Appendix 1: Organisations funding or preparing systematic reviews in the UK and globally

This section presents an overview of the key organisations both funding and producing SRs, health technology assessments, technology appraisals and guidelines in the UK and globally.

NIHR Programmes

NIHR Systematic Reviews (SR) Programme

The National Institute for Health Research (NIHR) Systematic Reviews Programme is comprised of two funding streams: Cochrane Incentive Awards and Cochrane Programme Grants; and infrastructure funding for a number of research entities:

- Cochrane UK and Cochrane Review Groups
- Complex Reviews Support Unit (CRSU)
- Technology Assessment Review (TAR) teams[3-5]
- Additional funding contributions are received from Health and Care Research Wales, Health and Social Care Research & Development (HSC R&D) in Northern Ireland, and case by case contributions from the Chief Scientist Office (CSO) in Scotland.[10, 3, 11, 12,13]

Funding

The NIHR SR Programme has an annual budget of £13.6 million to support:

- update of existing systematic reviews
- production of new systematic reviews

The annual budget is allocated to the following streams:

- Project Funding Streams approx. £1.3m
- CRG infrastructure approx. £3.2m
- Cochrane UK infrastructure approx. £0.8m
- CRSU approx. £0.4m
- TARs approx. £8m

NIHR Cochrane Programme Grant Scheme

The NIHR Cochrane Programme Grant scheme[14] was established to provide high quality SRs which are of benefit directly to users of the NHS in England. Calls for funding run every three years (2007, 2010 and 2013), with plans to launch the fourth round in autumn 2016.

The Cochrane Programme Grant scheme is open to all NHS organisations and universities in England in collaboration with an appropriate Cochrane Co-ordinating Editor or Editorial Base.

Areas covered are diverse and have included dementia, cardiovascular disease, public health and organisation of care in the NHS. Grants are awarded to support both new reviews and updates to existing reviews, funding is awarded with the expectation that the reviews will be

Funding

The Cochrane Programme Grant scheme supplements existing Cochrane infrastructure where applications are successful, to support a substantial and coherent programme of work. Funding is allocated on a banding, ranging from approximately £102,000 to £195,000 per annum.

Awards of £220,000 - £420,000 over three years,[5] with a total budget of £1.2 million a year.[9]

completed. Bidders for this funding must put forward a case outlining reasons why their particular topic is of importance to the NHS, together with supporting evidence.

At present there are 140 completed projects in the SR Programme portfolio and 26 active projects.[15] Of these 166 review projects, 134 relate to Cochrane Incentive Awards, 23 to Cochrane Programme Grants and nine to Cochrane NHS Engagement Awards.[15]

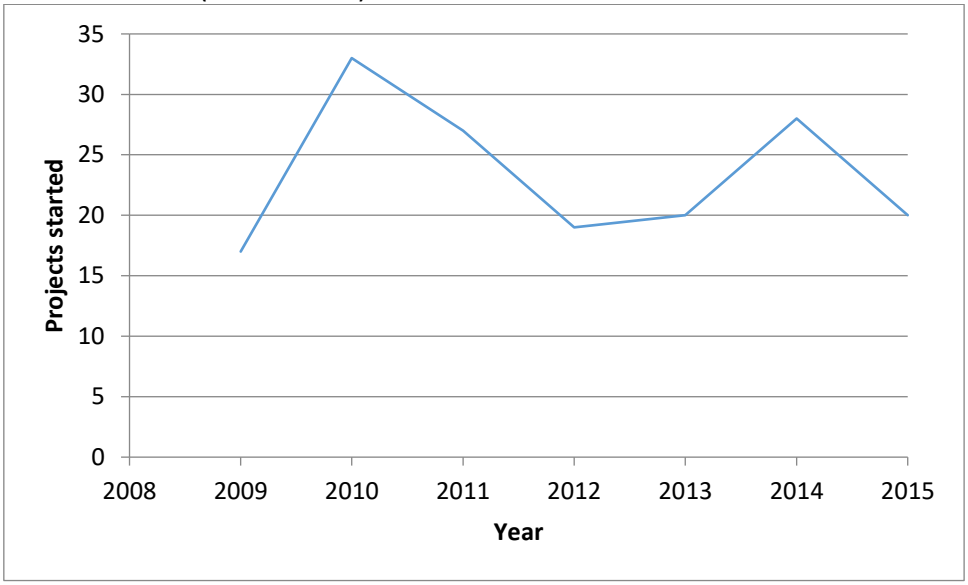
Table 1: Number of NIHR-funded SR projects; including Cochrane Programme Grant Scheme Projects, Cochrane Incentive Awards and Cochrane NHS Engagement Awards (2009-2016/02)[15] (Data compiled 9.2.16)

Type of funding	In Progress	Complete	Total number of awards
Cochrane Programme Grants	12	11	23
Cochrane Incentive Awards	14	120	134
Cochrane NHS Engagement Awards	0	9	9
Total	**26**	**140**	**166**

The purpose of Cochrane NHS Engagement Awards is to encourage development of innovative approaches to strengthen engagement between those who produce Cochrane SRs and users or potential users of SRs within the NHS.[16] Seventeen applications for the Engagement Awards funding were received, and nine projects were subsequently funded at a total cost of £0.8 million; all projects were completed by October 2012.[16]

One example of lasting impact from an Engagement Award is Project Cochrane Crowd.[17] This project is funded by an NIHR Engagement Award, and based on pilot work of the ALOIS Project where the methodology was tried and evaluated in trials for dementia.[16, 18] Project Cochrane Crowd[17] is a citizen science project that encourages members of the public to screen Embase RCT records for inclusion in Cochrane CENTRAL.[19]. Its achievements can be found at the Cochrane Crowd website.[17]

Figure 1: Number of NIHR-funded SR projects; including Cochrane Programme Grant Scheme Projects, Cochrane Incentive Awards and Cochrane NHS Engagement Awards. Start date by year from 2009 to 2015 (as of 8.2.16)[15]



NIHR Cochrane Incentive Awards

The NIHR Cochrane Incentive Awards are available to CRGs in order to complete new or update existing Cochrane reviews. Over the 12 years the scheme has been in operation there have been around 240 awards offered. The awards are small and are not intended to fund the full cost of a review but are used to facilitate and accelerate review activity that is already planned or underway (at the discretion of co-ordinating editors). Cochrane UK publicises the funding scheme, and is not involved in administration or allocation of funds.

Funding

The Department of Health has funded an annual scheme for the past 12 years.

- In most cases, funding of £5,000 is available.
- In exceptional cases, a higher amount may be agreed.

Eighteen CRGs received Cochrane Incentive Award funding during 2012, eight of which are UK-Based CRGs receiving Infrastructure funding.[20]

Funding

During 2012, the following CRGs received Cochrane Incentive Award funding:[20]

- Bone, Joint & Muscle Trauma Cochrane Review Group
- Breast Cancer Cochrane Review Group
- Cochrane Review Group
- Depression, Anxiety and Neurosis Cochrane Review Group
- Ear, Nose & Throat Disorders Cochrane Review Group
- Effective Practice and Organisation of Care (EPOC) Cochrane Review Group
- Heart Cochrane Review Group
- Hypertension Cochrane Review Group
- Menstrual Disorders and Subfertility Cochrane Review Group
- Methodology Cochrane Review Group
- Musculoskeletal Cochrane Review Group

- Pain, Palliative and Supportive Care Cochrane Review Group
- Pregnancy and Childbirth Cochrane Review Group
- Public Health Cochrane Review Group
- Schizophrenia Cochrane Review Group
- Sexually Transmitted Infections Cochrane Review Group
- Stroke Cochrane Review Group
- Hepato-Biliary Cochrane Review Group

The funding call is annual and open to all CRGs globally to apply, with applications requiring justification as to the importance and impact of the review topic specifically within the UK healthcare system.

Table 2: Cochrane Incentive Award Scheme applications and awards (2013-2015)[21]

Year of Award	All applications	All awards offered
2015	42 applications from 20 CRGs, of which 15 were NIHR-funded CRGS	18 awards offered to 15 CRGs, of which 11 were NIHR-funded CRGs
2014	53 applications from 26 CRGs, of which 14 were NIHR-funded CRGs	20 awards offered to 15 CRGs*, of which 8 were NIHR-funded CRGs. *An award was offered to the EPOC Group which was not NIHR-funded at the time, and later became an NIHR-funded CRG.
2013	62 applications from 32 CRGs, of which 15 were NIHR-funded CRGs	20 awards offered to 14 CRGs, of which 6 NIHR-funded CRGs

Incentive Awards are intended to expedite completion of Cochrane reviews, or updates, to ensure timely delivery of evidence to inform decision- and policy-making.

An example of an impactful Incentive Award relates to the SR entitled "Colloids versus crystalloids for fluid resuscitation in critically ill patients."[22] This Incentive Award is considered likely to have influenced calls to stop starch use within the NHS, a decision that has the potential to save both lives and money.[23] The Cochrane review, and follow-on research, led to a review by the European Medicines Agency and suspension of the use of hydroxyethyl starch.[24]

As another example of behaviour change, a Cochrane Incentive Award supported an update of the review "Cranberries for preventing urinary tract infections".[25] The review had previously concluded that there was some positive effect in using cranberries to treat urinary tract infections (UTI). The update incorporated an additional 14 trials, leading to the changed conclusion that any positive effect was limited. The review's findings were reported in both the press and on social media, as the SR failed to support the widely-held belief of beneficial effects of cranberries. This SR was ranked in the top 5% of all Cochrane reviews, according to Altmetrics analysis.

Technology Assessment Review (TAR) teams

Funding

The value of the five year TAR contract 2011-2016 was £36.1 million. This increased to £38.5 million over five years from April 2016[1-3]

An essential component of the Health Technology Assessment (HTA) programme are the Technology Assessment Review (TAR) teams,[1, 26] which consist of nine independent academic and commercial research centres. TAR funding comes from NIHR, the TARs are commissioned by NIHR on a five-yearly basis, to undertake work for NICE. These teams are contracted to support health policy makers in the UK. The TAR teams undertake high quality SRs, reviews of economic evaluations and cost-effectiveness models to inform TARs, as well as developing methods to underpin these research outputs.

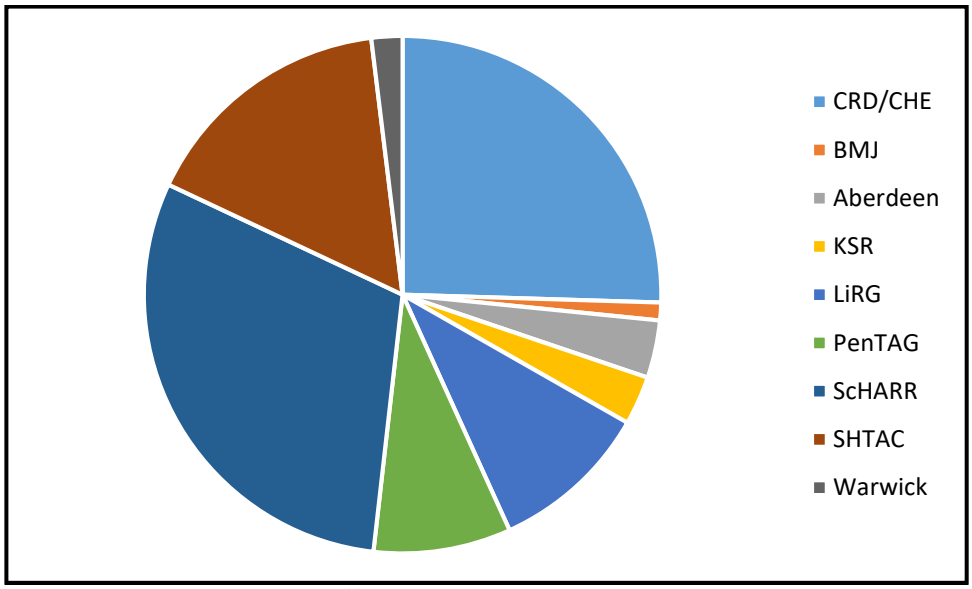
TARs provide evidence assessments of the benefits, harms and costs of particular healthcare interventions. Most TARs undertake work for support NICE's technology appraisal process, informing guidance decisions on new and existing drugs, treatments and procedures for use in the NHS.[27] Where time and capacity exists, TAR groups are encouraged to undertake other work of relevance to the NHS. Other stakeholders include the Chief Medical Officer, NHS England, and the National Screening Committee. Depending on scope and nature of topic, timescale, remit and purpose of assessment, commissioned projects may involve different types of technology appraisal outputs:

- Single Technology Assessment Reports (STAs)
- Multiple Technology Assessment Reports (MTAs)
- Highly Specialised Technologies (HST) evaluations[28]
- NICE Diagnostics (DA) guidance[29]

The Technology Assessment Review (TAR) teams are made up of nine specialist independent review centres which are contracted to undertake TARs in response to the urgent needs of NICE and other policy makers:

- Aberdeen HTA Group, University of Aberdeen
- BMJ Evidence Centre
- Centre for Reviews and Dissemination/Centre for Health Economics, University of York
- Kleijnen Systematic Reviews Ltd
- Liverpool Reviews and Implementation Group, University of Liverpool
- PenTAG, Evidence Synthesis & Modelling for Health Improvement (ESMI), University of Exeter
- School of Health and Related Research, University of Sheffield
- Southampton Health Technology Assessments Centre, University of Southampton
- Warwick Evidence, University of Warwick

Figure 2: HTA Journal Reports by current TAR group



Results from search of PubMed[30] (10.11.15)

TARs provide evidence assessments of the benefits, harms and costs of particular healthcare interventions. Most TARs undertake work for support NICE's technology appraisal process, informing guidance decisions on new and existing drugs, treatments and procedures for use in the NHS.[27] Other stakeholders include the Chief Medical Officer, NHS England, and the National Screening Committee.

TARs for NICE inform three guidance committees: NICE Technology Appraisals (TA) guidance; NICE Highly Specialised Technologies (HST) guidance; and NICE Diagnostics (DA) guidance.[31]

The majority of TAR work is carried out by the TAR teams. Depending on the type of project being undertaken, TAR teams are also known as Evidence Review Groups (ERGs) for STAs and HSTs, Technology Assessment Review (TAR) Groups for MTAs and External Assessment Groups (EAGs) for DA Reviews.

TA guidance assesses the clinical and cost-effectiveness of healthcare interventions of relevance to the NHS. There are two types of reports produced for the NICE TA guidance committee. Single Technology Assessment Reports (STAs) only investigate a single technology for a single indication. The STA process is expedited to enable decision-making as close to the point of product launch as possible. Rather than conduct a synthesis of the evidence, one of the Evidence Review Groups (ERGs) will critique evidence submitted by companies to NICE. The company's submission is assessed quickly, with the STA report being completed within eight weeks. Multiple Technology Assessment Reports (MTAs) investigate multiple technologies for a single indication, or one technology for multiple indications. In this case the TAR team will identify, assess and synthesise the research evidence themselves. MTAs provide estimates of the relative effectiveness and cost-effectiveness of the intervention or interventions. MTA reports are larger and more time consuming, and take up to 28 weeks to be completed.

