. However, these risk equations include many variables that cannot be informed using the HSE 2014 and that were not already in the model (eg platelet count, chronic liver disease, previous cancer diagnosis, oesophageal varices, previous bleed, use of antiplatelets; NSAIDS, anticonvulsants or steroids).

Excluding these would reduce the explanatory power of the risk equation so much that the benefits of using it would be little higher than implementing a simple prevalence depending only upon usage or not of anticoagulants.

Data about the general population incidence of 2 types of major bleeding events; intercranial bleed and upper gastrointestinal bleed, was taken directly from the QBleed publication[288]. These were assumed to represent bleeding risk in the absence of anticoagulants. Odds ratios of major bleed following anticoagulant usage were available from the same source used to estimate effectiveness of anticoagulants in preventing stroke (Guo et al., 2017[55]). As with the effectiveness estimates, a weighted mean bleed risk was calculated based upon the current usage of each type of anticoagulant[283]. Incidence rates in people taking anticoagulation were estimated from this as shown in Table 84. An additional risk of mortality in people suffering major bleed was also modelled. Fatality rates following major bleed were taken from a NICE Health Technology Assessment AF complete disease pathway modelling[194] identified as part of the model review.

Table 84: Fatality rates and age standardised incidence rates per person year of major bleed with and without anticoagulation

Type of Bleed	Without anticoagulation	With anticoagulation	Fatality
Intercranial Bleed	0.00055	0.00091	0.56
Upper GI Bleed	0.00134	0.00222	0.081

Mortality

Mortality from cardiovascular disease, cancer and major bleed are modelled as part of the disease risk equations. Cardiovascular mortality is included as an event within the QRISK2, and the statins HTA used to assign event types for first and subsequent CVD events includes both fatal stroke and fatal MI[279].

Other cause mortality describes the risk of death from any cause except CVD, bleeding and breast/bowel cancer. All-cause mortality rates by age and sex were extracted from the 2014 Office for National Statistics life tables[289]. ONS Death Registration data reports the number of deaths by ICD code for 5 year age groups. The CVD, breast and colorectal cancer and major bleed related deaths were subtracted from the all-cause mortality total to estimate other cause mortality rates by age and sex.

Interventions

The CVD Prevention ROI tool has been designed to enable 2 different types of analysis to be carried out: 1) the return on investment of improving detection and/or management of high risk conditions ('condition-focussed'); 2) the return on investment of improving usage of NICE recommended interventions for these high risk groups ('intervention focussed'). In order to model these 2 separate questions within the same framework, it was necessary to link detection and management with the interventions that promote detection and management, in a logical and consistent way. The model therefore takes a process based approach, in that users choosing to improve detection or management of high risk conditions are actually increasing the usage of the underlying NICE recommended interventions from current care levels to a higher level; thereby ensuring that the results that come out of the tool are based on evidence from the effectiveness reviews.

Detection interventions

Four mechanisms are used for detection of high risk conditions in the model. Three of these relate to evidence based interventions: NHS Health Checks, Annual Review and Cascade Testing; whilst a process of opportunistic detection is also used to account for all other detection of high risk conditions.

NHS Health Checks
NHS Health Checks are offered to people aged between 40 to 74 who have not yet been diagnosed with any of the high risk conditions. Within this subgroup people are eligible for a health check if they have never had 1, or if they have not had 1 in the last 5 years. The proportion of eligible people who get given a health check every year depends upon the current or target usage of NHS Health Checks. In an intervention focussed analysis, the current or target usage can be modified by the user, whereas in a condition focussed analysis, the default current usage is used, no matter what the user selects for detection.

According to NHS Health Check guidelines[183], all individuals that receive a Health Check will:

- have their blood pressure checked and be diagnosed with hypertension if eligible
- have their QRISK2 score calculated and be diagnosed with QRISK ≥ 10% if eligible this implicitly assumes that cholesterol and BMI have been measured
- if they have just been diagnosed with hypertension, they will also be tested for CKD, AF, non-diabetic hyperglycaemia and type 2 diabetes and diagnosed if eligible
- if they are obese they will also be tested for non-diabetic hyperglycaemia and type 2 diabetes and diagnosed if eligible

- be assigned a cost relating to NHS Health Check and an additional cost relating to diagnosis of any of the conditions for which they have been newly diagnosed (as this often requires additional tests and GP visits)

Annual review

Annual review is both a detection and a management intervention. Individuals are eligible for annual review if they have 1 or more of the high risk conditions already diagnosed. The proportion of eligible people who get given an annual review every year depends upon the current or target usage of annual review. In an intervention focussed analysis, the current or target usage can be modified by the user, whereas in a condition focussed analysis, the default current usage is used, no matter what the user selects for detection.

The process of detection of additional comorbid conditions within an annual review differs between individuals with different pre-existing high risk conditions, according to the NICE recommendations laid out in Table 44. There is also a management component of annual review, in that individuals are assumed to receive a medicines use review for any of the pharmacological management interventions that they are undergoing (described later). As with NHS Health Check, reviewed individuals are assigned a cost relating to the annual review itself and an additional cost relating to diagnosis of any of the conditions for which they have been newly diagnosed (as this often requires additional tests and GP visits).

FH detection and cascade testing

Individuals are eligible for FH testing if they have not previously been tested and if they have cholesterol ≥7.5 and this has been detected in the past year due to NHS Health Check or Annual Review, OR if they have had a CVD event in the past year aged < 60; in line with NICE Guideline CG71 criteria[19]. The proportion of eligible people who get tested every year depends upon the current or target usage of the FH detection and cascade testing tool input. In an intervention focussed analysis, the current or target usage can be modified by the user, whereas in a condition focussed analysis, the default current usage is used.

The process of FH testing is 2 step. Firstly, eligible individuals are tested and if they have FH are marked as index cases. Positive and negative test subjects are assigned different costs relating to the costs of genetic FH detection. Secondly, a process of cascade testing is simulated, using newly detected index cases only. The model does not include interaction between patients and therefore index cases do not have relatives per se. However, data about the average number of relatives tested per index case and the likelihood of a positive diagnosis in these relatives is used to determine how many additional individuals with and without FH should be tested, costed and diagnosed (Table 85). These proportions are fixed and therefore cannot be modified by tool users. It is important to note that given the low prevalence of FH in the population, there are

very few individuals with FH in each simulation and so the cascade testing process tends to lead to large jumps in proportion diagnosed.

Table 85: Model parameters used to simulate cascade testing

Parameter name	Value	Data source
Number of relatives tested per index case	1.331293	NICE Guideline CG71 2017 update[19] (Welsh, Scottish & Wessex FH Services)
Probability that a tested relative has FH	0.5089	

Opportunistic testing

Different methods of opportunistic testing were reviewed in the evidence reviews; however, these are not directly operationalised in the model as it is unclear what proportion of diagnosis they account for. Furthermore, many individuals are identified through other opportunistic methods or through symptomatic detection, and a method was required that would simulate this general process of detection outside of the formal detection mechanisms described above.

Every year in the simulation, the model first runs the detection interventions described above, resulting in a number of newly diagnosed individuals with each condition. Diagnosis costs are not yet applied at this point. Following this, the model assesses what the total new weighted proportion of individuals diagnosed with each condition is, and compares it against the current or target proportions detected from the tool. In a condition focussed analysis, the current or target detection can be modified by the user, whereas in an intervention focussed analysis, the default current detection is used, no matter which interventions the user has selected to optimise.

If insufficient individuals have been detected with a condition, additional eligible individuals are randomly selected to be detected. This opportunistic mechanism is associated with costs of diagnosis, but not with any additional costs for detection. If excess individuals have been detected with a particular condition, then some of those detected in the current year are randomly selected to become ‘undetected’ and so will not incur diagnostic costs. They will still incur costs relating to health check or annual review, as it is assumed that these individuals did undergo these processes but that tests failed to find their underlying condition. Note that only individuals diagnosed in the current year can become ‘undetected’ – it would not be logical to assume that historic detection can be reversed. The consequence of this is that in some cases the proportions detected for a condition can rise above the proportions selected by the user, if the amount of death in the undiagnosed population outweighs the number of people newly succumbing to the condition.

In the next step, the model reruns NHS Health Check and Annual Review to simulate additional Health Checks and Annual Reviews that are required if the tool user has

selected to improve usage of these interventions in the 'intervention focussed' part of the tool. This is necessary because the opportunistic detection module of the model evens out overall detection levels and therefore no additional detection would result. Costs of detection interventions and diagnosis are then applied. Note that simulating opportunistic detection when the user has chosen to ask intervention focussed questions may seem like an unnecessary complication, but is important to ensure that the pool of detected individuals (on whom management interventions will impact) remains fairly constant over time.

Management interventions

Once the diagnosis module has finished running, the management interventions are applied to diagnosed individuals.

Defining management through interventions

In the 'condition focussed' part of the tool, selecting to improve management of high risk conditions, implements improvements in usage of those management interventions recommended by NICE in individuals with that high risk condition. For each high risk condition, a set of relevant interventions has been defined, as shown in Table 86.

Table 86: Relating management of each of the high risk conditions to interventions

High risk condition	Interventions
Hypertension	Anti-hypertensive combination therapy; weight management; smoking cessation; blood pressure self-monitoring; medicine use reviews.
QRISK2 ≥ 10%	Lipid modification therapy; anti-hypertensive therapy; anti-coagulant therapy; weight management; smoking cessation; blood pressure self-monitoring; medicine use reviews.
Familial Hypercholesterolaemia	Lipid modification therapy; weight management; smoking cessation; medicine use reviews.
Atrial Fibrillation	Anti-coagulant therapy; weight management; smoking cessation; medicine use reviews.
Diabetes	Lipid modification therapy; anti-hypertensive therapy; blood glucose lowering therapy; diabetes education; weight management; smoking cessation; insulin pump; medicine use reviews.
Non-Diabetic Hyperglycaemia	NHS DPP; weight management; smoking cessation.
Chronic Kidney Disease	Lipid modification therapy; anti-hypertensive therapy; weight management; smoking cessation; nutritional advice for CKD; medicine use reviews.

It is assumed that current care management relates to current usage of interventions. This is the case even if the user chooses to select a different level of current

management than specified in the tool defaults. For target management, the increased usage of each relevant intervention for that high risk group is calculated in proportion with the increased management through the following equation:

New_usage = current_usage + (1 - current _usage)*(target_manage - current _manage)/(1 - current_manage)

If the user selects a target that is lower than current usage (possible if they wish to model disinvestment), the following equation is used to calculate the new usage of each intervention for that condition:

New_usage = current_usage - current_usage*(current_manage - target_manage)/ current_manage

Note that increased usage of the intervention does not happen in other high risk groups who may also be eligible for that intervention, unless the user has also selected to increase management in those groups too. This does create some conflicts as many individuals have more than 1 high risk condition. To resolve these, the model uses different variables to represent usage of each intervention for each relevant high risk condition. When the model applies interventions (see below) it does so by applying them to the group with the largest eligible population (at baseline) first, and then sequentially applies them to smaller risk groups. This ensures that increases in intervention usage in small populations can be applied.

Continuous interventions

Continuous interventions are those that people take continuously over a long period of time and include pharmacological interventions (lipid modification treatment (statins); antihypertensive combination therapy; ACE inhibitors (for people with CKD who don't have hypertension); anticoagulants and type 2 diabetes glucose lowering therapy (metformin, metformin plus sitagliptin or insulin depending upon treatment step)), blood glucose self-monitoring and insulin pump. At baseline, a certain proportion of diagnosed individuals are assumed to be taking continuous interventions, according to current care estimates of usage of each intervention and eligibility criteria. As the model runs, this proportion either stays constant (in the current care scenario), or is altered in response to tool user inputs. In an intervention focussed analysis, the current or target usage can be directly modified by the user, whereas in a condition focussed analysis, the usage is modified indirectly according to management targets set by the user, using the method outlined above. In order to achieve this within a dynamic simulation in which every year new individuals are becoming eligible through diagnosis, or existing individuals are dying; the model assesses the proportion taking the treatment, compares this against current or target usage of the intervention and adjusts the number taking treatment either by randomly selecting untreated individuals to become treated, or by removing

individuals from treatment. The process is similar to that described above for aligning the proportion diagnosed with each condition to tool user inputs.
Metabolic trajectories and CVD risk are altered in response to treatment and discontinuation of treatment, according to the effectiveness estimates obtained in the evidence review.