NICE highly specialised technologies (HST)[28] evaluations are a more recent addition to NICE guidance.[32] HST evaluations are similar to STAs in that they investigate a single technology for a single indication, and are assessments of research evidence, compiled and submitted by companies to NICE. Reports are also produced within eight weeks. HSTs differ as they investigate only highly specialised interventions for very rare 'orphan' conditions. Topics are identified by the NIHR Horizon Scanning Research and Intelligence Centre at the University of Birmingham[33] and aim to notify the Department of Health of new and emerging interventions that might need to the referred for marketing authorisation within 15 to 20 months.

NICE Diagnostics (DA) guidance[29] may cover a single diagnostic technology or product, or multiple diagnostic technologies or products. Diagnostics can include any type of measurement or test that is used to evaluate a patient's condition, such as physiological measurements, laboratory tests, and imaging tests. DA reports provide estimates of relative effectiveness and cost-effectiveness, and are usually completed within 24 weeks.

The main output of an STA is the report used by the NICE Appraisal Committee, which is made available on the NICE website. STAs are not typically published in academic journals nor are they published as HTA monographs, although a number of early STAs were published as HTA supplements.[34, 35] A few of the ERGs have managed to publish STA research in the journal Pharmacoeconomics: ScHARR, Centre for Reviews and Dissemination, Kleijnen Systematic Reviews Ltd, Liverpool Reviews and Implementation Group and Health Economics Research Unit.[36-40]

Health Technology Assessment (HTA) programme

NIHR funds the Health Technology Assessment (HTA) programme. Additional funding contributions are received from Health and Care Research Wales, Health and Social Care Research & Development (HSC R&D) in Northern Ireland, and case by case contributions from the Chief Scientist Office (CSO) in Scotland. [10], [3], [11], [12], [13] The HTA programme in turn funds independent research for the NHS about the clinical effectiveness, cost-effectiveness and impact of healthcare interventions. This research is aimed at a number of key decision and policy makers, including NICE.

Funding

The research budget for the HTA programme:

- £1 million at inception in 1993/4
- £8 million in 2003/4
- £60 million in 2012/13[8]
- over £74 million in 2014/15.[3]

Table 3: NIHR Portfolio projects status*[41] (as of 8.2.16)

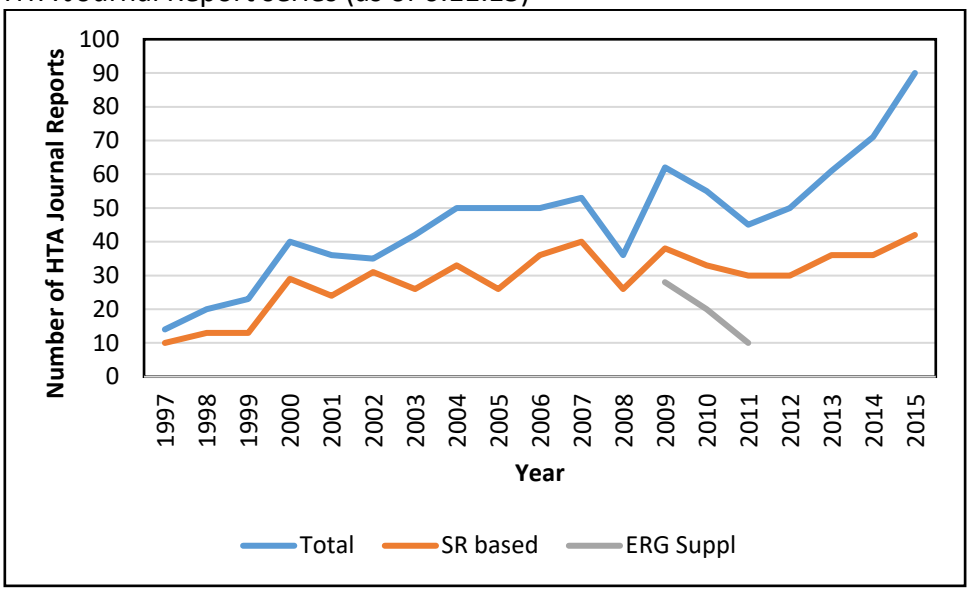
Research Type	Projects complete	Ongoing	Waiting to publish	Total
NICE Technology Assessment Report	162	2	8	172
NICE Diagnostic Assessment	18	6		24
NICE Evidence Review Group Report	167	29		196
HTA Technology Assessment Report	139	6	4	149
Methodology Research	123		1	124

Evidence Synthesis	482	81	33	596
Primary Research	586	556	116	1,258

*Status of projects accessed through browse function (8.2.16).

The majority of NIHR HTA funded research, including TAR research, is published online in the Health Technology Assessment (HTA) journal series. Published since 1997, HTA journals are open access and free to download from the NIHR Journals Library.[42] It is also possible to purchase print copies. The HTA journal is indexed in PubMed/MEDLINE, CINAHL, Embase, the Health Technology Assessment database (via the Cochrane Library and the Centre for Reviews and Dissemination (CRD)) and Science Citation Index.

Figure 3: HTA Journal Report series (as of 6.11.15)



Complex Review Support Unit (CRSU) and Diagnostic Evaluation Co-operatives (DEC)

The Complex Review Support Unit (CRSU)[43] was established in 2015 by the NIHR with an award of £1.9 million across five years to 2020. Its aim is to provide specialist expert advice to those producing methodologically complex reviews in the field of evidence-based medicine.

The CRSU provides timely and appropriate support for the successful delivery of complex reviews of importance to the NHS that are funded and/or supported by NIHR. These include reviews funded by the SR Programme and other NIHR programmes, Cochrane, and other NHS and NHS supported sources. The Unit also works closely with the NIHR to support scoping and prioritising of future complex reviews, and build capacity and capability within the research community.

The unit is led by Professor Olivia Wu and is made up of collaboration between the London School of Hygiene and Tropical Medicine, Leicester University and the University of Glasgow, providing advice on methodological fields such as:

- Diagnostic test accuracy
- Network meta-analysis

- Individual patient data/Clinical study report meta-analysis
- Causal pathway analysis
- Economic evaluations
- Non-randomised studies
- Prognostic reviews
- Prevalence reviews
- Realist synthesis
- Qualitative analysis
- Use of routine data

In 2013, the NIHR funded four Diagnostic Evidence Co-operatives (DECs) to act as centres of expertise for the clinical validity, clinical utility, cost-effectiveness and care pathway benefits of in vitro diagnostic devices. This support aims to help patients access the most appropriate treatments more quickly and help the NHS make the best use of its resources.

Health Services and Delivery Research (HS&DR) Programme

The HS&DR Programme[44] was formed in January 2012 through the merger of two existing NIHR programmes: Health Services Research (HSR) and Service Delivery and Organisation (SDO).[45] The HS&DR Programme aims to produce rigorous and relevant evidence to improve quality, accessibility and organisation of health services. It is focused on research to support decisions by frontline managers and clinical leaders on the appropriateness, quality and cost-effectiveness of care. The audience for this research is the public, service users, clinicians and managers. Additional funding contributions are received from Health and Care Research Wales, Health and Social Care Research & Development (HSC R&D) in Northern Ireland, and case by case contributions from the Chief Scientist Office (CSO) in Scotland.[10, 3, 11, 12,13]

Funding

- The HS&DR Programme receives up to £18.5 million annually in funding from the NIHR. [7]
- To date, including the HSR and SDO programmes, £90 million has been spent on over 400 different projects.

All HS&DR funded projects are eligible for publication in the HS&DR Journal published in the NIHR Journals Library. There are four volumes of the HS&DR Journal (2013-current) with a total of 136 reports published.

The HS&DR Programme is comprised of two workstreams: researcher-led and commissioned. Anyone who considers that they can carry out high-quality research is likely to be eligible to apply for funding from either workstream although researchers from Scotland are not eligible to respond to the commissioned workstream and should contact the CSO to discuss funding opportunities for healthcare delivery-type research.[12, 13, 46, 7]

Public Health Research Programme

The Public Health Research (PHR) Programme (PHR)[47] funds research to generate evidence to inform the delivery of non-NHS interventions intended to improve the health of the public and reduce inequalities in health. The remit of the PHR Programme is broad and aims to provide a variety of key stakeholders with up-to-date information and knowledge on costs, benefits acceptability and impacts of non-NHS public health interventions. Key stakeholders include: local government decision makers; primary care organisations; third sector organisations; national agencies such as NICE who are concerned with public health improvement; researchers; public health practitioners and the public.

Funding

The 2014/2015 NIHR annual report states the PHR Programme as having £9.9 million funding for all programmes in that financial year.[3] Further funding details are found in Figure 9 below. The amount allocated specifically for SRs was not specified.

Primary and secondary research is funded. Research costs are funded, but intervention and non-research costs are not. SRs are just some of the projects funded by the programme. Additional funding contributions are received from Health and Care Research Wales, Health and Social Care Research & Development (HSC R&D) in Northern Ireland, and case by case contributions from the Chief Scientist Office (CSO) in Scotland.[10, 3, 11, 12,13]

All PHR Programme funded projects are eligible for publication in the PHR Journal published in the NIHR Journals Library.[48] There are three volumes of the PHR Journal (2013-current) with a total of 23 reports published (an additional report is in process), currently 22% of reports published are SRs.

NICE Guidelines

Guidelines are produced to ensure that practitioners deliver the best possible care, the most effective treatments are available, interventions are cost-effective, and health uncertainty and inequality is reduced. Established in 1999, NICE has gained a reputation for being independent and objective, as guidelines are produced through collaboration between healthcare professionals, academic experts, NHS staff, and patients and carers. In 2013 NICE was given the wider responsibility of developing guidance for social care as well as health care.

Though guidelines produced by NICE are expected to be used by practitioners to help decision making when treating patients, they do not replace professional knowledge and skills.

NICE guidelines[49] include:

- Clinical guidelines:
  Clinical guidelines provide recommendations about the care of people with specific conditions. They give information and advice about the treatment, prevention, diagnosis or the long-term management of a condition. National Collaborating Centres

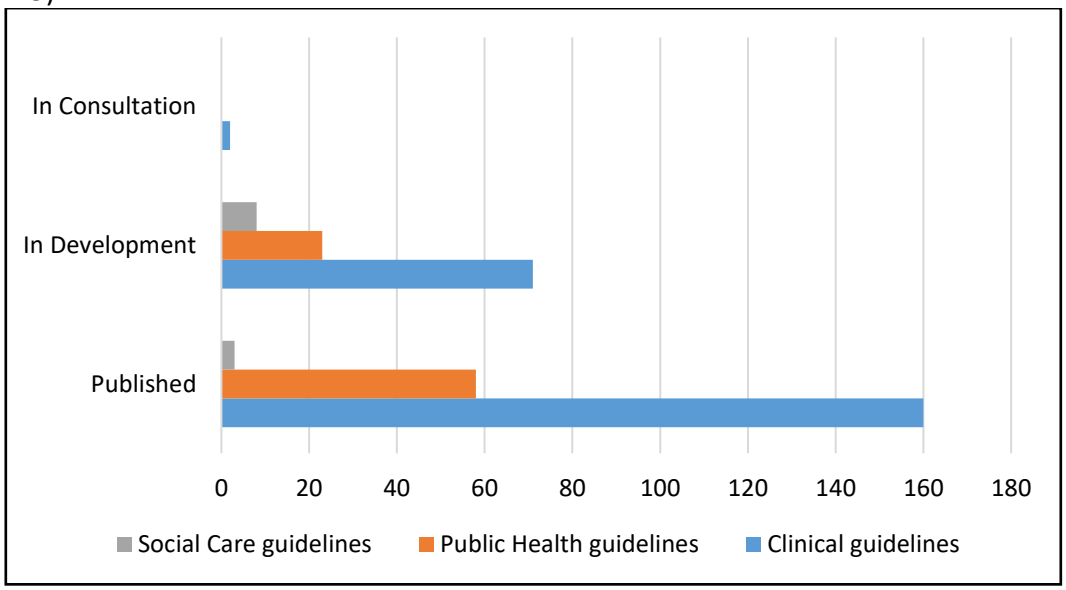
(NCCs) have been established to help develop clinical guidelines by using the expertise of the Royal medical colleges, professional bodies and patient/carer organisations.

There are presently 160 published NICE clinical guidelines.[50]

- Social care guidelines:
  Since 2013 NICE has produced guidelines to help improve social care support, by making recommendations based on evidence-based social care research. These guidelines are aimed at social care practitioners and providers, though they may also be relevant to healthcare practitioners and providers. The methods and processes used by NICE to develop social care guidelines are also used by the National Collaborating Centre for Social Care (NCCSC). The NCCSC in turn provides NICE with support about the development, adoption and dissemination of social care guidelines and quality standards (QS).

  There are currently three published social care guidelines, whilst there are a further eight in development.[50]

Figure 4: Number of NICE guidelines published, in development, and in consultation[50] (as of 10.11.15)



NICE Public Health

Public health guidelines are produced specifically to help prevent disease and to improve health. Guidelines are aimed at public health professionals in the NHS, and also in the wider community; local authorities, voluntary organisations, and the private sector. Public health guidelines usually specify a population, topic and/or setting. For example, there are a range of guidelines about physical activity aimed at people in the workplace, children, and adults in primary care. Similarly, there are various guidelines with recommendations about smoking prevention and cessation in schools, the workplace, South Asian communities, and pregnant women.

Currently there are 58 published public health guidelines, and 23 in development.[50]

DH Policy Research Programme

The Policy Research Programme (PRP)[51] is led by the Department of Health, Research and Development Directorate, and it works alongside other NIHR programmes. The function of the PRP is to commission, fund and manage timely, cutting edge research that focuses on the current needs of policy makers and ministers and building an evidence base for future policy-making. To achieve its objectives the PRP commissions both primary and secondary research covering a wide range of topics such as vaccines, resource allocation, safeguarding and treatment.

Research is commissioned by competitive tender within the Department of Health Research Governance Framework for health and social care (2005).[52] Details of commissioned projects[53] and summaries of final reports[54] received since 2011 are published by the programme, 122 commissioned projects are currently listed.

Charities

Charitable organisations might undertake or commission SRs, as a means of utilising existing primary research and utilising the findings to reinforce a reliable message. Charities are regulated by charity law, which places some restrictions on the use of their funds for research, such as funds not being used for research with commercial objectives and a provision to disseminate research results.

The Association of Medical Research Charities (AMRC)[55] has around 100 members and has published a briefing document to assist its members in commissioning medical research. Although the AMRC recognises their members may commission SRs, no specific guidance is provided.[56]

Examples of charitable organisations undertaking SRs include British Association for Counselling and Psychotherapy (BACP),[57] Joseph Rowntree Foundation (JRF),[58] Epilepsy Action[59] and the Alzheimer's Society.[60]

Academic groups

In the UK, there are many academic groups producing systematic reviews and publishing specialist methodology documents investigating different aspects of review methods. Some draw funding from programmes already mentioned, however much unfunded work is also undertaken. Groups undertaking SRs can be found in most universities; examples include the Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre),[61] the University of Stirling[62] and the Centre for Reviews and Dissemination at the University of York.[63]

Review work undertaken within these groups may be performed as research activity to make up postgraduate qualifications, such as Diplomas, Masters and PhDs. Review outputs might appear as discussion papers, reports, journal manuscripts, dissertations or theses. Publications in peer reviewed journals might be indexed on bibliographic databases, such as Medline or Embase.

Several examples of UK academic groups undertaking SR production and methodological developments are given below:

- **Example 1: Evidence for Policy and Practice Information and Co-ordinating Centre (*EPPI-Centre*)**

  The Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre)[61] is part of the Social Science Research Unit at the Institute of Education, University of London. As well as conducting reviews across a range of different topic areas, the EPPI-Centre is also involved in developing methods for SRs and research syntheses, and providing support for others to undertake SRs. The Centre is the Methods for Research Synthesis (MRS) node of the Economic and Social Research Council (ESRC) National Centre for Research Methods.

  The full texts of all EPPI-Centre reviews from 1996 to date are available free of charge via their website.

  The EPPI Centre has been funded by the Department of Health since 1995. Other funders include: the Centre for Excellence and Outcomes in Children's and Young People's Services, the Cochrane Collaboration, the Economic and Social Research Council, the European Commission, the Joint Information Systems Committee and the NIHR Health Technology Assessment Programme.

- **Example 2: University of Stirling**

  The Institute for Social Marketing[62] at the University of Stirling has been involved in the production of a range of SRs in three key areas:

  - the development and evaluation of behaviour change interventions
  - the impact of public policy on health and social welfare
  - the impact of commercial marketing on the health and behaviour of individuals and society

  Links to abstracts for their SRs are available on their website.

  Researchers from the School of Nursing, Midwifery and Health are involved in qualitative SR methodology. With NHS Quality Improvement Scotland they produced 'A guide to synthesising qualitative research for researchers undertaking health technology assessments and systematic reviews' in 2010, which provides those producing and using systematic reviews and HTAs with the methodology for synthesising qualitative research.[64]

  Research has also been conducted by researchers in this department on the application and reporting of methods in meta-ethnography journal papers.[65]

- **Example 3: Centre for Reviews and Dissemination (CRD)**

  The Centre for Reviews and Dissemination (CRD)[63] is a health services research department based at the University of York. It was established in January 1994, and was originally created as part of the Information Systems Strategy of the NHS Research and

Development Programme. CRD specialises in evidence synthesis, assembling and analysing data from multiple research studies to generate policy relevant research. It disseminates the results of research to decision-makers in the NHS. CRD produces SRs and economic evaluations, and has completed over 160 SRs covering a wide range of health care topics.

CRD received core funding through the National Institute for Health Research (NIHR) England[66] up to April 2015. Further funding is received from the Department of Health,[67] Public Health Agency, Northern Ireland[68] and the National Institute for Social Care and Health Research, Welsh Government.[69] In addition to this funding, CRD has undertaken research for a number of different agencies including: NICE,[70] the NIHR HTA Programme,[71] the Department of Health Policy Research Programme,[72] the Economic and Social Research Council (ESRC),[73] the Home Office,[74] the Medical Research Council (UK) (MRC),[75] the Social Care Institute for Excellence (SCIE),[76] the NHS Institute for Innovation and Improvement (NHS III)[77] and the NIHR Service Delivery & Organisation Programme (SDO).[45] CRD is one of the nine independent academic and commercial centres currently undertaking reviews commissioned by NICE.

CRD is currently funded to produce PROSPERO, the International Prospective Register of Systematic Reviews.[78]

CRD produces a number of publications based on the findings of SRs. Its Effective Health Care bulletin series[79] was produced between 1992 and 2004, and the CRD Report series[80] was produced between 1995 and 2012. CRD's Guidance for Undertaking Reviews in Health Care (2009)[81] remains a key guidance document for SR production. The majority of CRD publications and outputs are available from their website.

Commercial Agencies

Within the UK, there are a whole range of commercial agencies and consultancies undertaking SRs, either as their primary work or alongside health economics and outcomes research (HEOR). Most commercial groups are likely to work for a variety of commissioners, including public funding by the programmes mentioned previously, but also for the commercial pharmaceutical and manufacturing industry.

Some agencies might be independently commercial, others may operate alongside university research departments or are owned by universities; ranging from entirely academic to entirely commercial in focus.

Health Care Professionals

As in academia, SRs are undertaken within the health care system by clinicians, nurses, research staff and other health care professionals. SR work might be to address a need identified in clinical practice, or at an organisational, departmental or institutional level. This work might be produced to fulfil continuing professional development (CPD) objectives, as part of further advanced study or for other reasons, and might be published in the public

domain as a report or journal manuscript, produced as practice guidance, presented at conferences or workshop, or remain unpublished.

Cochrane UK

Cochrane UK, formerly known as the UK Cochrane Centre, is one of 41 regional centres and branches, making up global Cochrane. Cochrane UK is not strictly an organisation funding or producing SRs, however it has an integral supportive role both facilitating and advising CRGS, Cochrane entities, Cochrane users and funders in the UK.

Established in 1992, Cochrane UK is funded by NIHR and based in Oxford. Cochrane UK is hosted by the Oxford University Hospitals NHS Foundation Trust.[82]

Funding

The majority of funding for Cochrane UK is awarded by NIHR. Contributions towards production and maintenance of SR are also made by:[6]

- Department of Health, Social Services and Public Safety: Northern Ireland;
- Health Research Board, Ireland;
- Health and Care Research Wales; and
- Scottish Government, Health Directorates.

Cochrane UK receives £796,000 (£795,843.50) funding per annum, and approx. £3.2m to 2019.

Cochrane UK comprises of a core team, director and research fellows. Cochrane UK is overseen by two advisory groups, the Cochrane UK Advisory Board and the director's Clinical Advisory Group.

Twenty-four of the 53 CRGs have an editorial base in the UK.

Half of the 16 Cochrane Methods Groups are based in the UK (not NIHR-funded) including:

- Adverse Effects
- Agenda and Priority Setting
- Economic
- Individual Participant Data Meta-Analysis
- Information Retrieval
- Non-Randomised Studies
- Qualitative and Implementation
- Statistics

Organisations funding or preparing systematic reviews globally

A range of organisations are involved in systematic reviews globally, some important players are mentioned below. Cochrane has existing partnerships with most of these groups.

Cochrane world-wide

As mentioned, SRs conducted by Cochrane are undertaken by 53 CRGs[83] worldwide, of which 21 currently receive infrastructure costs funded by the NIHR,[3-5] and 24 have an editorial base in the UK.[84] Further details of these CRGs, included stated sources of funding and CRG website address, are presented in the table below:

Table 4: Stated sources of funding for CRGs not funded by NIHR*

Cochrane Review Group	Funders*	Web address
Acute Respiratory Infections	The National Health and Research Council (NHMRC) of Australia, The Australasian Cochrane Centre, Bond University	http://ari.cochrane.org/funding-and-support
Anaesthesia, Critical and Emergency Care	Region Hovedstaden, The Cochrane Steering Group, Danielsen Foundation, King Christian the X Foundation, Wedell-Wedellsborg Foundation, Jakob Madsen & Hustru Olga Madsens Foundation, Lippmann Foundation, plus other supporters	http://ace.cochrane.org/funding-and-support
Back and Neck	Institute for Work & Health. Funded by the Canadian Institutes of Health Research (CIHR) until September 2015, and the Ontario Ministry of Health and Long-Term Care	http://back.cochrane.org/our-funders
Breast Cancer	National Health and Medical Research Council of Australia and National Breast Cancer Foundation	http://breastcancer.cochrane.org/our-funders
Childhood Cancer	Kinderen Kankervrij (KiKa, Netherlands) and Department of Pediatrics and Pediatric Oncology of the Emma Children's Hospital/AMC (Amsterdam, Netherlands)	http://childhoodcancer.cochrane.org/funding-support
Colorectal Cancer	Danish Government; grants received over past 10 years from: Jacob Madsen & Wife's Olga Madsen's Fund, E. Danielsen & Wife's Fund, Karl Andersson's Fund, Else & Mogens Wedell-Wedellborg's Fund, Inge & Jørgen Larsen's Memorial Fund, Eva & Henry Frænkel's Memorial Fund, Pharmacist's Fund, H:S Research Fund, Leo Fund and Grosserer Chr. Andersen og hustru Ingeborg Andersen, f. Schmidts fund.	http://cc.cochrane.org/funding-and-support

Cochrane Review Group	Funders*	Web address
Consumers and Communication	Department of Health and Human Services (Victoria) and National Health and Medical Research Council	http://cccrg.cochrane.org/scope-our-work
Drugs and Alcohol	Department of Epidemiology, Lazio Regional Health Service of Lazio Region (Italy)	http://cda.cochrane.org/funders
Fertility Regulation	Netherlands Organisation for Health Research and Development, Ministry of Foreign/Developing Affairs (The Hague, Netherlands), World Health Organization (WHO) (Geneva, Switzerland) and Foundation Reproductive Medicine/Foundation Cochrane (Leiden, Netherlands)	http://fertility-regulation.cochrane.org/financial-support
Haematological Malignancies	German Federal Ministry of Education and Research (BMBF), Deutsche Krebshilfe e.V. and Köln Fortune from the Medical Faculty University of Cologne	http://hm.cochrane.org/funding-and-support
Hepato-Biliary	Danish Government's yearly financial support to The Copenhagen Trial Unit, Centre of Clinical Intervention Research, Rigshospitalet	http://hbg.cochrane.org/contributors
HIV/AIDS, part of Infectious Diseases Group	UK Government Department for International Development through the Effective Health Care Research Consortium (EHCRC)	http://cidg.cochrane.org/funding-and-support
Hypertension	Funded by CIHR until September 2015	http://hypertension.cochrane.org/
Infectious Diseases Group (CIDG)	UK Government Department for International Development through the Effective Health Care Research Consortium (EHCRC)	http://cidg.cochrane.org/funding-and-support

Cochrane Review Group	Funders*	Web address
Inflammatory Bowel Disease and Functional Bowel Disorders (IBD/FBD)	Funded by CIHR until September 2015 and the Ontario Ministry of Health and Long Term Care	http://ibd.cochrane.org/welcome
Kidney and Transplant	National Health and Medical Research Council (NHMRC), Centre for Kidney Research and University of Sydney	http://kidneyandtransplant.cochrane.org/sources-support
Lung Cancer	Supported by grants from the INCa (The French National Institute of Cancer), the French Cochrane Centre, and receives logistical support from the IFCT (Intergoupe Francophone de Cancérologie Thoracique)	http://lungcancer.cochrane.org/
Metabolic and Endocrine Disorders	CMED currently funds itself through Health-Technology Assessment (HTA) contract work and receives support from medical faculty of the Heinrich-Heine University (Düsseldorf, Germany)	http://endoc.cochrane.org/funding-and-support
Methods	Methodology Review Group has no dedicated funding but the editorial base for the Cochrane Methodology Review Group is based in the Northern Ireland Network for Trials Methodology Research in Queen's University of Belfast, Northern Ireland	http://methodology.cochrane.org/
Movement Disorders	(Source of funding not given)	http://mdg.cochrane.org/contacts
Multiple Sclerosis and Rare Diseases of the Central Nervous System	Funded by Italian Department of Health and The Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta. Additional support from Fondazione Italiana Sclerosi Multipla (FISM), Italian Cochrane Centre (through "AREAS-CCI O.N.L.U.S."), Associazione Volontari Aiuti per la Sclerosi Multiple (AVASM)	http://msrdcns.cochrane.org/

Cochrane Review Group	Funders*	Web address
	and Associazione Ricerca Epidemiologia delle Malattie Neurologiche (A.R.E.MA.N.)	
Musculoskeletal	Funded by CIHR until September 2015, the University of Ottawa, the National Health and Medical Research Council in Australia (NHMRC), and the Cabrini Institute (Melbourne, Australia)	http://musculoskeletal.cochrane.org/welcome
Neonatal	Funded in part with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services (USA) under Contract No. HHSN267200603418C	http://neonatal.cochrane.org/funding-and-support
Public Health	NHMRC (previously Commonwealth Department of Health and Ageing). Additional support from Victorian Health Promotion Foundation (VicHealth)	http://ph.cochrane.org/funding-and-support
Sexually Transmitted Infections (STI)	Universidad Nacional de Colombia	http://sti.cochrane.org/financing-and-conflict-interest
Stroke	Chief Scientist Office (part of the Scottish Government Health and Social Care Directorates)	http://stroke.cochrane.org/about-us
Upper Gastrointestinal and Pancreatic Diseases (UGPD)	Funded by CIHR until September 2015, McMaster University (Canada)* and National Institutes for Health Research (UK)	http://ugpd.cochrane.org/funding-and-support
Urology	Minneapolis VA Health Care System and the University of Minnesota Department of Urology (Minneapolis, Minnesota, USA)	http://urology.cochrane.org/about-us

Cochrane Review Group	Funders*	Web address
Vascular	Chief Scientist Office of the Scottish Executive (formerly the Scottish Office)	http://vascular.cochrane.org/origins-and-funding
Work	Finnish Institute of Occupational Health, the Finnish Ministry of Social Affairs and Health, the Coronel Institute of Occupational Health, Safe Work Australia and the Dutch Ministry of Social Affairs and Employment	http://work.cochrane.org/additional-contributors

*Information obtained from each CRG's website on 8.2.16; more current funding information may be available.

Joanna Briggs Institute (JBI)

The Joanna Briggs Institute (JBI)[85] is based within the Faculty of Health Sciences at the University of Adelaide, Australia. JBI is an independent not-for-profit research and development centre which collaborates with over 70 centres and groups around the globe, including seven in the UK. Together with collaborating entities (The Joanna Briggs Collaboration (JBC)) the Institute promotes and supports the synthesis, transfer and utilisation of evidence to assist in the improvement of healthcare outcomes globally through evidence based healthcare. JBI produces a variety of resources to meet the needs of service providers, health professionals and consumers. Evidence produced by the Institute can be used to inform clinical decision making. The Institute produces several resources such as resource databases, decision support systems and tools to perform SRs, and also offers training programs.

JBI produces two databases:

- The JBI Database of Systematic Reviews and Implementation Reports[86]
- JBI COnNECT+ (Clinical Online Network of Evidence for Care and Therapeutics)[87]

International Health Technology Assessment organisations

INAHTA: The International Network of Agencies for Health Technology Assessment

The International Network of Agencies for Health Technology Assessment (INAHTA)[88] is the most well-known international HTA organisation. Founded in 1993, it consists of a collaborative network of 55 international HTA agencies from 32 countries from as far afield as Brazil (CONITEC[89]), Finland (FinOHTA[90]), and New Zealand (NHC[91]). INAHTA enables HTA agencies to share information about their HTA methods, and encourages cooperation between agencies. The network also provides a useful guide to how different countries implement evidence-based research to support healthcare decision making and the implementation of guidelines.

To assist collaboration INAHTA has various task groups, committees and subcommittees that aim to advance the strategic objectives of the network. The INAHTA board is elected by members and is responsible for the development and implementation of the strategic plan, as well as the work of the task groups, committees and secretariat.

A central goal of the network is to disseminate the work of the member agencies using a variety of publications[92] that are added to the INAHTA website: INAHTA Briefs provide an overview of recently published reports; INAHTA Checklists provide information on the purpose, methods, and contents of an HTA report; INAHTA Impact Reports allow members to report on the impact of their HTA report on health system decision making. A vital resource for the dissemination of member organisations work is the NIHR HTA Database.[93] The HTA database is freely available, and provides access to bibliographic details of completed member reports, as well as ongoing projects. Established in 1998, the database has over 15,000 records of in progress and published HTAs.