Lipid modification therapy causes a reduction in LDL cholesterol of 43%[39]. LDL cholesterol is not modelled directly; instead an equivalent reduction in total cholesterol is implemented and it is assumed that HDL cholesterol is unchanged. The steering group advised that a proportional reduction in cholesterol was more clinically appropriate than an absolute reduction. An additional CVD risk reduction is also implemented in each individual as described in the Cardiovascular Events section. In addition, the adverse impact of statins in increasing HbA1c is modelled; implemented as an absolute increase of 0.17%[46]. These treatment effects endure for as long as an individual is treated, and are removed if they discontinue treatment. Eligible high risk groups for which proportional usage is modelled independently include people with QRISK ≥10%; people with type 1 diabetes or type 2 diabetes plus QRISK ≥10%; people with FH and people with CKD.

ACE inhibitors cause a reduction in systolic and diastolic blood pressure of 3% and 2% respectively[54]. The steering group advised that a proportional reduction in systolic blood pressure was more clinically appropriate than an absolute reduction. An additional CVD risk reduction is also implemented in each individual as described in the Cardiovascular Events section. ACE inhibitors are also assumed to slow down ACR transitions in CKD. These treatment effects endure for as long as an individual is treated, and are removed if they discontinue treatment. The only eligible high risk group for ACE inhibitors is people with CKD who do not also have hypertension. People treated with ACE inhibitors who become diagnosed with hypertension are assumed to automatically graduate to antihypertensive combination therapy, receiving the benefits of that intervention instead.

Antihypertensive combination therapy causes a reduction in systolic and diastolic blood pressure of 13%[51]. The steering group advised that a proportional reduction in systolic blood pressure was more clinically appropriate than an absolute reduction. An additional CVD risk reduction is also implemented in each individual as described in the Cardiovascular Events section. Antihypertensive combination therapy includes ACE inhibitors and therefore is also assumed to slow down ACR transitions in CKD.These treatment effects endure for as long as an individual is treated, and are removed if they discontinue treatment. Eligible high risk groups for which proportional usage is modelled independently include people with hypertension alone; people with hypertension plus QRISK ≥10%; people with hypertension plus type 1 or type 2 diabetes and people with hypertension plus CKD.

Anticoagulant therapy does not impact upon metabolic factors. It causes a CVD risk reduction based on weighted usage of the different types of anticoagulants in the English population, implemented in each individual. This treatment effect endures for as long as an individual is treated, and is removed if they discontinue treatment. Eligible high risk groups for which proportional usage is modelled independently include people with AF alone and people with AF plus QRISK ≥10%.

Blood glucose lowering therapy acts directly upon HbA1c, but has no direct impacts on CVD risk reduction (indirect effects act through the HbA1c modifications to QRISK described in Section 0). The magnitude of HbA1c reduction depends upon HbA1c at the point of treatment and is based on data from newly diagnosed diabetics in the UKPDS trial59. In the model, it is assumed that this treatment effect applies no matter how long after diagnosis an individual commences treatment, and is removed if they discontinue treatment. A 3 step treatment regimen is applied for cost purposes, but does not alter implementation of treatment effectiveness. The treatment effect is therefore applied when an individual starts metformin treatment (step 1), no matter what their HbA1c is at this point. In line with NICE guidelines, an individual is assumed to step up to metformin plus gliptins when their HbA1c reaches 7.5% (step 2), and up to insulin when their HbA1c reaches 8.5% (step 3)[22], but this does not alter their underlying HbA1c trajectory. One step is permitted per year after initiation of treatment. If an individual discontinues treatment, then restarts, they are assumed to restart with metformin again (although may then rapidly step up to insulin over the next 2 years if their HbA1c is very high). The only eligible high risk group is people with type 2 diabetes.

Blood pressure self-monitoring acts directly upon systolic blood pressure, resulting in an absolute reduction of 3.24 mm Hg[118]. Given that the improvements in blood pressure come through adherence to antihypertensive medication rather than lifestyle effects, an additional CVD risk reduction is also implemented in each individual in the same way as for antihypertensive combination therapy. These treatment effects endure for as long as an individual is treated, and are removed if they discontinue treatment. Eligible high risk groups for which proportional usage is modelled independently include people with hypertension taking antihypertensives; people with hypertension plus QRISK ≥10% taking antihypertensives; people with hypertension plus type 1 or type 2 diabetes taking antihypertensives; and people with hypertension plus CKD taking antihypertensives (either combination or ACE inhibitors).

Insulin pump acts directly upon HbA1c causing an absolute reduction of 0.61%[70], but has no direct impacts on CVD risk reduction (indirect effects act through the HbA1c modifications to QRISK described in Section 0). These treatment effects endure for as long as an individual is treated, and are removed if they discontinue treatment. The only eligible high risk group is people with type 1 diabetes. Unlike other interventions in the model, it is assumed that only a subset of 40% of the type 1 diabetes population will benefit, informed through expert opinion from the steering group.

One-off Interventions

One-off interventions are those that individuals are only eligible for once over their lifetime and comprise most of the lifestyle interventions in the model including the NHS DPP, structured education for diabetes, weight management and nutritional advice for CKD. Whilst it is theoretically possible that individuals could have these interventions multiple times, the steering group considered that it was more realistic to assume that people would not be offered the intervention again after having it once.

It is assumed that no individuals have previously had any of these interventions at baseline. In the first year, all individuals diagnosed with the relevant high risk condition are eligible for intervention. In subsequent years, only those who have not previously had the intervention are eligible. The proportion of those eligible getting the intervention depends upon current or target usage. In an intervention focussed analysis, the current or target usage can be directly modified by the user, whereas in a condition focussed analysis, the usage is modified indirectly according to management targets set by the user, using the method outlined above.

NHS DPP causes an absolute reduction in BMI, HbA1c, systolic blood pressure and total cholesterol. CVD risk reduction acts indirectly through these metabolic changes. Intervention effectiveness is assumed to linearly decline over the following 5 years. The only eligible high-risk group is people with non-diabetic hyperglycaemia.

Structured diabetes education causes an absolute reduction in HbA1c only, which differs for type 1 diabetes and type 2 diabetes. CVD risk reduction acts indirectly through these metabolic changes. Intervention effectiveness is assumed to linearly decline over the following 5 years. Only people with diabetes are eligible for this intervention.

Weight management causes an absolute reduction in BMI only. CVD risk reduction acts indirectly through these metabolic changes. Intervention effectiveness is assumed to linearly decline over the following 5 years. All overweight and obese individuals with at least 1 high risk condition are eligible for weight management. Proportional usage of weight management is therefore modelled independently in each of the high risk groups. In practice, individuals without a high risk condition will also be eligible for weight management if they are overweight or obese. However, this was not modelled in line with the scope of the tool, which does not include primary prevention in the general population.

Nutritional advice for CKD causes an absolute reduction in systolic blood pressure and BMI. CVD risk reduction acts indirectly through these metabolic changes. Intervention effectiveness is assumed to linearly decline over the following 5 years. Only people with CKD stage 3 to 5 are eligible for this intervention.

Repeated interventions

Repeated interventions are those which individuals may be eligible for repeatedly during their lifetime and include smoking cessation and medicine use review. The proportion of those eligible getting the intervention depends upon current or target usage. In an intervention focussed analysis, the current or target usage can be directly modified by the user, whereas in a condition focussed analysis, the usage is modified indirectly according to management targets set by the user, using the method outlined above.

Smoking cessation intervention is available to all individuals with high-risk conditions who smoke. In practice, individuals without a high risk condition will also be eligible for smoking cessation intervention if they smoke. However, this was not modelled in line with the scope of the tool, which does not include primary prevention in the general population. In line with NHS guidelines, individuals have an opportunity to quit every year until they are successful. 7.7% of individuals are assumed to be successful in each attempt[81], in which case they become past smokers. CVD risk reduction acts indirectly through changes in smoking status that are reflected in the QRISK2 and QStroke equations. An underlying rate of smoking cessation is not implemented in the model, so smokers who do not undergo smoking cessation interventions are assumed to remain smokers throughout their lifetime.

Medicine use review is implemented in 2 different ways. Individuals will get a medicines use review if they have undergone annual review in that year. Additionally, individuals have the possibility of receiving a new medicines review from a pharmacist if they have started a new pharmacological treatment of any type in that year. It is therefore available to all individuals with high-risk conditions who are treated with 1 or more pharmacological treatments. Both mechanisms result in the same effect of improving adherence to medicines by a relative risk of 1.17[116]. Adherence is assumed to improve for all pharmacological treatments that an individual takes. Improvements in adherence act by reducing those metabolic factors affected by pharmacological treatment by an additional percentage. So in those taking antihypertensive combination therapy or ACE inhibitors, an additional systolic and diastolic blood pressure effect is implemented; in those taking blood glucose lowering medication an additional HbA1c effect is implemented, and in those taking statins an additional cholesterol effect is implemented. An additional CVD risk reduction is implemented in those taking anticoagulants, but not in those taking other medications as it was too complex to implement this on top of all the other changes. These intervention effects are assumed to last for a single year, after which they will be removed unless the individual gets another medicine use review in the next year.

Costs and utilities

Utilities

Baseline utilities for all individuals in the cohort are derived from the responses to the 3 level EQ-5D from the HSE 2014. Utility is assumed to decline due to ageing independent of health status by 0.004. The utility decrements for transient and long-term chronic conditions are applied multiplicatively to the age adjusted EQ-5D score. CVD, end stage renal failure, amputation, foot ulcers, blindness, cancer, osteoarthritis, depression and major bleed are all assumed to result in utility decrements. Diabetes, AF, FH and CKD stages 1 to 4 were assumed to not be associated with utility decrements in the absence of complications. Whilst type 1 diabetes would be expected to be associated with utility decrements, all individuals are already diagnosed at baseline and therefore reductions in utility due to disease are already incorporated in their baseline EQ-5D estimates.

All utility estimates are unchanged from those used in the original SPHR Diabetes Model (Table 87). Additional utility decrements were required for major bleed. These were identified from a NICE Health Technology Assessment AF complete disease pathway modelling identified as part of the model review[194]. A mean lifetime utility multiplier of 0.829 was given for intercranial bleed. For upper gastrointestinal bleed, a utility multiplier of 0.776 was given over the 5 day acute phase, which corresponded to a transient utility multiplier of 0.997 over the year in which a GI bleed occurs.

Table 87: Utility decrements used in the model

	Mean absolute decrement	Baseline utility	Multiplicative utility factor	Source
Foot ulcer	-0.099	0.689	0.856	Coffey et al., 2002[290]
Amputation	-0.172	0.807	0.787	UKPDS, 2004[59]
Blind			1.00	Assumption (value from UKPDS, 2004[59] was higher than 1)
Renal failure	-0.078	0.689	0.887	Coffey et al., 2002[290]
Stable Angina			0.801	Ward HTA 2007[279]
Unstable Angina y1			0.770	Ward HTA 2007[279]
Unstable Angina y2			0.770	Ward HTA 2007[279]
Myocardial Infarction y1			0.760	Ward HTA 2007[279]
Myocardial Infarction y2			0.760	Ward HTA 2007[279]
TIA			1.000	Ward HTA 2007[279]
Stroke y1			0.629	Ward HTA 2007[279]
Stroke y2			0.629	Ward HTA 2007 [279]
Breast Cancer	-0.060	0.791	0.913	Yabroff et al., 2004[291]
Colorectal Cancer	-0.060	0.791	0.913	Yabroff et al., 2004[291]
Osteoarthritis	-0.101	0.791		Black et al., 2009[292]
Depression	-0.116	0.791	0.875	Benedict et al., 2010[293]

Congestive Heart Failure	-0.101		0.875	UKPDS[59]
Intercranial Bleed			0.821	Lord HTA 2013[194]
Upper GI Bleed y1			0.997	Lord HTA 2013[194]
Dementia MMSE 26-30		0.690		Jonsson et al., 2006[294]
Dementia MMSE 21-25	-0.05	0.690	0.93	Jonsson et al., 2006[294]
Dementia MMSE 15-20	-0.19	0.690	0.725	Jonsson et al., 2006[294]
Dementia MMSE 10-14	-0.20	0.690	0.710	Jonsson et al., 2006[294]
Dementia MMSE 0-9	-0.36	0.690	0.478	Jonsson et al., 2006[294]

Costs

Each health state in the model is associated with an average cost, which is accrued by all individuals for every time period for which the state is indicated. Resource use for each comorbidity is added together and no savings are assumed to be made from the use of the same resources for 2 or more comorbidities for an individual.