Current projects include the launch of the INAHTA Strategic Plan 2014-2017; external partnership development with other international and regional organisations (e.g., WHO, EUnetHTA, HTAi); and the development of the HTA glossary, a joint project with HTAi (Health Technology Assessment international), INESSS (Institut national d'excellence en santé et en services sociaux), AVALIA-T (Galician Agency for Health Technology Assessment), DIMDI (Deutsches Institut für Medizinische Dokumentation und Information) and AHTA (Adelaide Health Technology Assessment).

Health Technology Assessment international (HTAi)

Another prominent and renowned international HTA organisation is HTAi (Health Technology Assessment international).[94] HTAi acts as the professional society for anyone involved in the production or use of health technology assessment. Members include individual researchers, national agencies, health service providers and policy makers, industry, academia, and patients. The organisation acts as a forum for the collaboration and sharing of expertise in HTA.

HTAi holds regular meetings for its members, and the annual meeting is held in high esteem as one of the key international conferences for HTA. Recent meetings have been held in Oslo, Washington DC, Seoul and Dublin. There are several specific interest groups within HTAi, including an Information Resources Group, Ethical Issues Group, HTA in Developing Countries Group, a Policy Forum, and various other groups. The organisation also produces its own journal, the International Journal of Technology Assessment in Health Care (IJTAHC),[95] to act as a further source for sharing ideas, opinions and activities about HTA globally.

HTAi is governed by an elected board of directors that is supported by an executive committee, several advisory committees and a secretariat. It is funded through individual membership and a diversified pool of sponsors.

Regional and national HTA organisations

As well as global international HTA organisations, there are regional international collaborative organisations, such as: HTAsiaLink,[96] supporting Asian HTA agencies; EUnetHTA,[97] coordinating the evaluation of health technologies in Europe; and RedETSA,[98] a network of North and South American countries. There is a large number of national HTA agencies, such as CADTH, CENETEC, KEC, OSTEBA, and SBU.[89, 99-103]

Guidelines organisations

Guidelines and guidance are undertaken worldwide on a local, organisational, departmental, regional, institutional, national and international basis, by a variety of associations and organisations.

"Systematic reviews are essential building-blocks for guidelines".[104]

The Guidelines International Network (G-I-N) is an example of an international body focussed on the production and application of guidelines and guidance.

G-I-N is an international association of organisations and individuals involved in the development and implementation of evidence-based guidelines and health care information. Membership consists of 97 organisations working in the field of medical and health care guideline development and 139 individual experts, representing 47 countries and every continent.[105, 106] The mission of the network is "to lead, strengthen and support collaboration and work within the guideline development, adaptation and implementation community."[105]

Since August 2013 guideline developers have been asked to voluntarily fill out a G-I-N Standards Report.[107] This report asks for evidence to show that systematic evidence review methods have been used, that benefits and harms have been stated and that a rating system has been used to communicate the quality and reliability of the evidence.

G-I-N is largely funded by fees paid for by members. This brought in €286,730 in 2015. An additional income of €16,927 was brought in from charitable activities.[108]

Governmental

SRs may be commissioned and funded by government departments in areas such as education, health, infrastructure and humanitarian aid. Reviews may be undertaken by departments themselves or specific organisations commissioned to perform the review on their behalf. Reviews commissioned by government departments are often used by policymakers to inform decision making and funding. Outputs from government-funded reviews can include guidelines, policy changes and reimbursement decisions. SRs have been used by governments to guide policy making in areas such as tobacco control, blood alcohol levels for drivers and medicinal cannabis.[109, 110]

Government departments have also funded training for the production of SRs. For example, the Government of Ontario in Canada awarded $2.1 million to support Health Quality Ontario teams involved in SRs and health economics.[111]

Industry/commercial agencies

Worldwide, there are also a whole range of commercial agencies and consultancies undertaking SRs, either as their primary work or alongside health economics and outcomes research (HEOR). Most commercial groups are likely to work for a variety of commissioners, such as publically funded by the programmes mentioned previously, but also for the commercial pharmaceutical and manufacturing industry.

Some agencies might be independently commercial, others may operate alongside university research departments or are owned by universities; ranging from entirely academic to entirely commercial in focus.

"Systematic reviews have become a prolific business".[112]

On a global scale, commercial agencies and consultancies undertaking SRs are thriving. A conservative estimate of over 100 "service-offering" SRs companies[112] is likely to be many times more in reality. Both separate commercial consultancies undertaking SRs on behalf of industry, and teams based within pharma, are carrying out sophisticated SR methods,

including mixed treatment comparisons and network meta-analyses. It is likely their production is over three times of what appears in the published literature, as so much of their completed work remains unpublished and confidential. Given the commercially confidential and sensitive nature of this share of the work, it is not possible to estimate funding allocated to commercially conducted SRs. Consequently Cochrane's combined global output is dwarfed by commercially produced SRs, as illustrated in Figures 2 and 3.

"Cochrane has only a small percentage of the systematic review market".[112]

Academic Groups

As in the UK, SRs are undertaken within academic settings worldwide, either as research activity, towards education or as commissioned project work. Review outputs may appear in the public domain as journal articles or reports; or as grey literature and conference presentations.

Charities

International charitable organisations might commission SRs in order to provide an evidence-base on which to influence health and policy decision makers, or to promote specific healthcare interventions in the general population. Large international organisations may have a global remit, while national organisations may have a more specific regional scope.

For example, UNICEF[113] is a widely recognised international organisation which campaigns for the rights and safety of children worldwide, and has commissioned SRs, covering topics such as preventing HIV/AIDS in young people, encouraging breastfeeding, and management of malaria.[114-116] Similarly, Médecins Sans Frontières[117] researchers have conducted SRs investigating a wide range of health related issues, such as psychosocial programs in post-conflict settings, cholera in pregnancy, and hygiene interventions to control cholera.[118-120] Oxfam[121] has recently helped to establish the Humanitarian Evidence Programme[122] which aims to produce a series of reviews that will synthesise humanitarian evidence in order to improve policy and practice.

The UK government Department for International Development through its Research for Development Programme[123] provides information about how to conduct SRs and encourages international organisations to undertake reviews to provide a robust evidence base for policy makers and practitioners. Examples of national-level charitable organisations undertaking SRs include Prostate Cancer Foundation of Australia,[124] and Neurological Health Charities Canada,[125]

Health care professionals

SRs are also undertaken worldwide, within healthcare systems by clinicians, nurses and other healthcare professionals. This might be to address identified clinical, departmental or organisational needs; be part of professional development objectives or be part of advanced study by organisational staff members. This work will be in the public domain through journal manuscripts, practice guidance or presented at conferences and workshops. However, some will remain unpublished.

Further ways of accessing existing SRs

As SRs are funded and conducted by such a diverse range of commissioners, groups and reviewers, it is not surprising that SRs are published in disparate formats. At present, there is no single, exhaustive resource or database that enables identification of all published and unpublished SRs. Consequently the searcher must utilise multiple, often overlapping, resources in order to ensure comprehensive, but inevitably not absolute, retrieval of relevant reviews. A detailed description of resources and methods to identify SRs is presented in Appendix 2, however this is not intended to be an exhaustive list.

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Appendix 2: Further ways of accessing existing systematic reviews

This section is intended to act as a sign-posting guide to different resources and methods that can be employed to identify systematic reviews, however it is not expected to present a complete list of SR review resources in their entirety.

Cochrane Database of Systematic Reviews (CDSR)

A resource of SRs in healthcare produced by CRGs (limited to those in human health), the database contains Cochrane reviews, review protocols, editorials and occasionally supplements. The database is updated 'when ready' and takes the form of monthly issues.

There are several options to access the database. Accessed via the Cochrane Library published by Wiley,[1] it is free for many people in low-income and middle income countries via various initiatives. There are also national licences that allow access in specific countries or regions, and other subscription options. All residents in the UK have free access at the point of use, as funding is provided by NICE.[2]. Similarly, residents of Scotland, Northern Ireland and Wales have free access due to funding put in place by NHS Education for Scotland,[3] Research and Development Office[4] and the Welsh Government,[5] respectively. CDSR can also be accessed as part of Ovid's Evidence Based Medicine Reviews collection on a paid subscription basis.

There are currently 9,099 SRs and protocols in the database (73% reviews, 27% protocols). The content summary for 2015 is given in Table 1 below.

Table 1: CDSR content in 2015 [accessed 18.12.15][6]

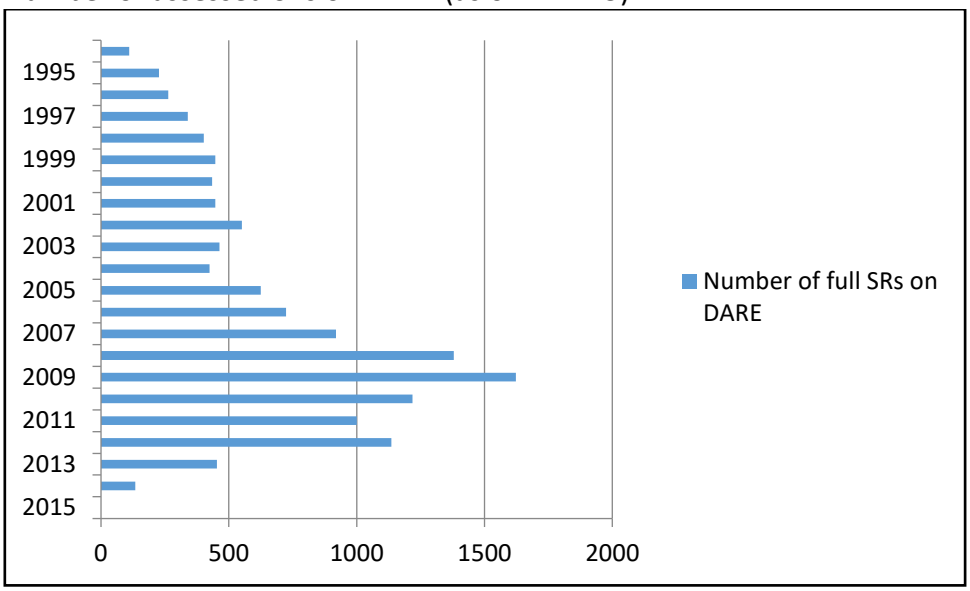
2015	Total Reviews	Total Protocols	Total Reviews and Protocols
Issue 1	6,275	2,356	8,631
Issue 2	6,307	2,370	8,677
Issue 3	6,355	2,380	8,735
Issue 4	6,388	2,411	8,799
Issue 5	6,421	2,420	8,841
Issue 6	6,466	2,437	8,901
Issue 7	6,505	2,432	8,937
Issue 8	6,538	2,425	8,963
Issue 9	6,583	2,432	9,017
Issue 10	6,621	2,429	9,050
Issue 11	6,670	2,427	9,099

The Cochrane Library can be accessed here: http://www.cochranelibrary.com/

Database of Abstracts of Reviews of Effectiveness (DARE)

Between 1994 and March 2015, CRD produced the Database of Abstracts of Reviews of Effects (DARE), a database of quality-assessed SRs of health and social care interventions related to, or of relevance to, the NHS. In March 2015, funding ceased for the production of DARE by CRD. The database currently contains over 45,000 references, including Cochrane reviews, Cochrane-based reviews and bibliographic references and over 13,000 full quality assessed abstracts of systematic reviews.

Figure 1: Number of assessed SRs on DARE (as of 4.11.15)



The archival version of DARE is still available to search via the CRD website,[7] the Cochrane Library[1] and several other resources, including: NHS Evidence,[8] Trip Database,[9] The Virtual Health Library,[10] Health Systems Evidence,[11] SUMSearch,[12] The Knowledge Network of NHS Scotland[13] and PubMed Health.[14] It still receives a small amount of funding to be maintained as a valuable archival resource - for example to update the CRD web version of DARE with 2016 MeSH indexing.

DARE is accessible via the Cochrane Library: http://www.cochranelibrary.com/ or free of charge via the CRD website: http://www.crd.york.ac.uk/CRDWeb/

International Prospective Register of Systematic Reviews (PROSPERO)

CRD produces PROSPERO,[15] an international database of prospectively registered SRs in health and social care. The development and ongoing management of PROSPERO was supported by CRD's core work funding up to April 2015, and is now funded by the Department of Health.

As of November 2015, there were over 10,000 published records of ongoing SRs registered on PROSPERO.

PROSPERO is free to use and can be accessed here: http://www.crd.york.ac.uk/prospero/

NHS Evidence Search

Evidence Search[8] is a database of over 300,000 references produced by NICE. It provides access to evidence in the fields of health, social care and public health from a range of trusted sources, including NICE documents, the Cochrane Library (CDSR and CENTRAL), the British National Formulary, Scottish Intercollegiate Guidelines Network (SIGN), Clinical Knowledge Summaries, Social Care Online, Gov.uk and the Royal Colleges. NICE accreditation on selected resources helps the user identify the most robustly produced guidance available.

Evidence Search is available to search free of charge, and is updated regularly. Resource types include guidance, SRs, evidence summaries and patient information. The database offers a

range of simple search features, and results can be limited by date, area of interest, type of information and source. Results can also be restricted to those which have NICE accreditation. For most search results, the full text is freely available to the end user.

NHS Evidence Search is free to use and can be accessed here: https://www.evidence.nhs.uk/

Epistemonikos

Epistemonikos is a collaborative, multilingual database of research evidence and knowledge translation products and aims to provide rapid access to systematic reviews and broad syntheses of reviews. It is a not-for-profit organisation based in Santiago, Chile and was founded by Gariel Rada and Daniel Pérez.[16, 17]

Epistemonikos is maintained by systematically searching electronic databases and other sources for SRs. Findings are processed by a network of collaborators who connect different types of evidence, check accuracy, extract additional information, and translate titles and abstracts. There are over 40,000 SRs and nearly 20,000 additional studies relevant to specific questions. Many of the institutions and individuals involved in the output of Epistemonikos do not receive payment for their contributions. The software used by Epistemonikos has been funded from multiple sources including the Evidence-Based Health Care Program of the Pontificia Universidad Católica de Chile and the Alliance for Health Policy and Systems Research (WHO).[18, 19]

Epistemonikos is free to use and can be accessed here: http://www.epistemonikos.org/en/

Trip

Trip is a clinical search engine which aims to allow quick and easy access to high quality research evidence to support health care practice and patient care. Results can be filtered by evidence type including SRs, evidence-based synopses or guidelines.[20]

Although Trip is a commercial company, it operates like a 'not-for-profit' company and all income goes towards wages, development or associated costs. Income is brought in via advertising, new content alerts, writing bespoke search engines for websites, consultancy, reviews and use of Trip's web service.[20]

Trip can be accessed here: https://www.tripdatabase.com/

Health Systems Evidence

Health Systems Evidence (HSE) is a free, continuously updated repository of syntheses of research evidence around the governance, finances and delivery of health systems. It is supported by collaboration between McMaster Health Forum's Impact Lab and Cochrane Canada. The types of syntheses includes evidence briefs, overviews of SRs, SRs (completed reviews, protocols and those in planning). Economic evaluations are also included and continuously updated. Links to summaries, scientific abstracts and full-text reports (where available) are provided, and for SRs HSE links to the studies contained in the review. HSE enables policymakers and stakeholders to identify syntheses of the best available research evidence on a particular topic. Key details of the syntheses are provided along with

information regarding is currency, countries involved and indication of quality. Sources of documents in the HSE repository include: Cochrane Library, Evidence Informed Policy Networks, McMaster PLUS, Paediatric Economic Database Evaluation and a number of listservs.[21]

Health Systems Evidence can be accessed here: https://www.healthsystemsevidence.org/

KSR Evidence

KSR Evidence is a user-friendly database of value-added critical appraisals of SRs and meta-analyses.[22] Appraisals include information about the reliability of findings as well as a clinically relevant bottom-line summary. The database aims to support decision making by access to clinically relevant, high quality, digestible critical appraisals using the Risk of Bias Assessment Tool (ROBIS). The database is funded by Kleijnen Systematic Reviews Ltd, an independent research company which produces SRs, cost-effectiveness analyses and health technology assessments.

More information about KSR Evidence can be accessed here:
http://www.ksrpainevidence.com/about

Evidence-Based Medicine Reviews (EBMR) (Ovid)

Evidence-Based Medicine Reviews (EBMR)[23] is a collection of seven core evidence based medicine resources in a single searchable database. The resources are:

- Cochrane Database of systematic Reviews (CDSR)
- Database of Abstracts of Reviews of effectiveness (DARE)
- Health Technology Assessments (HTA)
- NHS Economic Evaluation Database (NHSEED)
- Article Reviews - ACP Journal Club
- Definitive Controlled Trials – The Cochrane Central Register of Controlled Trials (CENTRAL)
- Methodology Reviews – Cochrane Methodology Register (CMR)

DynaMed and DynaMed Plus (EBSCO)

DynaMed[24] is a clinical reference tool comprising of summaries of best evidence and a subscription based database aimed at medical professionals. The content of over 500 medical journals is monitored on a daily basis to update clinically organised summaries for over 3,400 topics to represent a synthesis of the best available evidence. The evidence is ranked using easy to interpret 'levels'.

DynaMed's Systematic Literature Surveillance process includes:[25]

- Cover-to-cover surveillance of highest-yield content sources
- Targeted MEDLINE searches for SRs and RCTs for high-yield journals
- Targeted MEDLINE searches for selected subject areas (e.g., complementary therapies) across all indexed journals (approximately 5,200)
- Comprehensive MEDLINE searches for guidelines

Medical journals

SRs are widely published in many scientific journals, and can be found by searching journals directly or using resources such as PubMed and other bibliographic databases to find them.

Systematic Reviews in PubMed Health and PubMed

http://www.ncbi.nlm.nih.gov/pubmed

PubMed Health[14] specialises in SRs of effectiveness from 2003 onwards. In May 2015 there were over 39,000 reviews included.[26] Such as:

- Abstracts of SRs in DARE (Database of Abstracts of Reviews of Effects) (DARE ceased production in March 2015)
- Plain language summaries and abstracts from Cochrane
- Full text of reviews from public agencies (such as regulatory authorities, health technology agencies)
- Information developed by public agencies for consumers and clinicians which is based on SRs (e.g. guidelines)

PubMed[27] contains SRs published prior to 2003 and also those not restricted to healthcare. Not all the reviews in PubMed Health are in PubMed as DARE did not restrict itself to journals included in PubMed. As DARE ceased in March 2015 more recent SRs will be in PubMed only.

Searches in PubMed can be limited to systematic reviews using the "Clinical Queries" filter[28] or article type options in the search functions. Other bibliographic databases can be searched and specific filters containing combinations of indexing terms and text terms utilised to retrieved systematic reviews.

The JBI Database of Systematic Reviews and Implementation Reports

The JBI Database of Systematic Reviews and Implementation Reports[29] is an online journal indexed in MEDLINE, Embase, Scopus, Mosby's Index and CINAHL. It contains published SR protocols and SRs of healthcare research published by the Joanna Briggs Institute and its international collaborating centres; protocols and reviews follow the JBI methodology. The first tissue was published online in 1989. Reviews may be of quantitative or qualitative research data, text and/or opinion, relate to economic data or a combinations of these.

JBI COnNECT+ (Clinical Online Network of Evidence for Care and Therapeutics)

JBI COnNECT+ is a collection of evidence based resources from the JBI including:

- Evidence based recommended practices
- Evidence summaries
- Best practice information sheets
- SRs and SR protocols
- Consumer information sheets
- Technical reports

Particular therapeutic areas are grouped together in 'nodes' such as chronic disease, cancer care and mental health. JBI COnNECT+[30] is available via the OVID platform or from JBI directly; it has some information freely available and some available on a subscription basis.

Health Technology Assessment (HTA)

The Health Technology Assessment (HTA) database was developed by the Centre for Reviews and Dissemination as a single-point resource listing all the outputs and ongoing HTA projects submitted by INAHTA members.

The HTA database[31] collates information on over 14,000 completed and ongoing health technology assessments from over 70 international agencies. Database content is supplied by the 52 members of the International Network of Agencies for Health Technology Assessment (INAHTA)[32] and by 20 other international HTA organisations.

Guidelines

Guidelines may appear as grey literature on the producing or publishing organisation's website, or could be published in the form of a report or journal manuscript. For the latter, searches of biomedical databases, such as PubMed, can be designed to retrieve guideline publications. Alternatively, there are several guideline-specific databases that can be searched to produce highly-relevant results. Examples of such include the G-I-N Guidelines Library and the National Guidelines Clearinghouse.

G-I-N Guidelines Library

The Guidelines International Network (G-I-N) produces a guidelines library with over 6,000 documents. Some of these resources are available to the public while others are for members only. Only organisational members are able to submit guidelines.[33-35]

National Guideline Clearinghouse

The National Guideline Clearinghouse (NGC) is a public resource database of evidence-based clinical practice guidelines and related documents. It is maintained by AHRQ of the US Department of Health and Human Services in partnership with the American Medical Association (AMA) and American Association of Health Plans (AAHP) Foundation.[36, 37]

In 2013 the NGC revised their inclusion criteria to keep them current with advances in the field of guideline development. The new inclusion criteria insists that guidelines are based on an SR of the evidence and that there is an assessment of the benefits and harms of the recommended care and alternative care options:

> *Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.*[38]

The NGC reaches a large audience within the United States and abroad, offering developers an effective vehicle for the dissemination of guidelines. Over 350 organisations have contributed guidelines to the NGC and there are currently 2,236 individual guideline summaries.[39-41]

Research Programmes

Research programmes and governmental reports often fall under the category of unpublished or grey literature. As such, reports of this type might not be available in the public domain, either in full format or in part if confidential or sensitive information is included. Some organisations endeavour to publish as much as possible via their webpages, or an organisational portal. Where programmes have ceased to receive funding, publications might still be made available in archival portals, such as the NIHR Service Delivery and Organisation (SDO).[42]

Industry/Commercial

As mentioned previously, selected outputs from industry-commissioned or conducted reviews, might appear as journal manuscripts, conference presentations or as reports. There is no requirement for commercially produced SRs to be published in the public domain.

Dissertations and theses

Students and researchers often undertake 'systematic review' format projects as part of their dissertations or theses. Dissemination outputs might include journal manuscripts or conference presentations, and many full-text theses are made available by the education institution. This might be via a library catalogue, departmental webpage[43] or institutional repository.[44] Certain theses are retained by legal deposit libraries, such as the British Library,[45] and may be available for a fee. Many universities provide access to their theses via their websites. Alternatively, it might be possible to obtain a copy of a specific thesis by contacting the researcher directly.

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Appendix 3: KSR Evidence database bibliometric analysis

KSR Evidence[1] is a series of databases which present critically appraised systematic reviews and meta-analyses. KSR Evidence has been developed by Kleijnen Systematic Reviews Ltd. KSR Pain Evidence[2] is now publicly available on a subscription basis, and further topic specific KSR Evidence databases are under development on the following topics:

- Dementia
- Diabetes
- Lung Diseases
- Mental Health

An in-house administration version of the KSR Evidence database[1] was used to undertake a bibliometric analysis for this report, during February 2016. The in-house version of KSR Evidence was compiled through highly sensitive and comprehensive searches, using a systematic review methodological study design filter to identify systematic reviews published from 2010 onwards. Searches were run on a regular basis, on a range of biomedical and healthcare databases to ensure currency and coverage. Searches were not limited by language or publication status. Systematic reviews on KSR evidence are given one of four main classifications - Intervention; Diagnostic; Prognostic/predictive; Etiological. Identified reviews were summarised by experienced reviewers, and quality appraised using an adapted version of the ROBIS tool.[3] Reviews were assessed on four domains:

1. Study eligibility criteria
2. Identification and selection of studies
3. Data collection and study appraisal
4. Synthesis and findings.

From these domain-specific assessments, an overall summary of the risk of bias and clinical "bottom line" were produced for each systematic review. All review appraisals were checked by an independent second systematic reviewer for accuracy. Further information about the identification, selection and appraisal process can be found on the KSR Pain Evidence website.[2]

Searching and appraisals were initiated during 2014, and all work was undertaken independently of the 'Evaluation of NIHR investment in Cochrane infrastructure and systematic reviews' project.

The internal admin version of KSR Evidence, containing in-process and completed assessments, was analysed to look at comparative publication rates of reviews published by Cochrane, as well as those conducted by all other review producers (non-Cochrane reviews). Further analysis of the three levels of RoB summary was also conducted for completed appraisals on the topics of pain and lung disease only.

Table 1: Bibliometric analysis from KSR Evidence in-house database[1]

Topic	Publication Year: 2010-2015	TOTAL
Pain	**All SRs**	3,463
	Cochrane SRs	373
	Non-Cochrane SRs	3,090
Dementia	**All SRs**	984
	Cochrane SRs	48
	Non-Cochrane SRs	936
Lung	**All SRs**	4,176
	Cochrane SRs	403
	Non-Cochrane SRs	3,773
Diabetes	**All SRs**	2,386
	Cochrane SRs	72
	Non-Cochrane SRs	2,314
Mental Health	**All SRs**	7,411
	Cochrane SRs	257
	Non-Cochrane SRs	7,154
All topics combined	**All SRs**	**18,420**
	Cochrane SRs	**1,153**
	Non-Cochrane SRs	**17,267**

Table 2: Overall summary of Risk of Bias (RoB) assessments from KSR Evidence in-house database[1]

Topic		Overall Risk of Bias (RoB)			Completed Appraisals	Appraisals in process	TOTAL
		High	Low	Unclear			
Pain	**All SRs**	1347	509	73	**1929**	1533	3463
	Cochrane SRs	28	236	10	**274**	99	373
Lung	**All SRs**	1812	411	56	**2279**	1897	4176
	Cochrane SRs	18	243	11	**272**	131	403
Both topics combined	**All SRs**	3159	920	129	**4208**	3430	7639
	Cochrane SRs	46	479	21	**546**	230	776

This analysis was conducted by Sohan Deshpande and Kate Misso.

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Appendix 4: NIHR-funded CRG reviews used to inform NICE and SIGN Guidelines

Table 1: NIHR-funded CRG reviews used to inform NICE and SIGN Guidelines published between 2013 and February 2016[1]

NIHR-funded CRG	Number of reviews cited in guidelines	Note
1. Airways	59 reviews in 4 guidelines: 3 NICE; 1 SIGN	1 SIGN guideline references 53 Cochrane SRs
2. Bone, Joint and Muscle Trauma	10 reviews in 4 guidelines: 2 NICE; 2 SIGN	
3. Cystic Fibrosis and Genetic Diseases	No reviews/guidelines for this time period	2006: 1 review in 1 NICE guidelines 2008: 1 review in 1 NICE guideline
4. Dementia and Cognitive Improvement	No reviews/guidelines for this time period	2006: 19 reviews in 1 NICE guidelines 2010: 4 reviews in 1 NICE guideline
5. Common Mental Disorders	12 reviews in 6 guidelines: 5 NICE; 1 SIGN	
6. Ear, Nose and Throat Disorders	6 reviews in 2 guidelines (1 NICE; 1 SIGN)	
7. Epilepsy	14 reviews in 2 guidelines (1 NICE; 1 SIGN)	1 SIGN guideline references 13 Cochrane SRs
8. EPOC	21 reviews in 12 guidelines (10 NICE; 2 SIGN); 2 reviews in more than one guideline (frequency: 1 in 3; 1 in 2)	
9. Eyes and Vision	1 review in 1 SIGN guideline	
10. Gynaecological Cancer	15 reviews in 6 guidelines: 2 NICE; 4 SIGN	
11. Heart	23 reviews in 10 guidelines: 8 NICE; 2 SIGN; 3 reviews in more than one guideline (frequency: 3 in 2)	
12. Incontinence	20 reviews in 3 guidelines: 2 NICE; 1 SIGN	
13. Injuries	18 reviews in 8 guidelines: 7 NICE; 1 SIGN. 1 review in more than one guideline (frequency: 1 in 2)	

NIHR-funded CRG	Number of reviews cited in guidelines	Note
14. Neuromuscular Disease	10 reviews in 2 guidelines (1 NICE; 1 SIGN)	
15. Oral Health	21 reviews in 6 guidelines: 4 NICE; 2 SIGN. 5 reviews in more than one guideline (frequency: 5 in 2)	
16. PaPAS	32 reviews in 7 guidelines: 3 NICE; 4 SIGN. 1 review in more than one guideline (frequency: 1 in 2)	
17. Pregnancy and Childbirth	69 reviews in 14 guidelines: 11 NICE; 3 SIGN. 3 reviews in more than one guideline (frequency: 1 in 3; 2 in 2)	1 NICE guideline references 37 Cochrane SRs
18. Schizophrenia	46 reviews in 5 guidelines: 4 NICE; 1 SIGN. 4 reviews in more than one guideline (frequency: 4 in 2)	1 SIGN guideline references 25 Cochrane SRs
19. Skin	2 reviews in 1 NICE guideline	
20. Tobacco Addiction	26 reviews in 7 NICE guidelines. 12 reviews in more than one guideline (frequency: 11 in 2; 1 in 3): most cited review "Nicotine replacement therapy for smoking cessation"	
21. Wounds	10 reviews in 3 guidelines: 2 NICE; 1 SIGN	10 reviews in 3 guidelines: 2 NICE; 1 SIGN

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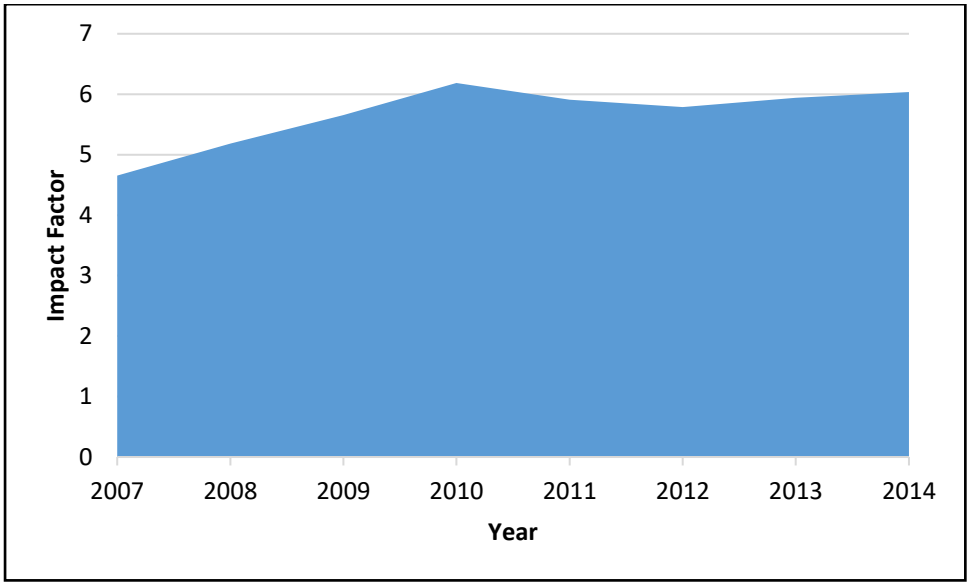
Appendix 5: Impact factor of CDSR (2007-2014)

Impact factors are produced by Thomson Reuters and published in the Journal Citation Reports (JCR) database, in both the Science and Social Sciences editions.[1]

Figure 1: Impact factor of CDSR 2007-2014[2]



The Cochrane Library's publisher, John Wiley & Sons, has calculated nominal "impact factors" for each CRG on an annual basis, beginning in 2010.[3] John Wiley's method of calculation by CRG differs to the official IF calculation for CDSR which is produced by Thomson Reuters. Wiley hand-match citation data for each Cochrane SR and individual CRG, against information collected from Thomson Reuters' Web of Science Citation Index.[4]

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Appendix 6: NIHR-funded CRG specialised registers

Table 1: Confidential. Studies in NIHR-funded CRG registers, July 2013: top five UK CRGs[1]

Rank	NIHR Funded CRG	Studies in specialised register
1	PAPAS	45,025
2	Heart	39,079
3	Depression, Anxiety and Neurosis (now called Common Mental Disorders)	32,025
4	Airways	31,047
5	Oral Health	28,929

Source: Quinquennial review,[1] July 2013.