All model costs were reviewed and updated to 2016/17 values for this analysis. The majority of the costs in the SPHR Diabetes Prevention Model were reused for the SPHR CVD Prevention model, with costs either being inflated using the Retail Price Indices (excluding mortgage interest)[169], or resource use estimates re-costed using information from the latest versions of the British National Formulary[170] (for costs of pharmacological treatments), NHS reference costs[172] (for secondary care), and the Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care167 (for primary care staff time). A newer cost source for CVD was recommended by PHE (Walker et al., 2016)[295] and values from this study were used in place of the older cost sources used previously. Information about the increased cost of stroke in people with AF, taken from a 2015 costing study in a Rotherham hospital[200], was also incorporated in the model. This estimated that stroke costs were 1.59 fold higher in people with AF than those without.

Additional costs were included for the new health states incorporated in the model. This included the costs of all interventions (already shown in Table 47); the cost of diagnosing each of the high-risk conditions following detection through Health Checks, Annual Review or opportunistic screening; and the cost of major bleed events. The cost of an upper GI bleed was estimated at £3,084 following inflation, from Campbell et al. 2013[296]. Cost of an intercranial bleed was assumed to be the same as costs of haemorrhagic stroke from Walker et al. 2016[295]. This was estimated at £9,331 in the first year and £2,680 in subsequent years, following inflation.

Diagnosis of hypertension (via ambulatory blood pressure monitoring) and diabetes were already costed in the SPHR Diabetes Prevention Model; these costs were inflated to 2016/17 values. Diagnosis of QRISK ≥10% was assumed to be through a single

additional lipid test at a cost of £1. Diagnosis of AF was costed from a NICE Health Technology Assessment AF complete disease pathway modelling identified as part of the model review[194], which assumed diagnosis would require a 12 lead ECG and staff time. Diagnosis of CKD was assumed to require a serum cystatin C test, a serum creatinine test and a urine test, costed at a total of £3.89 from NICE Guidelines CG18224. Diagnosis of non-diabetic hyperglycaemia was assumed to cost the same as a diabetes diagnosis.

It was assumed that no costs other than those of interventions associated with the condition would be incurred in people with AF and CKD stages 1 to 4. Individuals with FH taking statins were also assumed to incur a cost for Ezetimibe, a newer lipid lowering drug. Data from a UK FH audit[297] indicated that 46% of FH patients are taking Ezetimibe, and therefore a mean cost per patient with FH was calculated and added to each treated individual. Individuals with type 1 diabetes were assumed to all incur the costs of multiple daily injections of insulin, with additional costs being added if instead they switched to insulin pump.

In order to separate costs saved into primary and secondary care, an estimate of the proportion of costs relating to primary care was made for each of the costed disease states. In most cases, these proportions were taken from the DPP ROI tool costings, but where cost sources had changed, the proportion of primary care costs was estimated using information within the cost source itself. All costs other than those already presented in Table 47 for interventions are shown in

Table 88, together with the estimated proportions relating to primary care.

Table 88: Costs input parameters

Parameter description & resource use	Cost	Proportion primary care	Source
CVD COSTS			
Stable Angina annual cost	£1,005	52%	Walker et al. (2016)[295]
Unstable Angina acute costs in first year	£2,822	23%	NHS Reference Costs[172]
Unstable Angina annual cost	£1,566	33%	Walker et al. (2016)[295]
MI acute costs in first year	£8,275	8%	Walker et al. (2016)[295]
MI annual cost in subsequent years	£2,158	24%	Walker et al. (2016)[295]
Fatal MI	£1,948	0%	Walker et al. (2016)[295]
TIA annual cost	£2,796	19%	Luengo-Fernandez et al., (2012)[298]
Ischaemic stroke acute costs in first year	£9,333	7%	Walker et al. (2016)[295]
Ischaemic stroke annual cost in subsequent years	£2,010	26%	Walker et al. (2016)[295]
Stroke annual social care costs	£7,477	NA	Luengo-Fernandez et al., (2013)[299]
Fatal stroke	£2,323	0%	Walker et al. (2016)[295]
Congestive Heart Failure acute costs in first year	£1,824	57%	Alva et al., (2014)[300]
Congestive Heart Failure annual cost	£2,588	40%	Alva et al., (2014)[300]
COSTS OF OTHER CONDITIONS			
Retinopathy costs in first year	£2,068	51%	Alva et al., (2014)[300]
Retinopathy annual cost	£1,260	62%	Alva et al., (2014)[300]
Amputation costs in first year	£9,357	12%	Alva et al., (2014)[300]
Amputation annual cost	£3,601	47%	Alva et al., (2014)[300]
Renal Failure annual cost (weighted average of renal transplant, peritoneal dialysis and haemodialysis)	£25,341	0%	Baboolal et al., (2008)[301] NHS Reference Costs[172]
Foot ulcer annual cost (weighted average of non-infected, cellulitis and osteomyelitis)	£206	62%	Gordois et al., (2003)[302]
Colorectal cancer Dukes A	£10,364	6%	Tappenden et al., (2004)[303]
Colorectal cancer Dukes B	£17,783	6%	Tappenden et al., (2004)[303]
Colorectal cancer Dukes C	£27,268	6%	Tappenden et al., (2004)[303]
Colorectal cancer Dukes D	£17,075	6%	Tappenden et al., (2004)[303]
Osteoarthritis annual medical costs	£988	49%	Oxford Economics (2010)[304]
Osteoarthritis annual social care costs	£76	NA	Oxford Economics (2010)[304]
Depression annual costs (includes nurse time, medications, secondary care etc.)	£604.39	88%	Chalder et al., (2012)[305]
Gastrointestinal Bleed cost	£3,084	3%	Campbell et al., (2015)[296]
Intercranial Bleed acute costs in first year	£10,465	6%	Walker et al. (2016)[295]
Intercranial Bleed annual cost in subsequent years	£3,005	17%	Walker et al. (2016)[295]
DIAGNOSIS & OTHER COSTS			
GP appointment	£37	100%	PSSRU[167]
Diabetes and non-diabetic hyperglycaemia diagnosis (HbA1c tests & staff time)	£15.21	NA	NICE Guidance PH38[23]
Hypertension diagnosis (ambulatory blood pressure monitor)	£58.03	NA	NICE Guidance CG127[17]
AF diagnosis (12 lead ECG & staff time)	£34.77	NA	Lord et al., (2013)[194]
CKD diagnosis (urine test, serum cystatin C and serum creatinine tests)	£3.89	NA	NICE Guidance CG182[24]
QRISK ≥10% (lipid test)	£1	NA	NHS Reference Costs[172]

Model testing and validation

Following model development, a series of tests and validations were carried out to ensure that the model was working as planned.

Checking that proportions diagnosed and treated remain constant

Tool users select their target proportions for diagnosis, management and usage of interventions, and therefore these should stay constant throughout the model simulation, despite the dynamic changes in eligibility each year. The model was tested to ensure that it was simulating the correct proportions over time. Proportions were collected annually over the 20 year time horizon of a model run, under a number of different tool input values. These were then compared against the inputted value. Differences were investigated and changes made to the model where necessary.

Checking individual level trajectories

To ensure that each intervention is having the expected impact upon metabolic trajectories and CVD risk, trajectories for BMI, systolic blood pressure, HbA1c, cholesterol, QRISK and Qstroke for 100 individuals were followed over time with and without usage of each intervention in turn. Trajectories were examined to ensure that the correct reduction in response to intervention, duration of effect, and return back to baseline were being modelled. Following this, trajectories were examined for a scenario simulating current care usage of interventions (ie with all interventions acting together), to ensure that interactions between interventions were occurring as expected. Any anomalies were investigated and changes made to the model where necessary.

Validating against CVD events

To ensure that implementation of the QRISK and QStroke algorithms to estimate event rate was producing a similar number of total CVD events to those seen currently in England, total events in year 1 of a current care simulation was compared against total events from Hospital Episode Statistics for MI and Stroke[282]. Initially the absolute numbers of stroke and MI estimated by the model were far too high. An adjustment factor was therefore added to the QRISK and QStroke algorithms in order to ensure that the estimation of total events was roughly in line with current care.

Validation against previous versions of the model

Previous versions of the model have been used to estimate the cost-effectiveness and return on investment of the NHS DPP, including the version used to make the DPP ROI tool. A comparison of the results estimated by the DPP ROI model and the CVD

Prevention ROI model was carried out to provide face validity for the new model. The DPP ROI model implements the NHS DPP in the first year only. An equivalent scenario was simulated by setting the current care usage of the NHS DPP to 0, then setting a target usage that was phased, with year one set to 100%, and years 2 and 3 set to 0. Results were compared by dividing each by the numbers of people modelled and multiplying by 1000, to get results per 1000 people receiving the NHS DPP.

Table 89: Comparison between the DPP and CVD Prevention ROI models: results per 1000 people receiving the NHS DPP. Red text indicates increase in costs or clinical events. Black text represents cost savings, reduction in events (both shown as negative) or increase in life years and QALYs (shown as positive)

Output	**DPP Model**		**CVD Prevention Model**	
Year Cost-Saving	11		7	
Cumulative Results	**Year 1**	**Year 5**	**Year 1**	**Year 5**
NET TOTAL	£238,829	£142,799	£210,929	£45,296
CVD Savings	-£11,178	-£37,073	-£17,263	-£64,094
Non-CVD Savings**	-£4,393	-£32,625	-£2,404	-£39,901
Diabetes Treatment Savings	-£796	-£16,519	£0	-£23,126
Other Primary Care Savings*	-£14,803	-£40,983	£0	-£10,683
DPP Costs	£270,000	£270,000	£223,000	£223,000
MI	-0.3	-0.8	-0.1	-1.1
Stroke	-0.6	-1.3	-0.2	-0.8
Heart Failure	-0.5	-1.7	-0.2	-1.9
Total CVD events	-1.8	-4.1	-1.1	-6.0
End Stage Renal	-0.01	-0.06	0	0.01
Diabetes Diagnoses	-10.4	-41.4	0	-63
Life Years	0.06	4.9	0	3.7
QALYs	0.5	6.9	0.1	6.7

* For DPP model this comprises GP appointments, statins and antihypertensives; For CVD model this comprises statins, antihypertensives and all other included interventions but does not include GP appointments which are instead included within non-CVD savings
** All social care costs are included in this category in the DPP model, including social care costs of stroke which in the CVD model are included within CVD costs

Some differences were seen between the 2 sets of results, but this was expected due to the number of differences in methodology between the 2 models and were generally fairly minor. In particular, the DPP was found to be cost-saving by year 7 in the new model compared to year 11 in the DPP model, which is likely to be due mainly to the

lower intervention cost and the higher CVD savings in the new model. However, a range of other changes are also likely to have impacted upon the results as follows:

- the CVD prevention model uses HSE 2014 as a baseline population whereas the DPP model uses HSE 2011
- the CVD prevention model uses QRISK 2015 and QStroke 2015 plus modifications, whereas the DPP model uses QRISK 2011
- the CVD prevention model uses a lower intervention cost than the DPP model
- the CVD prevention model includes a range of additional interventions, most of which also see reduced usage as a result of the DPP, thereby increasing costs saved
- the CVD prevention model uses higher costs for CVD events than the DPP model
- the CVD prevention model uses a different method for predicting end stage renal disease in all people, whereas the DPP model only predicts ESRD as a consequence of diabetes. The increase in ESRD seen in the new model is probably due to competing risks for mortality as CKD has a large age component