Table 2: Confidential. Studies in NIHR-funded CRG registers, July 2013: top five UK CRGs[1]

Rank	NIHR Funded CRG	# of reviews per 1,000 register entries
1	Gynaecological Cancer	30.04
2	Cystic Fibrosis and Genetic Disorders	29.80
3	Epilepsy	27.81
4	Pregnancy and Childbirth	25.67
5	Neuromuscular Disease	22.50

Source: Quinquennial review,[1] July 2013.

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Appendix 7: Summary of NHS plans and White Papers

Overview of current NHS Plans

For Cochrane UK to meet its aim of informing healthcare decision-making, it needs to align its priorities, actions and output with those of NHS England, as summarised in Tables 1 and 2 below.

Table 1: Summary of the key factors outlined in the NHS "Five Year Forward View" strategy to promote a new relationship with patients and communities[1]

Getting serious about prevention
Incentivising and supporting healthier behaviour
Targeted prevention
NHS Support to health people get and stay in employment
Workplace health
Empowering patients
Improving information available to patients
Supporting people to manage and improve their own health
e.g. significant investment in evidence-based approaches
Giving patients more control and choice over their care
Engaging communities
Supporting carers
Encouraging community volunteering
Stronger partnerships with charitable and voluntary sector organisations
The NHS as a local employer
The NHS as a social movement

Table 2: Approaches to achieve change[1]

Backing diverse solutions and local leadership
Providing aligned national NHS Leadership
Supporting a modern workforce
Exploiting the information revolution
Accelerating useful health innovation
Accelerating innovation in new treatments and diagnostics
Accelerating innovation in new ways of delivering care
Driving efficiency and productive investment

Priorities to address the identified gaps in health and care are outlined in the related document the "NHS Fiver Year Forward View: time to deliver",[2] which emphasises the need to improving quality of healthcare, reducing preventable ill-health, and maximising value of investment and efficiency.

Table 3: Identified priorities to close the gaps in health care[2]

Closing the care and quality gap Raising the quality bar higher for everyone Narrowing the gap between the best and the struggling Closing the health and wellbeing gap Prevention of ill-health Closing the funding and efficiency gap Preventing and managing demand Maximising value of investment Redesigning more productive services

Many of the aims of the R&D strategy sit within the strengths of the Cochrane Collaboration, including promotion uptake research skills, training provider, collaboration between individuals and organisations, and engagement with patients and the public.

Table 4: Six key objectives and planned outcomes of the Research and Development Strategy[3]

1. Identify and prioritise commissioning health services research topics and coordinate this work with the DoH, NIHR, Health Research Authority, charities, industry and other stakeholders. • A planned and coordinated research activity plan • A policy research programme(PRP) reflecting and supporting NHS England research priorities and requirements, and contributing to the evidence base for commissioning high quality services • Research evidence to inform commissioning and improve patient safety • Identification of commissioning priorities • Increase of funded research programmes and projects reflecting commissioning priorities
2. Develop the evidence based in relation to models of commissioning to ensure the approach to commissioning services is based on the best evidence and effectiveness • A research-aware culture, research evidence translated into practice, and the rapid adoption of innovation • Clear interface between academic and science partners and the NHS to support translation of research into practice • Use of evidence for clinical improvement, and to informing planning of commissioning and design of health care • Implementation of effective knowledge translation models and development of knowledge champions
3. Increase capacity amongst NHS England and commissioning staff to undertake research, and to utilise the outcomes of research, thereby increasing the quality of care and treatment • Increased staff awareness of value of evidence to clinical practice, commissioning, organisation development and service management • More clinical and professional staff taking up research opportunities • Evidence-based commissioning • Raising awareness amongst commissioners of the value of evidence • Increasing research skills • Policy and process for Excess Treatment Costs
4. (i) Ensure the inclusion of patients in setting priorities for research and participation in the design, delivery and dissemination of research

(ii) Promote the ideal that every patient coming into the NHS is offered an opportunity to participate in research

- Research priorities reflecting patients' priorities
- Increasing patient participation in research
- Increased public awareness of research opportunity, activity and impact
- Establishment of a reference group to inform the development and implementation of the Research strategy
- Participation of skilled carers and patients in research

5. Increase the availability of information on current and completed research and outcomes to the public
   - Access to accurate and up-to-date public information about research opportunities, projects, outputs and outcomes
   - Increased patient participation in research in primary care and specialist service settings
   - Increase in patient engagement in research dissemination and translation
   - Positive and open relationships with other stakeholders in the research economy
   - Increased interest in the use of research and evidence
   - Accurate and up-to-date information for staff and the public
   - Sharing good practice and engagement of staff

6. Maximise the benefits of research through innovation, income, knowledge improvements and impact
   - Increasing translation of research into practice, and spreading innovation and good practice across the NHS
   - Completion of policy research projects to inform practice and organisational development and improvement
   - Collaborative working between academic and science partners, and the NHS to develop innovation and spread good practice
   - Collaborative working to develop and answer policy research between a range of partner agencies
   - Collaborative working with NIHR and research networks to develop research programmes in under-developed areas that increase the outcomes within the NHS Outcomes Framework
   - Increasing numbers of clinical and non-clinical staff with research skills, knowledge and contribution to the evidence base

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Appendix 8: Relevancy rating exercise undertaken by the NIHR Dissemination Centre raters

Table 1: Relevancy rating undertaken by the NIHR Dissemination Centre raters

NIHR-funded CRG	**Title** (*if applicable*, please indicate if this review included a summary of findings table by placing an (S) after the title)	Public Rater*		GP/AHP Rater*		Commissoning Rater*	
Airways	Aclidinium bromide for stable chronic obstructive pulmonary disease (S)	Y	N	Y	Y	Y	Y
Airways	Anticoagulation therapy versus placebo for pulmonary hypertension	Y	N	N	Y	U	
Airways	Bronchial thermoplasty for moderate or severe persistent asthma in adults (S)	N	N	Y	Y	Y	Y
Bone, Joint and Muscle Trauma	Acupuncture for treating acute ankle sprains in adults	N		N	N	Y	Y
Bone, Joint and Muscle Trauma	Anabolic steroids for rehabilitation after hip fracture in older people	N		N	N	Y	Y
Bone, Joint and Muscle Trauma	Aspiration of the elbow joint for treating radial head fractures (S)	N		N	Y	Y	Y
Cystic Fibrosis	Immune tolerance induction for treating inhibitors in people with congenital haemophilia A or B (S)	Y		Y			
Cystic Fibrosis	Appetite stimulants for people with cystic fibrosis (S)	Y		Y			
Cystic Fibrosis	Interventions for treating acute bleeding episodes in people with acquired hemophilia A	Y		Y			

NIHR-funded CRG	**Title** (*if applicable*, please indicate if this review included a summary of findings table by placing an (S) after the title)	Public Rater*		GP/AHP Rater*		Commissoning Rater*	
Dementia	Psychological treatments for depression and anxiety in dementia and mild cognitive impairment (S)	Y	Y	Y	Y	U	
Dementia	Interventions for preventing delirium in older people in institutional long-term care (S)	Y	Y	Y	Y	Y	
Dementia	Pharmacotherapies for sleep disturbances in Alzheimer's disease	Y	Y	Y	Y	Y	
Common Mental Disorders	Azapirones versus placebo for panic disorder in adults (S)	Y	U	Y	Y	U	Y
Common Mental Disorders	Repetitive transcranial magnetic stimulation (rTMS) for panic disorder in adults (S)	U	U	N	Y	N	N
Common Mental Disorders	Psychological, social and welfare interventions for psychological health and well-being of torture survivors (S)	Y	N	Y	Y	N	Y
Ear, Nose and Throat	Amplification with hearing aids for patients with tinnitus and co-existing hearing loss (S)	Y	Y	N		N	
Ear, Nose and Throat	De-escalation treatment protocols for human papillomavirus-associated oropharyngeal squamous cell carcinoma	Y	?	Y		N	
Ear, Nose and Throat	Photodynamic therapy for recurrent respiratory papillomatosis (S)	Y	U	N		N	
Epilepsy	EEG for children with complex febrile seizures	Y	Y				

NIHR-funded CRG	**Title** (*if applicable*, please indicate if this review included a summary of findings table by placing an (S) after the title)	Public Rater*		GP/AHP Rater*		Commissoning Rater*	
Epilepsy	Stiripentol for focal refractory epilepsy	Y	Y				
Epilepsy	Sulthiame monotherapy for epilepsy (S)	Y	Y				
Eyes and Vision	Accommodative intraocular lens versus standard monofocal intraocular lens implantation in cataract surgery	Y	N	Y			
Eyes and Vision	Antimetabolites in cataract surgery to prevent failure of a previous trabeculectomy	Y	N	N			
Eyes and Vision	Anti-vascular endothelial growth factor for proliferative diabetic retinopathy	Y	N	Y			
Gynaecological, Neuro-oncology and Orphan Cancer	Image guided surgery for the resection of brain tumours	Y		Y		Y	N
Gynaecological, Neuro-oncology and Orphan Cancer	Laparoscopy for diagnosing resectability of disease in patients with advanced ovarian cancer	N		N		Y	Y
Gynaecological, Neuro-oncology and Orphan Cancer	Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases	Y		N		U	Y

NIHR-funded CRG	**Title** (*if applicable*, please indicate if this review included a summary of findings table by placing an (S) after the title)	Public Rater*		GP/AHP Rater*		Commissoning Rater*	
Heart	Inotropic agents and vasodilator strategies for acute myocardial infarction complicated by cardiogenic shock or low cardiac output syndrome (S)	Y	Y	U	N	Y	
Heart	Red cell transfusion management for patients undergoing cardiac surgery for congenital heart disease	N	U	U	N	U	
Heart	Stem cell therapy for chronic ischaemic heart disease and congestive heart failure (S)	Y	Y	Y	Y	Y	
Incontinence	Intermittent self-dilatation for urethral stricture disease in males (S)	U		N	Y	Y	Y
Incontinence	Single-incision sling operations for urinary incontinence in women	N		N	Y	Y	Y
Incontinence	Surgical management of functional bladder outlet obstruction in adults with neurogenic bladder dysfunction	U		Y	Y	Y	Y
Injuries	Non-operative versus operative treatment for blunt pancreatic trauma in children	Y		U		Y	
Injuries	Oral or parenteral iron supplementation to reduce deferral, iron deficiency and/or anaemia in blood donors	Y		Y		Y	
Injuries	Interventions for primary prevention of suicide in university and other post-secondary educational settings	N		Y		Y	

NIHR-funded CRG	**Title** (*if applicable*, please indicate if this review included a summary of findings table by placing an (S) after the title)	Public Rater*		GP/AHP Rater*		Commissoning Rater*	
Neuromuscular	Endoscopic release for carpal tunnel syndrome (S)	Y		Y	Y	Y	Y
Neuromuscular	Ephedrine for myasthenia gravis, neonatal myasthenia and the congenital myasthenic syndromes	N		U	N	U	Y
Neuromuscular	Interventions for fatigue in peripheral neuropathy (S)	U		N	U	Y	Y
Oral Health	Direct composite resin fillings versus amalgam fillings for permanent or adult posterior teeth (0089)	Y	Y	Y	Y	Y	
Oral Health	Interventions for iatrogenic inferior alveolar and lingual nerve injury (0094)	N	Y	N	Y	Y	
Oral Health	Systemic antibiotics for symptomatic apical periodontitis and acute apical abscess in adults (0272)	Y	Y	N	U	Y	
PaPaS	Psychological therapies (Internet-delivered) for the management of chronic pain in adults	Y		Y	Y	Y	
PaPaS	Imipramine for neuropathic pain in adults (s x1)	N		Y	U	Y	
PaPaS	Zolmitriptan for acute migraine attacks in adults (s x1)	N		Y	Y	Y	
Pregnancy	Hyaluronidase for reducing perineal trauma	N		Y		U	
Pregnancy	Probiotics for preventing gestational diabetes	Y		Y		Y	

NIHR-funded CRG	**Title** (*if applicable*, please indicate if this review included a summary of findings table by placing an (S) after the title)	Public Rater*		GP/AHP Rater*		Commissoning Rater*	
Pregnancy	Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes	Y		N		Y	
Schizophrenia	HIV prevention advice for people with serious mental illness (S)	Y	Y	N		Y	U
Schizophrenia	Implementation of treatment guidelines for specialist mental health care (S)	N	Y	Y		U	N
Schizophrenia	Information and communication technology based prompting for treatment compliance for people with serious mental illness (S)	N	N	N		Y	Y
Skin	Topical anti-inflammatory agents for seborrhoeic dermatitis of the face or scalp (s)	Y	Y	Y	Y	Y	
Skin	Topical antifungal treatments for tinea cruris and tinea corporis (s)	Y	Y	Y	Y	Y	
Skin	H1-antihistamines for chronic spontaneous urticaria (s)	Y	Y	N	Y	Y	
Tobacco	Oral and sublingual immunotherapy for egg allergy (S)	Y		N		N	
Tobacco	School policies for preventing smoking among young people (S)	Y		N		N	
Tobacco	Electronic cigarettes for smoking cessation and reduction (S)	Y		Y		N	
Wounds	Subcutaneous closure versus no subcutaneous closure after non-caesarean surgical procedures (S)	Y	Y			Y	Y

NIHR-funded CRG	**Title** (*if applicable*, please indicate if this review included a summary of findings table by placing an (S) after the title)	Public Rater*		GP/AHP Rater*		Commissoning Rater*	
Wounds	Continuous versus interrupted skin sutures for non-obstetric surgery	Y	Y			Y	Y
Wounds	Repositioning for pressure ulcer prevention in adults	Y	Y			Y	Y

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Appendix 9: NICE Cochrane Quality and Productivity topics: 2 examples

Two examples of Cochrane reviews are presented below:

- ***Bariatric surgery for non-alcoholic steatohepatitis in obese patients***

This QP[1] referred to the review CD007340,[2] produced by the non-NIHR-funded Hepato-Biliary CRG. The implications for practice section of the SR stated " The lack of randomised clinical trials to demonstrate the beneficial or harmful effects of bariatric surgery procedures for treatment of NASH could not enable us to reach any scientifically sustained conclusion".[1] As a consequence, the NICE QP stated "Reducing or stopping bariatric surgery for non-alcoholic steatohepatitis in obese patients is likely to improve quality of patient care and result in productivity savings by avoiding unnecessary operations."[1]

Although no usage evidence was available to estimate current levels of NHS use, the QP anticipated that the change could be achieved quickly (0-3 months), with real cash savings likely due to reduced activity for this condition. Furthermore, there was potential to improve clinical quality by reducing the use of unproven therapies. There were expected improvements in patient safety by avoiding the risk of adverse events associated with surgery, and improved patient and carer experience by reducing unnecessary surgery.[1]

- ***Neoadjuvant chemotherapy for cervical cancer***

This QP[3] referred to the review CD007406,[4] produced by the NIHR-funded Gynaecological, Neuro-oncology and Orphan Cancer CRG. The QP summarises the SR's implications for practice section as concluding it is "unclear whether neoadjuvant chemotherapy consistently offers a benefit over surgery alone. Therefore adding neoadjuvant chemotherapy to surgery cannot be recommended."[3] This change in practice was anticipated as having no impact on patient safety or the patient or carer experience. Furthermore, stopping or reducing unnecessary neoadjuvant chemotherapy was likely to improve patient care and clinical quality, and to have productivity and cash savings through reduced activity and expenditure.