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Appendix: Search terms

Scoping search terms

Interventions for CVD prevention in high risk groups

Test Search Medline 31.08.2017
Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:
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1. *Hypertension/ (163789)
2. *Atrial Fibrillation/ (38082)
3. *Hyperlipoproteinemia Type II/ (4950)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (144249)
5. *Hyperglycemia/ (14530)
6. *Renal Insufficiency, Chronic/ (12607)
7. 1 or 2 or 3 or 4 or 5 or 6 (369417)
8. (risk* or prevent* or reduce* or protect* or limit* or control*).ti. (1455367)
9. early detection.ti,ab. (51423)
10. *risk reduction behavior/ or *risk factors/ (5283)
11. 8 or 9 or 10 (1504249)
12. 7 and 11 (53448)
13. (MEDLINE or systematic review).tw. or meta analysis.pt. (202017)
14. 12 and 13 (1994)
15. limit 14 to ‘review articles’ (1165)

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Search produced 1189 results on Medline 7th September 2017
With duplicates removed 1090

Multiple interventions for CVD Prevention

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:
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1. ((multiple or multi) and intervention*).ti,ab. (71514)
2. *Cardiovascular Diseases/pc [Prevention & Control] (17491)
3. 1 and 2 (343)
4. limit 3 to ‘review articles’ (107)

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Effectiveness review search terms

Effectiveness of anti-hypertensives: search for reviews

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:
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1. *Hypertension/ (168757)
2. *Atrial Fibrillation/ (39629)
3. *Hyperlipoproteinemia Type II/ (5200)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (150588)
5. *Hyperglycemia/ (15088)
6. *Renal Insufficiency, Chronic/ (13220)
7. 1 or 2 or 3 or 4 or 5 or 6 (383309)
8. (hypertension or atrial fibrillation or hyperlipoproteinemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency).ti,ab. (828012)
9. 7 or 8 (913669)
10. exp Antihypertensive Agents/ (259457)
11. (antihypertensive or lower* blood pressure).ti,ab. (50745)
12. 10 or 11 (280975)
13. systolic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (159391)
14. 9 and 12 and 13 (17081)
15. (MEDLINE or systematic review).tw. or meta analysis.pt. (213005)
16. 14 and 15 (518)

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Effectiveness of anti-hypertensives in other high risk groups: search for reviews

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:
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1. *Hypertension/ (168781)
2. *Atrial Fibrillation/ (39636)
3. *Hyperlipoproteinemia Type II/ (5200)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (150628)
5. *Hyperglycemia/ (15092)
6. *Renal Insufficiency, Chronic/ (13222)

7. 1 or 2 or 3 or 4 or 5 or 6 (383380)
8. (hypertension or atrial fibrillation or hyperlipoproteinemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency).ti,ab. (828446)
9. 7 or 8 (914110)
10. exp Antihypertensive Agents/ (259472)
11. (antihypertensive or lower* blood pressure).ti,ab. (50775)
12. 10 or 11 (281017)
13. systolic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (159466)
14. 9 and 12 and 13 (17086)
15. (MEDLINE or systematic review).tw. or meta analysis.pt. (213246)
16. 14 and 15 (518)
17. 2 or 3 or 4 or 5 or 6 (219889)
18. (atrial fibrillation or hyperlipoproteinemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency).ti,ab. (542392)
19. 17 or 18 (587261)
20. 12 and 13 and 19 (3145)
21. 15 and 20 (103)

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Effectiveness of lipid modification therapy: search for reviews

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:

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1. *Hypertension/ (168757)
2. *Atrial Fibrillation/ (39629)
3. *Hyperlipoproteinemia Type II/ or *Hypercholesterolemia/ or *Hyperlipidemias/ (38118)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (150588)
5. *Hyperglycemia/ (15088)
6. *Renal Insufficiency, Chronic/ (13220)
7. 1 or 2 or 3 or 4 or 5 or 6 (413294)
8. (hypertension or atrial fibrillation or hyperlipidemia or hyperlipoproteinemia or hypercholesterolemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency).ti,ab. (852981)
9. 7 or 8 (952429)
10. exp *Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (26491)
11. (lipid modification* or statin* or lipid lower*).ti,ab. (48721)
12. 10 or 11 (57761)

13. (ldl cholesterol or low density lipoprotein cholesterol or total cholesterol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (71800)
14. *Cholesterol, LDL/ (6879)
15. 13 or 14 (73849)
16. 9 and 12 and 15 (7827)
17. (MEDLINE or systematic review).tw. or meta analysis.pt. (213005)
18. 16 and 17 (218)

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Effectiveness of Atorvastatin 20mg: search for RCTs

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:

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1. Atorvastatin Calcium/ (6493)
2. atorvastatin.mp. or Atorvastatin Calcium/ (9256)
3. 1 or 2 (9256)
4. randomized controlled trial.pt. or randomized controlled trial.mp. (537511)
5. *Hypertension/ (173425)
6. *Atrial Fibrillation/ (41856)
7. *Hyperlipoproteinemia Type II/ (5408)
8. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (158929)
9. *Hyperglycemia/ (15751)
10. *Renal Insufficiency, Chronic/ (14830)
11. (hypertension or atrial fibrillation or hyperlipidemia or hyperlipidaemia or hyperlipoproteinemia or hyperlipoproteinaemia or hypercholesterolemia or hypercholesterolaemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency).ti,ab. (896768)
12. or/5-11 (981217)
13. (practice nurses or primary care or primary healthcare or primary health care or gps or general practitioners or family physicians or health visitors or pharmacists or health trainers).ti,ab. (351652)
14. 3 and 12 (2785)
15. 4 and 14 (711)
16. limit 15 to yr=‘2013 -Current’ (168)

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Impact of statins on diabetes prevalence and HbA1c: search for reviews

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:
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1. *Hypertension/ (169148)
2. *Atrial Fibrillation/ (39845)
3. *Hyperlipoproteinemia Type II/ or *Hypercholesterolemia/ or *Hyperlipidemias/ (38237)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (151489)
5. *Hyperglycemia/ (15160)
6. *Renal Insufficiency, Chronic/ (13494)
7. 1 or 2 or 3 or 4 or 5 or 6 (415177)
8. (hypertension or atrial fibrillation or hyperlipidemia or hyperlipoproteinemia or hypercholesterolemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency).ti,ab. (856945)
9. 7 or 8 (956732)
10. (MEDLINE or systematic review).tw. or meta analysis.pt. (215232)
11. making every contact count.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (17)
12. ((brief or opportunists or concise or short or direct or lifestyle or written or oral or verbal or personalised or individualised) adj2 (advice or counselling or counselling or negotiations or guidance or discussions or encouragement or interventions or programs or meetings or sessions)).ti,ab. (32895)
13. (patients adj2 (leaflets or flyers or information or pamphlets or booklets or posters)).ti,ab. (28032)
14. *Patient Education as Topic/ (37675)
15. *Health Education/ (34716)
16. *Health Literacy/ (2732)
17. Directive Counseling/ (2207)
18. pamphlets/ (3778)
19. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (134578)
20. 9 and 19 (12358)
21. 10 and 20 (475)
22. *Atrial Fibrillation/ (39845)
23. *Renal Insufficiency, Chronic/ (13494)
24. models, economic/ (9035)
25. Cost-Benefit Analysis/ (76136)
26. (cost effectiveness or cost utility or economic analysis).ti,ab. (56395)

27. 22 or 23 (53192)
28. 24 or 25 or 26 (108190)
29. 27 and 28 (505)
30. limit 29 to yr=‘2007 -Current’ (403)
31. 20 and 28 (376)
32. *Hypertension/ (169148)
33. *Atrial Fibrillation/ (39845)
34. *Hyperlipoproteinemia Type II/ or *Hypercholesterolemia/ or *Hyperlipidemias/ (38237)
35. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (151489)
36. *Hyperglycemia/ (15160)
37. *Renal Insufficiency, Chronic/ (13494)
38. 32 or 33 or 34 or 35 or 36 or 37 (415177)
39. (hypertension or atrial fibrillation or hyperlipidemia or hyperlipoproteinemia or hypercholesterolemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency).ti,ab. (856945)
40. 38 or 39 (956732)
41. exp *Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (26636)
42. (lipid modification* or statin* or lipid lower*).ti,ab. (48979)
43. 41 or 42 (58035)
44. (ldl cholesterol or low density lipoprotein cholesterol or total cholesterol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (72124)
45. *Cholesterol, LDL/ (6917)
46. 44 or 45 (74182)
47. 40 and 43 and 46 (7856)
48. (MEDLINE or systematic review).tw. or meta analysis.pt. (215232)
49. 47 and 48 (217)
50. *Hypertension/ (169148)
51. *Atrial Fibrillation/ (39845)
52. *Hyperlipoproteinemia Type II/ or *Hypercholesterolemia/ or *Hyperlipidemias/ (38237)
53. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (151489)
54. *Hyperglycemia/ (15160)
55. *Renal Insufficiency, Chronic/ (13494)
56. 50 or 51 or 52 or 53 or 54 or 55 (415177)
57. (hypertension or atrial fibrillation or hyperlipidemia or hyperlipoproteinemia or hypercholesterolemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency).ti,ab. (856945)
58. 56 or 57 (956732)

59. exp *Hydroxymethylglutaryl-CoA Reductase Inhibitors/ (26636)
60. (lipid modification* or statin* or lipid lower*).ti,ab. (48979)
61. 59 or 60 (58035)
62. (ldl cholesterol or low density lipoprotein cholesterol or total cholesterol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (72124)
63. *Cholesterol, LDL/ (6917)
64. 62 or 63 (74182)
65. 58 and 61 and 64 (7856)
66. (MEDLINE or systematic review).tw. or meta analysis.pt. (215232)
67. 65 and 66 (217)
68. diabetes.mp. (563992)
69. 4 or 68 (564535)
70. 43 and 69 (8954)
71. (blood sugar or blood glucose or hba1c).mp. (209784)
72. 70 and 71 (1292)
73. 66 and 72 (27)

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Effectiveness of anti-coagulants for AF: search for reviews

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:

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1. *Atrial Fibrillation/ (41856)
2. atrial fibrillation.mp. (75152)
3. 1 or 2 (75152)
4. *Warfarin/ (11650)
5. *Dabigatran/ (659)
6. *Rivaroxaban/ (664)
7. (warfarin or apixaban or dabigatran or rivaroxaban).mp. (34184)
8. 4 or 5 or 6 or 7 (34184)
9. 3 and 8 (8489)
10. (MEDLINE or systematic review).tw. or meta analysis.pt. (227891)
11. 9 and 10 (413)

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Effectiveness of anti-coagulants in people with CKD: search for RCTs

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:

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1. *Atrial Fibrillation/ (41856)
2. atrial fibrillation.mp. (75152)
3. *Renal Insufficiency, Chronic/ (14830)
4. (atrial fibrillation or chronic kidney disease or chronic renal insufficiency).mp. (122338)
5. 1 or 2 or 3 or 4 (125596)
6. exp Anticoagulants/ (218521)
7. (apixaban or dabigatran or rivaroxaban or 4-hydroxycoumarins or acenocoumarol or ancrod or blood coagulation factor inhibitor* or citric acid or dalteparin or dermatan sulfate or dextrans or dicumarol or edetic acid or enoxaparin or ethyl biscoumacetate or fibrin fibrinogen degradation product* or gabexate or heparin or heparinoids or nadroparin or pentosan sulfuric polyester or phenindione or phenprocoumon or protein c or protein s or warfarin or beta 2-glycoprotein i).ti,ab. (148069)
8. (anti-coagulant* or anticoagulant*).ti,ab. (58911)
9. 6 or 7 or 8 (300690)
10. 5 and 9 (14939)
11. randomized controlled trial.pt. or randomized controlled trial.mp. (537511)
12. 10 and 11 (846)
13. (atrial fibrillation or chronic kidney disease or chronic renal insufficiency).ti,ab. (105229)
14. 1 or 3 or 13 (114929)
15. 9 and 14 (14017)
16. 11 and 15 (815)
17. exp *Anticoagulants/ (117455)
18. 7 or 8 or 17 (226953)
19. 14 and 18 (12548)
20. 11 and 19 (752)