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Appendix 10 NICE Cochrane Quality and Productivity topics: list of topics

Example: Interventions for treating pain and disability in adults with complex regional pain syndrome- an overview of systematic reviews

National Institute for Health and Care Excellence. Interventions for treating pain and disability in adults with complex regional pain syndrome - an overview of systematic reviews, 2015 [accessed 15.12.15]. 5p. Available from: https://www.nice.org.uk/savingsandproductivityandlocalpracticeresource?ci=http%3A%2F%2Farms.evidence.nhs.uk%2Fresources%2FQIPP%2F1045548%3Fniceorg%3Dtrue

Interventions for treating pain and disability in adults with complex regional pain syndrome- an overview of systematic reviews

NICE has developed the Cochrane Quality and Productivity topics to help the NHS identify practices that could be significantly reduced or stopped completely, releasing cash and/or resources without negatively affecting the quality of NHS care. Each topic has been derived from a Cochrane systematic review that has concluded that the evidence shows that the practice is harmful or ineffective and should not be used, or that there is insufficient evidence to support widespread use of the practice.

Unless otherwise stated, the information is taken with permission from the Cochrane systematic review.

NICE summary of Cochrane review conclusions

Complex regional pain syndrome (CPRS) is characterised by pain and a variety of other local symptoms that are disproportionate to the injury sustained. This comprehensive review identified a number of systematic reviews of clinical evidence. However, despite the identification of numerous papers in the area, there was insufficient evidence to recommend an effective treatment approach. There is low quality evidence for several treatment options and no firm recommendations could be made about their efficacy and use. However, moderate quality evidence suggests intravenous regional blockade with guanethidine is not effective and may be associated with complications.

The 'Implications for practice' section of the Cochrane review stated:

'There is insufficient high quality evidence on which to base comprehensive clinical guidance on the management of CRPS. However, there is moderate quality evidence that intravenous regional blockage guanethidine is not effective. There is low or very low quality evidence relating to the efficacy of a range of therapies in CRPS although all of this evidence, both positive and negative, should be interpreted with caution and does not reliably aid clinical decision making. Until further larger trials are undertaken an evidence-based approach to managing CRPS will remain difficult.'

Details of Cochrane review

Cochrane review title

Interventions for treating pain and disability in adults with complex regional pain syndrome- an overview of systematic reviews (Review)

Citation

O'Connell NE,Wand BM, McAuley J,Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome- an overview of systematic reviews. *Cochrane Database of Systematic Reviews* 2013, Issue 4. Art. No.CD009416. DOI:

10.1002/14651858.CD009416.pub2.

When the review content was assessed as up to date
1 March 2013

Quality and productivity category
Right care, Long-term conditions

Relevant codes	OPCS	ICD10	HRG
	U51.3	R529	M2550 and VC10Z

Programme budget:
Neurological

Evidence

Relevance to the NHS

Complex regional pain syndrome (CRPS) is an umbrella term for a variety of clinical presentations, characterised by chronic persistent pain, usually in the hands or feet, that is disproportionate in severity to any underlying injury. It often involves a variety of other symptoms such as swelling, discolouration, stiffness, weakness and changes to the skin. As there is no strong consensus regarding the optimal management of this condition, a range of different therapeutic interventions are currently utilised. The objective of this Cochrane review was to summarise the evidence from Cochrane and non-Cochrane systematic reviews of the efficacy of any therapeutic intervention used to reduce pain, disability or both in adults with CRPS.

Six Cochrane reviews and 13 non-Cochrane systematic reviews, that included evidence relating to a broad range of treatments, from drugs to surgical procedures, rehabilitation and alternative therapies, were included in this review. Participants of the trials reviewed where adults 18 years or older described as suffering from CRPS or an alternative descriptor for this condition (for example reflex sympathetic dystrophy, causalgia). Studies also included participants with post-stroke shoulder-hand syndrome, which is considered a form of CRPS and is distinct from mechanical post-stroke shoulder pain.

Cochrane reviews demonstrated better methodological quality than non-Cochrane reviews. For most treatments, there were only a small number of published trials and the quality of these trials was mixed. As such, most of the evidence for different therapeutic interventions is of low or very low quality and cannot be regarded as reliable.

None of the studies included demonstrated a significant effect on pain of using an intravenous regional blockade (IVRB) using guanethidine compared with placebo. Ramamurthy (1995) found no difference between groups receiving varying numbers of guanethidine blocks. Adverse events were reported in studies included in the reviews by Jaded (1995) and Tran (2010).

Moderate quality evidence suggests that an IVRB using guanethidine is not effective and that the procedure appears to be associated with a risk of significant adverse events. For a wide range of other interventions, there is either no evidence, low quality or very low quality evidence available from which no conclusions should be drawn.

Based on the existing evidence it is difficult to draw firm conclusions as to which interventions should be offered to patients with CRPS. There is a clear need for further research for most existing treatments for CRPS as reasonably confident conclusions can only be drawn for the ineffectiveness of IVRB guanethidine.

Relevant NICE guidance and products

Neuropathic pain- pharmacological management: The pharmacological management of neuropathic pain in adults in non-specialist settings
November 2013

Ultrasound-guided regional nerve block [IPG285]
January 2009

Other accredited guidance and products

Royal College of Physicians: Pain: Complex regional pain syndrome guideline
May 2012

Estimate of current NHS use

- Approximately 1 in 3,800 people develop CRPS each year. In England this equates to approximately 7,100 people aged 40 years and over (NHS Choices, accessed 2015).
- In 2012/13 there were 7,700 finished consultant episodes (primary diagnoses ICD10 codes -M89.0 and G56.4) of complex regional pain syndrome in the NHS in England.
- Specific numbers of people receiving the different types of interventions for the condition are not available. (The Health and Social Care Information Centre, 2013).

Level of productivity savings anticipated

- This Cochrane review is not saying do not use the interventions but that until further larger trials are undertaken an evidence-based approach to managing CRPS will remain difficult. However, organisations using these interventions may save if they were to stop them. The Cochrane review highlights use of IVRB guanethidine as the key recommendation to stop.
- The tariff for IVRB using is likely to be included in minor pain procedures. This is equal to £522 (NHS National Tariff Payment, 2013).
- The cost of admitted patient rehabilitation of pain syndromes varies depending on the level of pain (level 3, 2 and1) from £279 to £1646 (Department of Health, 2013a).
- Community occupational therapist services cost £70 and £66 (currency code A06A1 and A06AG) for one to one and group respectively. Community physiotherapist services cost £50 and £39 (A08A1 and A08AG) for one to one and group respectively (Department of Health, 2013b).

Type of saving

- Savings are likely to be productivity savings to providers rather than cash savings.

Any costs needed to achieve the savings

- No costs required to achieve change.

Other information

- There is potential saving if the interventions such as neurostimulation, rehabilitation of pain, occupational therapy and physiotherapy are discontinued.

Potential impact on quality of NHS care

Impact on clinical quality

Potential to improve clinical quality to a slight extent by ending ineffective treatments.

Impact on patient safety

Stopping the use of IVRB using guanethidine would be expected to improve patient safety as the risk of associated adverse events is reduced.

Impact on patient and carer experience

Not anticipated to have any impact on patient and carer experience.

Likely ease of implementation

Time taken to implement

Can be achieved quickly: 0-3 months.

Healthcare sectors affected

Affects one department or team.

Stakeholder support

Likely to achieve good buy-in from key influencers.

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Appendix 11: Evaluation of NIHR investment in Cochrane. Report from Stakeholder interviews for review

Crowe S. *Evaluation of NIHR investment in Cochrane. Report from Stakeholder interviews for review*. Oxford: Crowe Associates Ltd., February 2016 (updated January 2017) [accessed 17.2.16]. 22p.

Evaluation of NIHR investment in Cochrane - Report from Stakeholder interviews

Prepared by Crowe Associates Ltd - February 2016

Contents

Summary

Thirty four interviews were conducted with a range of Cochrane review users and producers, many of whom have multiple roles and interests in evidence synthesis and how this is used in health care in the UK. The final interviewee summed up what they expected as outputs from the NIHR investment in Cochrane, "*culture change in the NHS (towards using evidence) and better decision making"* and this seemed to sum up the overall findings of this interview process.

Cochrane is a trusted and valued source of evidence for many NHS health professionals, technical experts developing clinical guidance and information producers and intermediaries. Cochrane is also a trusted source of evidence for another group of people, but they find it more challenging to use in practice, namely health commissioners, policy developers, NHS managers and the public.

Cochrane reviews are seen as a quality product with a robust process underpinning review production. The identity and brand is strong and visible to those who are 'research aware'. However relevance of Cochrane reviews is an issue for some of the people interviewed in this sample, and despite the quality of the product Cochrane reviews will have limited value if they do not address questions of importance and relevance to the NHS. "*You have pieces of very well done research that have limited use and interest to policy and practice development and/or commissioning".*

They are well received when they have clearly described interventions, are not too narrow in scope address current and ongoing uncertainty, explain the treatment effect (or not) simply, and attempt to place the review in context.

It is encouraging to see UKCC's efforts in using social media as a channel for communicating and providing context for the results and implications of Cochrane reviews. However some UK review groups are perceived as risk averse about having a public conversation about their reviews, restricting themselves to posting a review title and expecting users to do the rest of the work.

Systematic reviews is now a crowded market place and interviewees wanted to know who Cochrane thought were its' most important users in the NHS? There wasn't consensus from interviewees about who these groups of people or organisations are, but many were very interested in having a dialogue about this with Cochrane.

There was a certain amount of push back about Cochrane's policy of focussing on high quality randomized controlled trials for reviews ('gold standard'), although many realised that this was Cochrane's core offer of evidence. Many were interested in exploring how to incorporate different types of primary research; pragmatic trials and realist evaluations of treatments, qualitative research, cohort studies and large data sets (such as the National Joint Registry).

Perhaps the biggest challenge is getting the balance right between full reviews of high importance and relevance to the NHS and quicker (automated?) routes for updates, rapid reviews to assess critical and time sensitive questions and reviewing the value of 'empty reviews' which are important markers for research gaps also use up precious resource.

Most of the interviewees described the current NIHR spend on Cochrane as good value for money and commented that Cochrane reviews are much less expensive than primary research. They are the most appropriate unit of knowledge translation and are generally far more informative in this respect than a single trial.

They also welcomed this review, and the close analysis of value to the NHS, and the challenge of how to measure this in the future.

1. Introduction

Cochrane commissioned an external stakeholder consultation in mid 2015, and publisher Wiley commissioned a 'Cochrane User' research project in late 2015, and both reports from these exercises were submitted for the review. The panel felt that there were some limitations with these stakeholder consultation exercises; specifically they were conducted to inform general Cochrane and Wiley strategy development (rather than value to the NHS) and were worldwide (not UK or NHS focussed).

A decision was taken to augment this material with a series of interviews with stakeholders to access experiences, perceptions and expectations of Cochrane, with a specific UK and NHS focus. The themes from these interviews are described in this report. The results will be added to the other sources of stakeholder feedback to build a more complete picture and the results of this will be reflected in the overall review report.

2. Interviewee profile

The focus of the interview sample was primarily NHS and Non NHS users of Cochrane Reviews. Suggestions for interviewees with variable degrees of connection and experience with Cochrane were taken from the evaluation panel and the NIHR, Evaluation, Trials and Studies Coordinating Centre.

A total of 34 people were interviewed spanning organisations and sectors that Cochrane reviews have the potential to inform and impact including; NHS health professionals, NHS and health service

commissioners, health guideline producers, health policy makers (as distinct from commissioners), health research charities, members of the public (and patients), professional health and wellbeing membership organisations, health knowledge brokers, health bloggers and health and research publishing houses. UK based Cochrane and non Cochrane systematic review editors, authors and methodologists were also interviewed.

Many of the interviewees have multiple roles e.g. Clinician and Cochrane Author, Patient and Chief Executive Officer of a charity, clinician and health commissioner.

Table 1: Spread of expertise and roles across interviewees

Primary areas of experience represented in the interview sample	Substantive roles for interviewees
Patients and public	5
Clinicians and health professionals	8
Professional associations and membership groups	3
Guideline producers	2
Policy developers	4
Commissioners	4
Knowledge and information brokers e.g. publishers and bloggers	6
Health research charities	3
NHS management	2
Systematic reviewers (e.g. co-ordinating editors, authors, methodologists) Cochrane and non Cochrane	12

3. Interview methods

Interviews were approximately 45 minutes long, conducted mostly on the phone and followed an agreed topic guide, which the evaluation panel helped to shape. They took place during November and December 2015. Interviewees were recorded with permission. Interviewees were asked to indicate if they wanted to be named contributors to this process and most did, but several wanted to remain anonymous, so for the purposes of this report all content is anonymised. The results of several face to face interviews conducted at the 2015 Cochrane Colloquium Meeting in Vienna are added into the material for this stakeholder exercise.

The broad direction of discussion in the interviews was the health and economic impact of Cochrane reviews from 2005-2014. Questions for users of Cochrane reviews concerned;

1. Quantity, quality and impact of reviews on health commissioning, policy, practice and patient benefit
2. Relevance of the Cochrane output to the NHS and patients and the public
3. Wider benefits which contribute to the return on the NIHR investment
4. Views about the current funding package and conditions

For review producers some of the questions from the core list plus:

- Examples of reviews impacting substantially on the NHS practice and policy?
- Is the current Cochrane structure fit for purpose?
- What are the main problems facing Cochrane? Are these being adequately addressed?
- Some say that Cochrane focuses on its authors rather than its readers. What do you think?