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Effectiveness of educational programmes for diabetes: search for reviews

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:
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1. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (158929)
2. diabetes.ti,ab. (482234)
3. 1 or 2 (505050)
4. *Health Behavior/ or *Health Knowledge, Attitudes, Practice/ or *Patient Education as Topic/ or *Risk Reduction Behavior/ or *Self Care/ or *Self Efficacy/ (137986)
5. (structured education or self-management or self management or self-monitoring or self monitoring or self-care or self care).ti,ab. (35260)
6. (patient adj3 education).ti,ab. (20441)
7. (Pro-active Interdisciplinary Self-Management or Dose Adjustment for normal eating or dafne or ‘Diabetes Education and Self-Management for Ongoing and Newly Diagnosed’ or desmond).ti,ab. (256)
8. or/4-7 (174234)
9. 3 and 8 (17256)
10. (hba1c or BMI or body mass index or systolic or cholesterol).mp. (670916)
11. *Cholesterol/ (49897)
12. *Body Mass Index/ (19258)
13. 10 or 11 or 12 (670916)
14. 9 and 13 (3767)
15. (MEDLINE or systematic review).tw. or meta analysis.pt. (227891)
16. 14 and 15 (165)

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Effectiveness of weight management programmes: search for reviews

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
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1. *Hypercholesterolemia/ (16774)
2. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (152836)
3. *Hyperglycemia/ (15292)
4. *Renal Insufficiency, Chronic/ (13975)
5. (hypercholesterol?emi* or high cholesterol or high cholestrol or prediabet* or diabet* or hyperglycemi* or hyperglycaemi* or chronic renal insufficiency or chronic kidney disease*).mp. (737939)

6. or/1-5 (740559)
7. (MEDLINE or systematic review).tw. or meta analysis.pt. (218964)
8. meta analysis.mp,pt. or review.pt. or search:.tw. (2762318)
9. Weight Reduction Programs/ (1551)
10. (weight adj2 (manag* or reduc* or los*) adj3 (program* or intervention* or strateg* or tier*)).mp. (8893)
11. ((obes* or overweight or BMI) adj2 intervention*).mp. (2915)
12. (weight adj2 (manag* or reduc* or los*)).ti. (17852)
13. 7 and *Weight Reduction Programs/ (57)
14. 9 or 10 or 11 (11353)
15. 6 and 7 and 14 (103)
16. 6 and (7 or 8) and 12 (356)
17. 13 or 15 or 16 (469)
18. remove duplicates from 17 (435)

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Effectiveness of smoking cessation interventions: search for reviews

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

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1. *Hypertension/ (169165)
2. *Atrial Fibrillation/ (39857)
3. *Hyperlipoproteinemia Type II/ or *Hypercholesterolemia/ or *Hyperlipidemias/ (38245)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (151569)
5. *Hyperglycemia/ (15164)
6. *Renal Insufficiency, Chronic/ (13517)
7. 1 or 2 or 3 or 4 or 5 or 6 (415314)
8. (hypertension or high blood pressure or atrial fibrillation or hyperlipid?emi* or hyperlipoprotein?emi* or hypercholesterol?emi* or prediabet* or diabet* or hyperglycemi* or hyperglycaemi* or chronic renal insufficiency or chronic kidney disease*).mp. (1194417)
9. 7 or 8 (1196700)
10. (MEDLINE or systematic review).tw. or meta analysis.pt. (215590)
11. meta analysis.mp,pt. or review.pt. or search:.tw. (2734135)
12. exp ‘tobacco use cessation’/ or smoking cessation/ (27691)
13. (smok* adj3 (stop* or quit* or cessation)).m_titl. (12023)
14. (smok* adj3 (stop* or quit* or cessation)).mp. (41570)
15. (smok* adj5 (intervention* or program* or advice or strateg* or therap* or pharmacotherap*)).mp. (17070)
16. 12 or 14 or 15 (47474)

17. 9 and 10 and 16 (120)
18. 9 and 11 and (*smoking cessation/ or 13) (73)
19. 17 or 18 (180)
20. (cardio-vascular or cardiovascular).m_titl. (118111)
21. exp *Cardiovascular Diseases/ (1961879)
22. (20 or 21) and 11 and (*smoking cessation/ or 13) (160)
23. (20 or 21) and 10 and (*smoking cessation/ or 13) (35)
24. 15 and 22 (68)
25. 17 or 18 or 23 or 24 (251)

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Effectiveness of exercise referral: search for reviews

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:

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1. exp Great Britain/ (369322)
2. (national health service* or nhs*).ti,ab,in. (165812)
3. (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (93953)
4. (gb or ‘g.b.’ or britain* or (british* not ‘british columbia’) or uk or ‘u.k.’ or united kingdom* or (england* not ‘new england’) or northern ireland* or northern irish* or scotland* or scottish* or ((wales or ‘south wales’) not ‘new south wales’) or welsh*).ti,ab,jw,in. (1977648)
5. (bath or ‘bath's’ or ((birmingham not alabama*) or (‘birmingham's’ not alabama*) or bradford or ‘bradford's’ or brighton or ‘brighton's’ or bristol or ‘bristol's’ or carlisle* or ‘carlisle's’ or (cambridge not (massachusetts* or boston* or harvard*)) or (‘cambridge's’ not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or (‘canterbury's’ not zealand*) or chelmsford or ‘chelmsford's’ or chester or ‘chester's’ or chichester or ‘chichester's’ or coventry or ‘coventry's’ or derby or ‘derby's’ or (durham not (carolina* or nc)) or (‘durham's’ not (carolina* or nc)) or ely or ‘ely's’ or exeter or ‘exeter's’ or gloucester or ‘gloucester's’ or hereford or ‘hereford's’ or hull or ‘hull's’ or lancaster or ‘lancaster's’ or leeds* or leicester or ‘leicester's’ or (lincoln not nebraska*) or (‘lincoln's’ not nebraska*) or (liverpool not (new south wales* or nsw)) or (‘liverpool's’ not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or (‘london's’ not (ontario* or ont or toronto*)) or manchester or ‘manchester's’ or (newcastle not (new south wales* or nsw)) or (‘newcastle's’ not (new south wales* or nsw)) or norwich or ‘norwich's’ or nottingham or ‘nottingham's’ or oxford or ‘oxford's’ or peterborough or ‘peterborough's’ or plymouth or ‘plymouth's’ or portsmouth or ‘portsmouth's’ or preston or ‘preston's’ or ripon or ‘ripon's’ or salford or ‘salford's’ or salisbury or ‘salisbury's’ or sheffield or ‘sheffield's’ or southampton or ‘southampton's’ or st albans or stoke or ‘stoke's’ or sunderland or ‘sunderland's’ or truro or ‘truro's’ or

wakefield or ‘wakefield's’ or wells or westminster or ‘westminster's’ or winchester or ‘winchester's’ or wolverhampton or ‘wolverhampton's’ or (worcester not (massachusetts* or boston* or harvard*)) or (‘worcester's’ not (massachusetts* or boston* or harvard*)) or (york not (‘new york*’ or ny or ontario* or ont or toronto*)) or (‘york's’ not (‘new york*’ or ny or ontario* or ont or toronto*))))).ti,ab,in. (1316145)
6. [or/25-27] (0)
7. [or/32-34] (0)
8. Exercise/ (99619)
9. Exercise Therapy/ (37613)
10. (exercise* or physical*).ti,ab. (866012)
11. 8 or 9 or 10 (893580)
12. ‘Referral and Consultation’/ (64825)
13. 11 and 12 (3430)
14. ((physical* or exercise*) adj2 (superv* or subsid* or prescrib* or promot* or program* or intervention* or referral*)).ti,ab. (35029)
15. (‘exercise on prescription’ or exercise referral or ‘physical activity referral’ or supervised exercise).ti,ab. (1728)
16. 13 or 14 or 15 (38210)
17. *Hypertension/ (173425)
18. *Atrial Fibrillation/ (41856)
19. *Hyperlipoproteinemia Type II/ (5408)
20. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (158929)
21. *Hyperglycemia/ (15751)
22. *Renal Insufficiency, Chronic/ (14830)
23. (hypertension or atrial fibrillation or hyperlipidemia or hyperlipidaemia or hyperlipoproteinemia or hyperlipoproteinaemia or hypercholesterolemia or hypercholesterolaemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency).ti,ab. (896768)
24. or/17-23 (981217)
25. 16 and 24 (3338)
26. (MEDLINE or systematic review).tw. or meta analysis.pt. (227891)
27. 25 and 26 (221)
28. limit 27 to yr=‘2012 -Current’ (160)

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Effectiveness of brief advice for diet and physical activity: search for reviews

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:
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1. *Hypertension/ (168822)
2. *Atrial Fibrillation/ (39668)
3. *Hyperlipoproteinemia Type II/ or *Hypercholesterolemia/ or *Hyperlipidemias/ (38142)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (150781)
5. *Hyperglycemia/ (15111)
6. *Renal Insufficiency, Chronic/ (13252)
7. 1 or 2 or 3 or 4 or 5 or 6 (413642)
8. (hypertension or atrial fibrillation or hyperlipidemia or hyperlipoproteinemia or hypercholesterolemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency).ti,ab. (853612)
9. 7 or 8 (953099)
10. (MEDLINE or systematic review).tw. or meta analysis.pt. (213337)
11. making every contact count.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (17)
12. ((brief or opportunists 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 negotiations or guidance or discussions or encouragement or interventions or programs or meetings or sessions)).ti,ab. (32729)
13. (patients adj2 (leaflets or flyers or information or pamphlets or booklets or posters)).ti,ab. (27909)
14. *Patient Education as Topic/ (37596)
15. *Health Education/ (34646)
16. *Health Literacy/ (2687)
17. Directive Counseling/ (2191)
18. pamphlets/ (3771)
19. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (134099)
20. 9 and 19 (12307)
21. 10 and 20 (469)

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Effectiveness of alcohol brief interventions: search for reviews

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
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1. *Hypertension/ (170111)
2. *Atrial Fibrillation/ (40735)
3. *Hyperlipoproteinemia Type II/ or *Hypercholesterolemia/ or *Hyperlipidemias/ (38469)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (152836)
5. *Hyperglycemia/ (15292)
6. *Renal Insufficiency, Chronic/ (13975)
7. 1 or 2 or 3 or 4 or 5 or 6 (419093)
8. (hypertension or high blood pressure or atrial fibrillation or hyperlipid?emi* or hyperlipoprotein?emi* or hypercholesterol?emi* or diabet* or hyperglycemia or hyperglycaemia or chronic renal insufficiency or chronic kidney disease*).mp. (1201974)
9. 7 or 8 (1204650)
10. (MEDLINE or systematic review).tw. or meta analysis.pt. (218964)
11. meta analysis.mp,pt. or review.pt. or search:.tw. (2762318)
12. ABI.mp. (6174)
13. alcohol*.mp. (396187)
14. ((harmful or heavy or excess* or dangerous*) adj2 drinking*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (7336)
15. 13 or 14 (396827)
16. Psychotherapy, Brief/ or brief intervention*.mp. (6564)
17. (brief adj3 (counsel* or motivational interview* or advice or psychotherap* or therap* or intervention*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (11467)
18. (((cognitive or behavio?ral) adj1 (counsel* or therap*)) or psychotherap* or motivational interview*).mp. (115645)
19. exp *Cardiovascular Diseases/ (1981631)
20. (cardio-vascular or cardiovascular).m_titl. (119057)
21. 9 or 19 or 20 (2797676)
22. 16 or 17 or 18 (121777)
23. 15 and 22 (7369)
24. 10 and 23 (297)

25. 16 or 17 (11467)
26. 10 and 15 and 25 (176)
27. 9 and 11 and 15 and 22 (34)
28. 11 and 15 and 21 and 22 (41)
29. 24 or 26 or 27 or 28 (332)
30. 21 and 29 (42)
31. 29 not 30 (290)
32. remove duplicates from 30 (38)
33. remove duplicates from 31 (265)

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Effectiveness of blood pressure self-monitoring: search for reviews

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:

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1. exp Great Britain/ (369322)
2. (national health service* or nhs*).ti,ab,in. (165812)
3. (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (93953)
4. (gb or ‘g.b.’ or britain* or (british* not ‘british columbia’) or uk or ‘u.k.’ or united kingdom* or (england* not ‘new england’) or northern ireland* or northern irish* or scotland* or scottish* or ((wales or ‘south wales’) not ‘new south wales’) or welsh*).ti,ab,jw,in. (1977648)
5. (bath or ‘bath's’ or ((birmingham not alabama*) or (‘birmingham's’ not alabama*) or bradford or ‘bradford's’ or brighton or ‘brighton's’ or bristol or ‘bristol's’ or carlisle* or ‘carlisle's’ or (cambridge not (massachusetts* or boston* or harvard*)) or (‘cambridge's’ not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or (‘canterbury's’ not zealand*) or chelmsford or ‘chelmsford's’ or chester or ‘chester's’ or chichester or ‘chichester's’ or coventry or ‘coventry's’ or derby or ‘derby's’ or (durham not (carolina* or nc)) or (‘durham's’ not (carolina* or nc)) or ely or ‘ely's’ or exeter or ‘exeter's’ or gloucester or ‘gloucester's’ or hereford or ‘hereford's’ or hull or ‘hull's’ or lancaster or ‘lancaster's’ or leeds* or leicester or ‘leicester's’ or (lincoln not nebraska*) or (‘lincoln's’ not nebraska*) or (liverpool not (new south wales* or nsw)) or (‘liverpool's’ not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or (‘london's’ not (ontario* or ont or toronto*)) or manchester or ‘manchester's’ or (newcastle not (new south wales* or nsw)) or (‘newcastle's’ not (new south wales* or nsw)) or norwich or ‘norwich's’ or nottingham or ‘nottingham's’ or oxford or ‘oxford's’ or peterborough or ‘peterborough's’ or plymouth or ‘plymouth's’ or portsmouth or ‘portsmouth's’ or preston or ‘preston's’ or ripon or ‘ripon's’ or salford or ‘salford's’ or salisbury or ‘salisbury's’ or sheffield or ‘sheffield's’ or southampton or ‘southampton's’ or st albans or stoke or ‘stoke's’ or sunderland or ‘sunderland's’ or truro or ‘truro's’ or

wakefield or ‘wakefield's’ or wells or westminster or ‘westminster's’ or winchester or ‘winchester's’ or wolverhampton or ‘wolverhampton's’ or (worcester not (massachusetts* or boston* or harvard*)) or (‘worcester's’ not (massachusetts* or boston* or harvard*)) or (york not (‘new york*’ or ny or ontario* or ont or toronto*)) or (‘york's’ not (‘new york*’ or ny or ontario* or ont or toronto*))))).ti,ab,in. (1316145)
6. (bangor or ‘bangor's’ or cardiff or ‘cardiff's’ or newport or ‘newport's’ or st asaph or ‘st asaph's’ or st davids or swansea or ‘swansea's’).ti,ab,in. (49988)
7. 1 or 2 or 3 or 4 or 5 or 6 (2493216)
8. *Blood Pressure Monitors/ (1437)
9. *Blood Pressure Determination/is [Instrumentation] (1970)
10. 8 or 9 (3277)
11. (watchbp or ‘watch bp’).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (39)
12. microlife.af. (121)
13. ((blood pressure or BP) adj3 (home or self)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3487)
14. (self-monitoring or ‘home monitoring’).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (12896)
15. ‘self check*’.mp. (122)
16. *Self Care/ (17905)
17. exp Hypertension/ (259382)
18. (‘high blood pressure’ or hypertens*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (506623)
19. 17 or 18 (506623)
20. 8 or 9 or 11 or 12 or 13 or 14 or 15 or 16 (35578)
21. 19 and 20 (4529)
22. (MEDLINE or systematic review).tw. or meta analysis.pt. (227891)
23. 21 and 22 (129)
24. 7 and 23 (41)

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Effectiveness of pharmacy medicine use review: search for reviews

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
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1. *Hypertension/ (169154)
2. *Atrial Fibrillation/ (39847)
3. *Hyperlipoproteinemia Type II/ (5254)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (151545)
5. *Hyperglycemia/ (15164)
6. *Renal Insufficiency, Chronic/ (13504)
7. (hypertension or high blood pressure or atrial fibrillation or hyperlipidemia or hyperlipidaemia or hyperlipoproteinemia or hyperlipoproteinaemia or hypercholesterolemia or hypercholesterolaemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency or chronic kidney disease*).mp. (1116112)
8. or/1-7 (1118947)
9. exp Antihypertensive Agents/ (259786)
10. exp Hypolipidemic Agents/ (133939)
11. exp Anticoagulants/ (212662)
12. exp Hypoglycemic Agents/ (241355)
13. (anti-hypertensive or antihypertensive or ACE inhibitor* or diuretic* or calcium channel blocker* or angiotensin II receptor* antagonist* or adrenergic receptor antagonist* or vasodilator* or benzodiazepine* or renin inhibitor* or aldosterone receptor* or endothelin receptor*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (296673)
14. (statin* or Atorvastatin or fluvastatin or lovastatin or pitavastatin or pravastatin or rosuvastatin or simvastatin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (55393)
15. (vitamin b3 or niacin or nicotinic acid*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (21989)
16. (fibrate* or Gemfibrozil or fenofibr*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (7665)

17. (2-Azetidione* or ezetimibe).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3000)
18. (anticoagulant* or anti-coagulant* or NOAC* or DOAC* or heparin or vit* k antagonis* or direct thrombin inhibitor* or factor Xa inhibitor* or warfarin or Coumadin or Jantoven or enoxaparin or dalteparin or lovenox or fragmin or bivalirudin or Angiomax or argatroban or Acova or dabigatran or Pradaxa or antithrombin III or Thrombate III or apixaban or Eliquis or fondaparinux or Arixtra or rivaroxaban or Xarelto or edoxaban or Savaysa).mp. (191745)
19. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or HMG-CoA reductase inhibitor*.mp. (38802)
20. (antidiabetic* or anti-diabetic* or hypolipid?emic* or hypoglyc?emic*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (97281)
21. (Insulin or exenatide or liraglutide or pramlintide).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (402936)
22. metformin.mp. (18100)
23. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (1298114)
24. (pharmacist* or pharmacy or pharmacies or community).mp. (559496)
25. *Medication Adherence/ (9190)
26. ‘medicine use review*’.mp. (9)
27. ((medicine* or drug* or medication) adj2 (‘use’ or using or adher* or compliance)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (118650)
28. meta analysis.mp,pt. or review.pt. or search:.tw. (2732850)
29. 24 and 27 (15261)
30. (8 or 23) and 29 (2544)
31. 28 and 30 (186)
32. 8 or 23 (2047348)
33. 25 and 32 (2255)
34. 28 and 33 (228)
35. 31 or 34 (376)
36. remove duplicates from 35 (349)

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Effectiveness of pharmacy medicine use review: search for RCTs

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:
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1. *Hypertension/ (173425)
2. *Atrial Fibrillation/ (41856)
3. *Hyperlipoproteinemia Type II/ (5408)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (158929)
5. *Hyperglycemia/ (15751)
6. *Renal Insufficiency, Chronic/ (14830)
7. (hypertension or high blood pressure or atrial fibrillation or hyperlipidemia or hyperlipidaemia or hyperlipoproteinemia or hyperlipoproteinaemia or hypercholesterolemia or hypercholesterolaemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency or chronic kidney disease*).mp. (1157155)
8. or/1-7 (1160189)
9. exp Antihypertensive Agents/ (265534)
10. exp Hypolipidemic Agents/ (138385)
11. exp Anticoagulants/ (218521)
12. exp Hypoglycemic Agents/ (248347)
13. (anti-hypertensive or antihypertensive or ACE inhibitor* or diuretic* or calcium channel blocker* or angiotensin II receptor* antagonist* or adrenergic receptor antagonist* or vasodilator* or benzodiazepine* or renin inhibitor* or aldosterone receptor* or endothelin receptor*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (305315)
14. (statin* or Atorvastatin or fluvastatin or lovastatin or pitavastatin or pravastatin or rosuvastatin or simvastatin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (57978)
15. (vitamin b3 or niacin or nicotinic acid*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (22342)
16. (fibrate* or Gemfibrozil or fenofibr*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (8011)

17. (2-Azetidione* or ezetimibe).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3180)
18. (anticoagulant* or anti-coagulant* or NOAC* or DOAC* or heparin or vit* k antagonis* or direct thrombin inhibitor* or factor Xa inhibitor* or warfarin or Coumadin or Jantoven or enoxaparin or dalteparin or lovenox or fragmin or bivalirudin or Angiomax or argatroban or Acova or dabigatran or Pradaxa or antithrombin III or Thrombate III or apixaban or Eliquis or fondaparinux or Arixtra or rivaroxaban or Xarelto or edoxaban or Savaysa).mp. (197777)
19. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or HMG-CoA reductase inhibitor*.mp. (40737)
20. (antidiabetic* or anti-diabetic* or hypolipidemic* or hypoglycemic*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (101680)
21. (Insulin or exenatide or liraglutide or pramlintide).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (416601)
22. metformin.mp. (19179)
23. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (1336833)
24. (pharmacist* or pharmacy or pharmacies or community).mp. (580013)
25. *Medication Adherence/ (9831)
26. ‘medicine use review*’.mp. (11)
27. ((medicine* or drug* or medication) adj2 (‘use’ or using or adher* or compliance)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (123823)
28. meta analysis.mp,pt. or review.pt. or search:.tw. (2850639)
29. 24 and 27 (16006)
30. (8 or 23) and 29 (2703)
31. 28 and 30 (208)
32. 8 or 23 (2113468)
33. 25 and 32 (2428)
34. 28 and 33 (256)
35. 31 or 34 (423)
36. remove duplicates from 35 (369)
37. 10 or 11 or 12 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (904929)
38. 25 or 26 or 27 (123823)
39. 24 and 38 (16006)
40. 10 or 11 or 14 or 15 or 17 or 18 or 19 or 20 or 21 or 22 (891637)

41. 39 and 40 (1052)
42. randomized controlled trial.pt. or randomized controlled trial.mp. (537511)
43. 41 and 42 (119)
44. 37 and 39 (1054)
45. 42 and 44 (121)
46. (pharmacist* or pharmacy or pharmacies).mp. (79225)
47. 38 and 46 (7301)
48. 37 and 47 (779)
49. 42 and 48 (93)

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Effectiveness of annual review: search for reviews

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:
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1. *Hypertension/ (168941)
2. *Atrial Fibrillation/ (39730)
3. *Hyperlipoproteinemia Type II/ (5215)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (151024)
5. *Hyperglycemia/ (15134)
6. *Renal Insufficiency, Chronic/ (13324)
7. (hypertension or atrial fibrillation or hyperlipidemia or hyperlipidaemia or hyperlipoproteinemia or hyperlipoproteinaemia or hypercholesterolemia or hypercholesterolaemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency).ti,ab. (861013)
8. or/1-7 (942597)
9. (annual review or annual medication review or monitoring or audit or follow-up).ti,ab. (1292104)
10. (advice or education or lifestyle or diet or exercise or smoking).ti,ab. (1128555)
11. (insulin regimen* or hba1c test or eGFR creatinine test or ACR test).ti,ab. (1665)
12. ((anti-coagulants or anticoagulants or blood pressure or medication blood sugar monitoring or blood glucose or bmi or body mass index or medicine* or medication*) adj3 (check or monitor* or review* or observation* adherence or adhere or comply or compliance or concordance or uptake or side effect*or stroke risk*)).ti,ab. (31506)
13. *Patient Education as Topic/ or *mass screening/ or *preventive health services/ or *health promotion/ or exp *Patient Compliance/ (169808)
14. or/9-13 (2452533)
15. *Primary Health Care/ or *Primary prevention/ or *Physicians, Family/ or *general practitioners/ or *physicians primary care/ or exp *general Practice/ or *primary care

nursing/ or *Public health nursing/ or *Family nursing/ or *house calls/ or *community pharmacy services/ (123799)
16. (practice nurses or primary care or primary healthcare or primary health care or gps or general practitioners or family physicians or health visitors or pharmacists or health trainers).ti,ab. (338997)
17. ((family or general or physicians or doctors) adj practices).ti,ab. (49975)
18. or/15-17 (414245)
19. 8 and 14 and 18 (12018)
20. (MEDLINE or systematic review).tw. or meta analysis.pt. (214320)
21. 19 and 20 (327)

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Effectiveness of NHS Health Checks: search for reviews

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
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1. *Hypertension/ (169154)
2. *Atrial Fibrillation/ (39847)
3. *Hyperlipoproteinemia Type II/ (5254)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (151545)
5. *Hyperglycemia/ (15164)
6. *Renal Insufficiency, Chronic/ (13504)
7. (hypertension or high blood pressure or atrial fibrillation or hyperlipidemia or hyperlipidaemia or hyperlipoproteinemia or hyperlipoproteinaemia or hypercholesterolemia or hypercholesterolaemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency or chronic kidney disease*).mp. (1116112)
8. or/1-7 (1118947)
9. NHS health check*.mp. (119)
10. *National Health Programs/ or *State Medicine/ (47117)
11. (NHS or national health service or general practi* or GP* or family doctor*).mp. (286577)
12. (‘health check*’ or ‘check up’ or checkup or ‘regular check*’).mp. (11826)
13. Mass Screening/ (98022)
14. meta analysis.mp,pt. or review.pt. or search:.tw. (2732850)
15. 9 and 14 (4)
16. 8 and (10 or 11) and (12 or 13) and 14 (65)
17. (10 or 11) and 12 and 14 (55)
18. 15 or 16 or 17 (111)

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Effectiveness of NHS Health Checks: search for observational studies

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:
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1. *Hypertension/ (173425)
2. *Atrial Fibrillation/ (41856)
3. *Hyperlipoproteinemia Type II/ (5408)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (158929)
5. *Hyperglycemia/ (15751)
6. *Renal Insufficiency, Chronic/ (14830)
7. (hypertension or high blood pressure or atrial fibrillation or hyperlipidemia or hyperlipidaemia or hyperlipoproteinemia or hyperlipoproteinaemia or hypercholesterolemia or hypercholesterolaemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency or chronic kidney disease*).mp. (1157155)
8. or/1-7 (1160189)
9. NHS health check*.mp. (123)
10. *National Health Programs/ or *State Medicine/ (47825)
11. (NHS or national health service or general practi* or GP* or family doctor*).mp. (296114)
12. (‘health check*’ or ‘check up’ or checkup or ‘regular check*’).mp. (12412)
13. Mass Screening/ (101024)
14. meta analysis.mp,pt. or review.pt. or search:.tw. (2850639)
15. 9 and 14 (6)
16. 8 and (10 or 11) and (12 or 13) and 14 (68)
17. (10 or 11) and 12 and 14 (59)
18. 15 or 16 or 17 (117)
19. 9 or 10 or 11 or 12 or 13 (440835)
20. 8 and 19 (26284)
21. 9 or 11 (296114)
22. 8 and 9 (37)
23. ‘NHS Health Check Programme’.kw. (1)
24. ‘NHS health check’.kw. (6)
25. national health service health check.ti,ab. (11)
26. 11 and 12 (670)
27. 9 or 23 or 24 or 25 or 26 (670)
28. 8 and 27 (135)
29. Epidemiologic studies/ (8323)
30. exp case control studies/ (1003048)
31. exp cohort studies/ (1913617)

32. Case control.tw. (117067)
33. (cohort adj (study or studies)).tw. (165543)
34. Cohort analys.tw. (6642)
35. (Follow up adj (study or studies)).tw. (48803)
36. (observational adj (study or studies)).tw. (86565)
37. Longitudinal.tw. (220429)
38. Retrospective.tw. (454254)
39. Cross sectional.tw. (293226)
40. Cross-sectional studies/ (285879)
41. or/29-40 (2792133)
42. randomized controlled trial.pt. or randomized controlled trial.mp. (537511)
43. 28 and 42 (15)
44. 28 and 41 (52)
45. 43 or 44 (63)
46. limit 45 to yr=‘2010 -Current’ (39)
47. clinical trial.mp. or clinical trial.pt. or random:.mp. or tu.xs. (5696057)
48. 28 and 47 (47)
49. 44 or 48 (83)
50. limit 49 to yr=‘2010 -Current’ (53)

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Effectiveness of opportunistic detection: search for reviews

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---

1. *Hypertension/ (169154)
2. *Atrial Fibrillation/ (39847)
3. *Hyperlipoproteinemia Type II/ (5254)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (151545)
5. *Hyperglycemia/ (15164)
6. *Renal Insufficiency, Chronic/ (13504)
7. (hypertension or high blood pressure or atrial fibrillation or hyperlipidemia or hyperlipidaemia or hyperlipoproteinemia or hyperlipoproteinaemia or hypercholesterolemia or hypercholesterolaemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency or chronic kidney disease*).mp. (1116112)
8. or/1-7 (1118947)
9. (((opportunistic* or symptomatic* or non-routine) adj3 (screen* or detect* or test* or diagnos* or strateg* or program*)) or case-finding).mp. (11866)
10. GRASP-AF.mp. (5)

11. watch bp.mp. (3)
12. alivecor.mp. (26)
13. (pulse adj2 (palpation* or check*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (285)
14. ((blood pressure adj2 (check* or test*)) and (community or pharmacy or pharmacist* or pharmacies or GP or general practi* or primary care)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (176)
15. 9 or 10 or 11 or 12 or 13 or 14 (12339)
16. meta analysis.mp,pt. or review.pt. or search:.tw. (2732850)
17. 8 and 15 and 16 (194)
18. remove duplicates from 17 (182)

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Effectiveness of opportunistic detection: search for RCTs

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:
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1. *Hypertension/ (173425)
2. *Atrial Fibrillation/ (41856)
3. *Hyperlipoproteinemia Type II/ (5408)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (158929)
5. *Hyperglycemia/ (15751)
6. *Renal Insufficiency, Chronic/ (14830)
7. (hypertension or high blood pressure or atrial fibrillation or hyperlipidemia or hyperlipidaemia or hyperlipoproteinemia or hyperlipoproteinaemia or hypercholesterolemia or hypercholesterolaemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency or chronic kidney disease*).mp. (1157155)
8. or/1-7 (1160189)
9. (((opportunistic* or symptomatic* or non-routine) adj3 (screen* or detect* or test* or diagnos* or strateg* or program*)) or case-finding).mp. (12260)
10. GRASP-AF.mp. (5)
11. watch bp.mp. (3)
12. alivecor.mp. (26)
13. (pulse adj2 (palpation* or check*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol

supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (291)

14. ((blood pressure adj2 (check* or test*)) and (community or pharmacy or pharmacist* or pharmacies or GP or general practi* or primary care)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (180)
15. primis.mp. (25)
16. 9 or 10 or 11 or 12 or 13 or 14 or 15 (12767)
17. 8 and 16 (1122)
18. exp Great Britain/ (369322)
19. (national health service* or nhs*).ti,ab,in. (165812)
20. (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (93953)
21. (gb or ‘g.b.’ or britain* or (british* not ‘british columbia’) or uk or ‘u.k.’ or united kingdom* or (england* not ‘new england’) or northern ireland* or northern irish* or scotland* or scottish* or ((wales or ‘south wales’) not ‘new south wales’) or welsh*).ti,ab,jw,in. (1977648)
22. (bath or ‘bath's’ or ((birmingham not alabama*) or (‘birmingham's’ not alabama*) or bradford or ‘bradford's’ or brighton or ‘brighton's’ or bristol or ‘bristol's’ or carlisle* or ‘carlisle's’ or (cambridge not (massachusetts* or boston* or harvard*)) or (‘cambridge's’ not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or (‘canterbury's’ not zealand*) or chelmsford or ‘chelmsford's’ or chester or ‘chester's’ or chichester or ‘chichester's’ or coventry or ‘coventry's’ or derby or ‘derby's’ or (durham not (carolina* or nc)) or (‘durham's’ not (carolina* or nc)) or ely or ‘ely's’ or exeter or ‘exeter's’ or gloucester or ‘gloucester's’ or hereford or ‘hereford's’ or hull or ‘hull's’ or lancaster or ‘lancaster's’ or leeds* or leicester or ‘leicester's’ or (lincoln not nebraska*) or (‘lincoln's’ not nebraska*) or (liverpool not (new south wales* or nsw)) or (‘liverpool's’ not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or (‘london's’ not (ontario* or ont or toronto*)) or manchester or ‘manchester's’ or (newcastle not (new south wales* or nsw)) or (‘newcastle's’ not (new south wales* or nsw)) or norwich or ‘norwich's’ or nottingham or ‘nottingham's’ or oxford or ‘oxford's’ or peterborough or ‘peterborough's’ or plymouth or ‘plymouth's’ or portsmouth or ‘portsmouth's’ or preston or ‘preston's’ or ripon or ‘ripon's’ or salford or ‘salford's’ or salisbury or ‘salisbury's’ or sheffield or ‘sheffield's’ or southampton or ‘southampton's’ or st albans or stoke or ‘stoke's’ or sunderland or ‘sunderland's’ or truro or ‘truro's’ or wakefield or ‘wakefield's’ or wells or westminster or ‘westminster's’ or winchester or ‘winchester's’ or wolverhampton or ‘wolverhampton's’ or (worcester not (massachusetts* or boston* or harvard*)) or (‘worcester's’ not (massachusetts* or boston* or harvard*)) or (york not (‘new york*’ or ny or ontario* or ont or toronto*)) or (‘york's’ not (‘new york*’ or ny or ontario* or ont or toronto*))))).ti,ab,in. (1316145)

23. (bangor or ‘bangor's’ or cardiff or ‘cardiff's’ or newport or ‘newport's’ or st asaph or ‘st asaph's’ or st davids or swansea or ‘swansea's’).ti,ab,in. (49988)
24. 18 or 19 or 20 or 21 or 22 or 23 (2493216)
25. Economics/ (27566)
26. exp ‘costs and cost analysis’/ (230239)
27. Economics, Dental/ (1908)
28. exp economics, hospital/ (23906)
29. Economics, Medical/ (9246)
30. Economics, Nursing/ (4020)
31. Economics, Pharmaceutical/ (3412)
32. (economics or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomics).ti,ab. (703961)
33. (expenditures not energy).ti,ab. (26984)
34. value for money.ti,ab. (1519)
35. budgets.ti,ab. (26883)
36. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (852259)
37. ((energy or oxygen) adj cost).ti,ab. (4001)
38. (metabolic adj cost).ti,ab. (1319)
39. ((energy or oxygen) adj expenditure).ti,ab. (24080)
40. 37 or 38 or 39 (28398)
41. 36 not 40 (845717)
42. letter.pt. (1056943)
43. editorial.pt. (480356)
44. historical article.pt. (361818)
45. or/42-44 (1880584)
46. 41 not 45 (810833)
47. exp animals/ not humans/ (4816906)
48. 46 not 47 (759740)
49. bmj.jn. (76249)
50. ‘cochrane database of systematic reviews’.jn. (14838)
51. health technology assessment winchester england.jn. (1313)
52. or/49-51 (92400)
53. 48 not 52 (753504)
54. 17 and 24 and 53 (42)
55. limit 54 to yr=‘2010 -Current’ (22)
56. 16 and 24 and 53 (343)
57. limit 56 to yr=‘2010 -Current’ (172)
58. (hyperlipidemia or hyperlipidaemia or hyperlipoproteinemia or hyperlipoproteinaemia or hypercholesterolemia or hypercholesterolaemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency or chronic kidney disease*).mp. (702158)
59. 3 or 4 or 5 or 6 or 58 (705519)
60. randomized controlled trial.pt. or randomized controlled trial.mp. (537511)

61. 16 and 59 (693)
62. 60 and 61 (35)
63. clinical trial.mp. or clinical trial.pt. or random:.mp. or tu.xs. (5696057)
64. 61 and 63 (208)
65. limit 64 to yr='2010 -Current' (101)
66. limit 61 to yr='2010 -Current' (337)
67. 24 and 64 (38)
68. 24 and 64 (38)
69. limit 68 to yr='2010 -Current' (24)

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Cost-effectiveness review search terms

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:
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1. *Hypertension/ (170345)
2. *Atrial Fibrillation/ (40974)
3. *Hyperlipoproteinemia Type II/ (5307)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (153493)
5. *Hyperglycemia/ (15340)
6. *Renal Insufficiency, Chronic/ (14132)
7. (hypertension or high blood pressure or atrial fibrillation or hyperlipidemia or hyperlipidaemia or hyperlipoproteinemia or hyperlipoproteinaemia or hypercholesterolemia or hypercholesterolaemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency or chronic kidney disease*).mp. (1131206)
8. or/1-7 (1134132)
9. (((opportunistic* or symptomatic* or non-routine) adj3 (screen* or detect* or test* or diagnos* or strateg* or program*)) or case-finding).mp. (12041)
10. GRASP-AF.mp. (5)
11. 1watch bp.mp. (3)
12. alivecor.mp. (24)
13. (pulse adj2 (palpation* or check*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (288)
14. ((blood pressure adj2 (check* or test*)) and (community or pharmacy or pharmacist* or pharmacies or GP or general practi* or primary care)).mp. [mp=title, abstract, original title, name of substance word, subject heading word,

keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (178)
15. primis.mp. (23)
16. 9 or 10 or 11 or 12 or 13 or 14 or 15 (12539)
17. 8 and 16 (1097)
18. exp Great Britain/ (365947)
19. (national health service* or nhs*).ti,ab,in. (162204)
20. (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (93204)
21. (gb or ‘g.b.’ or britain* or (british* not ‘british columbia’) or uk or ‘u.k.’ or united kingdom* or (england* not ‘new england’) or northern ireland* or northern irish* or scotland* or scottish* or ((wales or ‘south wales’) not ‘new south wales’) or welsh*).ti,ab,jw,in. (1946828)
22. (bath or ‘bath's’ or ((birmingham not alabama*) or (‘birmingham's’ not alabama*) or bradford or ‘bradford's’ or brighton or ‘brighton's’ or bristol or ‘bristol's’ or carlisle* or ‘carlisle's’ or (cambridge not (massachusetts* or boston* or harvard*)) or (‘cambridge's’ not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or (‘canterbury's’ not zealand*) or chelmsford or ‘chelmsford's’ or chester or ‘chester's’ or chichester or ‘chichester's’ or coventry or ‘coventry's’ or derby or ‘derby's’ or (durham not (carolina* or nc)) or (‘durham's’ not (carolina* or nc)) or ely or ‘ely's’ or exeter or ‘exeter's’ or gloucester or ‘gloucester's’ or hereford or ‘hereford's’ or hull or ‘hull's’ or lancaster or ‘lancaster's’ or leeds* or leicester or ‘leicester's’ or (lincoln not nebraska*) or (‘lincoln's’ not nebraska*) or (liverpool not (new south wales* or nsw)) or (‘liverpool's’ not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or (‘london's’ not (ontario* or ont or toronto*)) or manchester or ‘manchester's’ or (newcastle not (new south wales* or nsw)) or (‘newcastle's’ not (new south wales* or nsw)) or norwich or ‘norwich's’ or nottingham or ‘nottingham's’ or oxford or ‘oxford's’ or peterborough or ‘peterborough's’ or plymouth or ‘plymouth's’ or portsmouth or ‘portsmouth's’ or preston or ‘preston's’ or ripon or ‘ripon's’ or salford or ‘salford's’ or salisbury or ‘salisbury's’ or sheffield or ‘sheffield's’ or southampton or ‘southampton's’ or st albans or stoke or ‘stoke's’ or sunderland or ‘sunderland's’ or truro or ‘truro's’ or wakefield or ‘wakefield's’ or wells or westminster or ‘westminster's’ or winchester or ‘winchester's’ or wolverhampton or ‘wolverhampton's’ or (worcester not (massachusetts* or boston* or harvard*)) or (‘worcester's’ not (massachusetts* or boston* or harvard*)) or (york not (‘new york*’ or ny or ontario* or ont or toronto*)) or (‘york's’ not (‘new york*’ or ny or ontario* or ont or toronto*))))).ti,ab,in. (1291536)
23. (bangor or ‘bangor's’ or cardiff or ‘cardiff's’ or newport or ‘newport's’ or st asaph or ‘st asaph's’ or st davids or swansea or ‘swansea's’).ti,ab,in. (48977)
24. 18 or 19 or 20 or 21 or 22 or 23 (2457108)
25. Economics/ (27500)
26. exp ‘costs and cost analysis’/ (225520)

27. Economics, Dental/ (1905)
28. exp economics, hospital/ (23631)
29. Economics, Medical/ (9207)
30. Economics, Nursing/ (4020)
31. Economics, Pharmaceutical/ (3005)
32. (economics or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomics).ti,ab. (688481)
33. (expenditures not energy).ti,ab. (26362)
34. value for money.ti,ab. (1464)
35. budgets.ti,ab. (26436)
36. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (835350)
37. ((energy or oxygen) adj cost).ti,ab. (3952)
38. (metabolic adj cost).ti,ab. (1293)
39. ((energy or oxygen) adj expenditure).ti,ab. (23595)
40. 37 or 38 or 39 (27849)
41. 36 not 40 (828900)
42. letter.pt. (1036662)
43. editorial.pt. (471334)
44. historical article.pt. (358490)
45. or/42-44 (1848210)
46. 41 not 45 (794500)
47. exp animals/ not humans/ (4750449)
48. 46 not 47 (744895)
49. bmj.jn. (75781)
50. ‘cochrane database of systematic reviews’.jn. (14642)
51. health technology assessment winchester england.jn. (1298)
52. or/49-51 (91721)
53. 48 not 52 (738715)
54. 17 and 24 and 53 (41)
55. limit 54 to yr=‘2010 -Current’ (22)
56. 16 and 24 and 53 (337)
57. limit 56 to yr=‘2010 -Current’ (168)
58. from 55 keep 1-22 (22)
59. from 57 keep 1-168 (168)
60. *Atrial Fibrillation/ (40974)
61. *Renal Insufficiency, Chronic/ (14132)
62. models, economic/ (9259)
63. Cost-Benefit Analysis/ (77322)
64. (cost effectiveness or cost utility or economic analysis).ti,ab. (57434)
65. 60 or 61 (54951)
66. 62 or 63 or 64 (109980)
67. 65 and 66 (515)
68. limit 67 to yr=‘2007 -Current’ (412)

69. (familial hypercholesterolemia or familial hypercholesterolaemia).ti,ab. (6159)
70. (hyperlipoproteinemia or hyperlipoproteinaemia).ti,ab. (4149)
71. 69 or 70 (10132)
72. or 71 (11350)
73. 66 and 72 (104)
74.

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Model review search terms

Search terms for AF and CKD Model Review (combined)

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:

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1. *Hypertension/ (164987)
2. *Atrial Fibrillation/ (38591)
3. *Hyperlipoproteinemia Type II/ (5010)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (145660)
5. *Hyperglycemia/ (14647)
6. *Renal Insufficiency, Chronic/ (12850)
7. 1 or 2 or 3 or 4 or 5 or 6 (372859)
8. (risk* or prevent* or reduce* or protect* or limit* or control*).ti. (1469089)
9. early detection.ti,ab. (51943)
10. *risk reduction behavior/ or *risk factors/ (5335)
11. 8 or 9 or 10 (1518464)
12. 7 and 11 (54064)
13. (MEDLINE or systematic review).tw. or meta analysis.pt. (204996)
14. 12 and 13 (2037)
15. models, economic/ (8687)
16. Cost-Benefit Analysis/ (73590)
17. (cost effectiveness or cost utility or economic analysis).ti,ab. (54178)
18. 2 or 6 (51302)
19. 15 or 16 or 17 (104664)
20. 18 and 19 (483)
21. limit 20 to yr=‘2007 -Current’ (385)

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Search terms for FH model review

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

Search Strategy:

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1. *Hypertension/ (170345)
2. *Atrial Fibrillation/ (40974)
3. *Hyperlipoproteinemia Type II/ (5307)
4. *Diabetes Mellitus, Type 1/ or *Prediabetic State/ or *Diabetes Mellitus, Type 2/ (153493)
5. *Hyperglycemia/ (15340)
6. *Renal Insufficiency, Chronic/ (14132)
7. (hypertension or high blood pressure or atrial fibrillation or hyperlipidemia or hyperlipidaemia or hyperlipoproteinemia or hyperlipoproteinaemia or hypercholesterolemia or hypercholesterolaemia or diabetes or hyperglycemia or hyperglycaemia or chronic renal insufficiency or chronic kidney disease*).mp. (1131206)
8. or/1-7 (1134132)
9. (((opportunistic* or symptomatic* or non-routine) adj3 (screen* or detect* or test* or diagnos* or strateg* or program*)) or case-finding).mp. (12041)
10. GRASP-AF.mp. (5)
11. 1watch bp.mp. (3)
12. alivecor.mp. (24)
13. (pulse adj2 (palpation* or check*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (288)
14. ((blood pressure adj2 (check* or test*)) and (community or pharmacy or pharmacist* or pharmacies or GP or general practi* or primary care)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (178)
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19. (national health service* or nhs*).ti,ab,in. (162204)
20. (english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab. (93204)
21. (gb or ‘g.b.’ or britain* or (british* not ‘british columbia’) or uk or ‘u.k.’ or united kingdom* or (england* not ‘new england’) or northern ireland* or northern irish* or scotland* or scottish* or ((wales or ‘south wales’) not ‘new south wales’) or welsh*).ti,ab,jw,in. (1946828)
22. (bath or ‘bath's’ or ((birmingham not alabama*) or (‘birmingham's’ not alabama*) or bradford or ‘bradford's’ or brighton or ‘brighton's’ or bristol or ‘bristol's’ or carlisle* or ‘carlisle's’ or (cambridge not (massachusetts* or boston* or harvard*)) or

(‘cambridge's’ not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or (‘canterbury's’ not zealand*) or chelmsford or ‘chelmsford's’ or chester or ‘chester's’ or chichester or ‘chichester's’ or coventry or ‘coventry's’ or derby or ‘derby's’ or (durham not (carolina* or nc)) or (‘durham's’ not (carolina* or nc)) or ely or ‘ely's’ or exeter or ‘exeter's’ or gloucester or ‘gloucester's’ or hereford or ‘hereford's’ or hull or ‘hull's’ or lancaster or ‘lancaster's’ or leeds* or leicester or ‘leicester's’ or (lincoln not nebraska*) or (‘lincoln's’ not nebraska*) or (liverpool not (new south wales* or nsw)) or (‘liverpool's’ not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or (‘london's’ not (ontario* or ont or toronto*)) or manchester or ‘manchester's’ or (newcastle not (new south wales* or nsw)) or (‘newcastle's’ not (new south wales* or nsw)) or norwich or ‘norwich's’ or nottingham or ‘nottingham's’ or oxford or ‘oxford's’ or peterborough or ‘peterborough's’ or plymouth or ‘plymouth's’ or portsmouth or ‘portsmouth's’ or preston or ‘preston's’ or ripon or ‘ripon's’ or salford or ‘salford's’ or salisbury or ‘salisbury's’ or sheffield or ‘sheffield's’ or southampton or ‘southampton's’ or st albans or stoke or ‘stoke's’ or sunderland or ‘sunderland's’ or truro or ‘truro's’ or wakefield or ‘wakefield's’ or wells or westminster or ‘westminster's’ or winchester or ‘winchester's’ or wolverhampton or ‘wolverhampton's’ or (worcester not (massachusetts* or boston* or harvard*)) or (‘worcester's’ not (massachusetts* or boston* or harvard*)) or (york not (‘new york*’ or ny or ontario* or ont or toronto*)) or (‘york's’ not (‘new york*’ or ny or ontario* or ont or toronto*))))).ti,ab,in. (1291536)

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