Interviewees were also invited to suggest improvements to reviews and to the Cochrane UK structure (in relation to the NHS), examples of NHS impact and suggestions of measurements of value, impact and performance of Cochrane reviews in the UK.

At the midway stage (16 interviews) an initial thematic analysis was done and this altered the interview guide to invite comments on ideas previous interviewees had contributed. At about interview 30 no new themes were emerging from the interviews.

Where additional material was provided by interviewees as this was forwarded to the review chair for consideration as evidence for the review.

3.2 Identifying themes within the topic areas of the interviews

All interviews were written up in summary format, from the audio recordings and each interviewee was invited to validate these notes from their interview via email; about 60% chose this option.

A review of these summary notes helped to create a map of the main discussion topic areas. Interview notes were then checked in turn to allocate particular content within each topic area and capture ideas, observations and quotes that illustrated this content well.

The map was then converted into a table with high level topic headings and relevant thematic content, and source interview ID tagged in the table. To assess agreement within themes, where six or more interviewees suggested a similar idea, or made similar observations this was marked up.

Colour coding of cells in the table allowed identification of consensus from interviewees for a positive aspect of value of NIHR investment in Cochrane (blue) or an area for improvement in NIHR investment in Cochrane (yellow). Some areas of consensus in the interview sample were large 21/34 (need for increased relevance of Cochrane reviews for the NHS), others much smaller. Themes identified by the largest number of interviewees in each topic area are described in more detail and are at the beginning of the section, and then in ascending order.

Where necessary audio recordings were re visited to check for correct interpretations and to verify the quotes used in the report.

4. Topic areas

1. Value of NIHR investment in Cochrane to the NHS

1.1. Relevance of Cochrane reviews to the NHS

No matter how good a Cochrane review is the issue of relevance of reviews to patient need and health services development was a common theme across interviews. Many interviewees were able to cite relevant Cochrane reviews that had informed their individual practice and more collectively health care disciplines e.g. "Elective repeat caesarean versus planned induction of labour for women with previous caesarean"; or "Replacing peripheral venous catheter when clinically indicated versus routine" and "Interventions for preventing falls in older people living in the community". This was reflected in interviewees, across several disciplines especially clinicians and information providers...

However there was a much larger group of interviewees that wanted Cochrane reviews to be more relevant for patient needs, clinical practice and policy and health commissioning.

> *"I recently blogged about Chronic Fatigue Syndrome /ME and got a lot of flak - I went to Cochrane to see what was there - basically it was exercise and cognitive behavioural therapy (which the community feel are of no use to many of them) they already think that there is a bias in Cochrane that probably doesn't exist (Int 19)*

> *"In summary it is the difference between the internal validity of the systematic review process that occupies the minds of Cochrane rather than the external validity of the review and how much it can be generalized and used in populations that is a better measure of value. (Int 21)*
> *"The current model encourages too much self interest in deciding which reviews should be supported, and the motivation to do a systematic review is more personal than professional. This encourages reviews that are divorced from clinical need." (Int 6)*

> *"A sense that Cochrane reviews are not linked to health care delivery perspectives or experiences – certainly not in our field of CAM (Complimentary and Alternative Medicine)" (Int 9)*

Some interviewees suggested that UK review groups need to use a more 'bottom up' approach to identifying and scoping Cochrane reviews if they are to be more useful and used in the NHS (there is more on developing relationships in Theme 5.3). Whilst many interviewees acknowledged that Cochrane reviews concern clinical effectiveness questions they sometimes felt overly academic in nature and didn't reflect the "decision problems" that exist in the NHS.

Encouragingly there were plenty of offers and opportunities for Cochrane to have dialogue with people at the heart of decision making for the NHS, especially commissioners and policy makers, as well has health professionals and patients and the public.

Several interviewees asked if Cochrane reviews were addressing the 'big questions' that the NHS is currently facing. Multi-morbidity, aging and long term conditions are the back drop for the application and use of Cochrane reviews in the NHS.

"The current medical model of the Cochrane structure feels outdated and doesn't help how we address reviews that need to span disease and health areas.....this is what the NHS is grappling with" (Int 22).

Interviewees also wanted to see *less* narrowly defined Cochrane reviews and more that compared several similar interventions, these were perceived more useful for review users. Cochrane interviewees recognised that the 'salami slicing' approach to scoping reviews perhaps reflects the current performance metrics rather than how useful it will be to users.

"Current structure doesn't play well for reviews that are cross cutting (such as nutrition) and there is still too much emphasis on chunking down reviews to very specific questions that may have limited use in real life". (Int 8)

NHS commissioning and policy development decision making will encompass comparisons of different dimensions of treatments and care. One interviewee suggested that Cochrane experiment with how it currently presents related systematic reviews - perhaps grouping them together so that users can see how their results relate to each other taking the current 'you may also be interested in these reviews ' tool on the current Cochrane website one step further. For more detail see range of review products in Theme 4.1.

Some interviewees expressed frustration about the chosen outcomes used in Cochrane reviews. They recognised the tension for Cochrane reviewers working with 'what they have in the primary research" but also described how outcomes development as part of Cochrane review process could contribute to relevance and use of the review.

1.2 Clinical guidance and Cochrane reviews

Many interviewees saw clear links between Cochrane reviews and the development of clinical guidance from National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), and Royal College guidance such as Royal College of Obstetricians and Gynaecologists (RCOG) 'Green Tops'.

Up to date and relevant Cochrane reviews make developing guidance more efficient and UK Cochrane groups that anticipate guidance and prepare reviews to support these were cited and others that don't are to be encouraged. Cochrane reviews that incorporate economic elements of value of interventions are particularly welcomed.

> *"Not forget the importance of guidance and reviews that underpin financial and commissioning decision making - this could be a powerful indicator of value for money of Cochrane reviews .....they also provide us with examples of potential disinvestment in ineffective practice". (Int 27)*

Clinical guidance in theory should affect clinical practice and policy, and thus patient benefit but several interviewees expressed frustration at the challenges of implementing evidence based clinical guidelines in practice in the NHS, accepting that this may not be Cochrane's agenda, (more on this in

Theme 1.9). Efforts by the UKCC to audit the flow of UK generated Cochrane reviews into UK clinical guidance were appreciated, and noted by several interviewees.

1.3 Cochrane's contribution to evidence based health and medicine

The impact over 20 years that Cochrane and Cochrane reviews have had on the culture of evidence based health and medicine in the NHS was described many times.

> *"Cochrane was in the vanguard of suggesting that research is not just for researchers and has contributed to the wider health and research culture in this regard" (Int 1)*

There are ongoing debates about the hierarchy of evidence as the basis for the evidence based approach and this is explored in more detail in Theme 3.3. There are also concerns that the NHS isn't properly organised to receive knowledge generated from NIHR generally and Cochrane Systematic Reviews specifically. This makes it more difficult for NHS decision makers and practitioners to find what they need.

1.4 Cochrane shaping future NIHR/NHS research

The continued investment in Cochrane in the UK has helped shape NIHR and NHS research to a certain extent. This included for example the discipline of assessing existing evidence and research gaps (serviced very well by Cochrane reviews) for NIHR research applications. Specific UK review groups e.g. Wounds and Schizophrenia were given as examples of supporting 'unsexy' but important research relevant to the NHS championing better evidence of effectiveness. Some interviewees lamented situations where good evidence from Cochrane has been ignored, or where a particular research community doesn't seem to 'need' Cochrane , and that research synthesis (often called secondary research), should in fact be thought of as primary research, preceding original or replicated clinical studies.

1.5 Cochrane reviews for health information

Using Cochrane reviews to underpin and support information used by NHS health professionals, service users and the public was cited as an example of the value of the NIHR investment in Cochrane. The Information Standard seems to have been a catalyst for small to medium health and research charities to improve the quality of their public information, and for some this was their first awareness of Cochrane as an evidence source.

> *"I came across Cochrane at an Information Standard workshop as the charity was working towards this. The session explained about systematic reviews and the Cochrane Library - I was previously unaware of Cochrane and I suspect that this is true for other smaller charities" (Int 16)*

Other examples included NHS Choices and NHS Evidence (now known as Evidence Search).

1.6 Transferable skills into the NHS workforce

Much of the NIHR investment has been aimed at capacity building information and knowledge management in the research infrastructure and to some extent in the NHS.

Skills cited as 'NHS relevant' included searching for evidence, critical appraisal of research and a critical thinking mindset in decision making. Examples of Cochrane activity undertaken by NHS

health professionals have included contributions to fellowships, and post graduate qualifications. Two interviewees did wonder if more could be made of these skills in the NHS (no solutions were suggested) and one interviewee also wondered if a NHS employee who had contributed to a Cochrane review would ever do one again?

1.7 Cochrane reviews in journals and blogs

Many interviewees (NHS and other) wouldn't say that the Cochrane Library is their preferred access point for reading about Cochrane reviews and evidence generally, so the role of other information providers here is important. For clinicians the BMJ as well as specialist journals were cited as important access points for keeping up to date. The BMJ reports that where authors choose to submit Cochrane reviews for publication in BMJ they perform very well in downloads and access (Between 2005 - 2014 over 10,000 downloads and highly accessed). An internal audit of approx 250 research articles per annum showed that Cochrane reviews perform well compared to other types of research content with high downloads, access, Altmetrics scores and media interest.

Social media is providing an important access point for Cochrane evidence, especially for a wider group of users. For example The National Elf Service 'Mental Elf' (which blogs about mental health to a wide range of users) has approx - 1,300 blogs that address mental health and about 10% of these are from Cochrane Reviews, with the most useful and clinically relevant coming from the Schizophrenia Group.

1.8 Cochrane reviews produced outside the UK Whilst not all interviewees understood the complex structure of Cochrane some recognised that there was an amplified effect of the value of UK funding of Cochrane by the provision of Cochrane reviews produced by review group's external to the UK but of relevance to the NHS. It was also acknowledged that NHS health professionals are actively involved in Cochrane review activity managed outside the UK.

> *"...overseas review groups may contribute systematic reviews that have relevance and use in the UK - in the same way that some UK review groups will produce reviews that may not have traction in the UK, but be more useful overseas, this international collaboration and NIHR being a key part of that is positive" (Int 26)*

1.9 Getting research into practice in the NHS

Evidence alone is not sufficient, whilst this is not necessarily Cochrane's problem the issue of getting Cochrane evidence into practice in the NHS should be concerning everyone.

> *"The even bigger problem (and this is <u>not</u> Cochrane's fault) is the need to get an ever growing amount of evidence into practice - the GRIP (getting research into practice) problem still exists 20 years on from the evolution of evidence based medicine"(Int 30)*

One interviewee had been asked to do an evidence review for a commissioning organisation on a musculoskeletal surgical procedure - this is the fourth review on this topic that they had personally been involved in. They felt that the evidence (based on Cochrane) is clear yet there still seems to be no use of this evidence in practise with NHS activity of this surgical procedure proceeding apace.

Solutions suggested by interviewees vexed by this issue were; clinical champions (and these could be from within Cochrane whereby an author takes responsibility for disseminating the review widely),

more involvement in Cochrane from 'on the floor' practitioners so that the output has academic rigour, but also practical applications. Another interviewee (Int 29) suggested a series of tough questions for each intervention addressed by a Cochrane review;

- What is it we don't know?
- What do we know but can't do and why?
- What is the cost effectiveness of the intervention?
- What is the variation in practice that we see with the intervention?
- Can we audit this for capturing impact?

This is echoed in work more generally in value of health care, led by Sir Muir Gray one of the founders of Cochrane. The concepts of value for the NHS are categorised into 'personalised value' (to the individual), 'allocative value' how well resources are distributed to populations, and technical value i.e. overuse of low or zero value interventions, and underuse of high value (preventable death and disability) interventions.

2. Value of NIHR investment in Cochrane - general

2.1 Methods and perspectives in evidence synthesis

The long term and sustained support for evidence synthesis generally, and Cochrane in particular was seen by many to have contributed to a culture of sharing methods, ideas and approaches both across Cochrane and wider. The establishment of handbooks, guidance and other online resources that are freely available were seen as a way of 'giving back' some of the value of the funding from NIHR.

> *"The Cochrane infrastructure and networks (UK and international) allows people to give something back to the health evidence system and builds capacity" (Int 10)*

Methods development and 'meta research' on rapid reviews, complex reviews and reviews that incorporate mixed methods were seen as important developments in the world of evidence synthesis. Some feel that the prescriptive 'cook book' approach Cochrane has adopted to achieve consistency and set quality expectations could be restricting for some methodologists. Cochrane has traditionally led methodologically, but may now have to 'keep up'.

2.2 Debates about evidence

Cochrane is seen by some as an organisation that can challenge the status quo in clinical research and evidence based healthcare, its history of declarations of conflicts of interest for example. Examples given were acknowledging the importance of unpublished trials and evidence, exposing fraudulent research activity, publication bias and trials registries.

> *"They take a moral approach to research evidence and are have a 'good guy' license in their pocket.....their relative neutrality means that they can challenge and generally are interested in the truth (unlike some other organisations)" (Int 2)*

3. Quality of Cochrane reviews

3.1 Cochrane reviews perceived as high quality

A recurring theme in interviews was the perception of Cochrane reviews as high quality and reliable evidence. Some interviewees wouldn't even critically appraise a Cochrane Review - they trust it that much. Interviewees appreciate the skills and resources that are used in assembling a Cochrane review - especially the Meta analysis element.

"Cochrane is invaluable - one of the few evidence sources that as a clinician I would trust (I buy into the hierarchy of evidence). I like the rigour and methods of a Cochrane review." (Int 7)

When interviewees were asked to define what they meant by 'quality' they generally identified

1. Rigour of the review process (searching, appraisal, statistical analysis, editing) Relevance and quality assessment of the existing published and unpublished primary research)
2. Author team (technical skills and understanding of clinical issue).

There is a marked distinction however between what Cochrane users and Cochrane review producers think about the quality of Cochrane reviews. Insiders were much more likely to be critical (e.g. inclusion of published and unpublished trials, measures of bias) than Cochrane users. In fact it was suggested by several interviewees that Cochrane could usefully think about *how* methodological developments and changes are discussed and agreed. - Current arrangements for this (methods board and methods groups) is unsatisfactory, creativity and 'in time' decision making is being stifled by a complex web of groups and boards. It was noted that with such a hard won trust in the product and Cochrane brand - significant methodological developments do have to be 'water tight' before being implemented in the Cochrane production pathway.

3.2 'Empty Cochrane reviews'

Many interviewees accepted the premise of 'empty reviews' and that these are useful in pointing up research gaps and reducing uncertainty *"we know what we don't know"* (Int 32). The theory is that empty reviews are a catalyst for more or better primary research however how much this actually happens in practice was challenged in some interviews.

Nearly half the interviewees expressed frustration that there were so many empty reviews and whether this was a good use of NIHR funding?

> *"There are too many null (empty) reviews and one has to question what drives this agenda?" (Int 1)*
>
> *"Probably too many of these sorts of conclusions to merit investment..... a review of the processes that lead to decisions where it is fairly obvious that there is either not a lot of new research or that research is not going to change the overall conclusion of the review should be explored." (Int 26)*

Cochrane needs to explore a more efficient (and expedient?) process to identify potentially empty reviews. Several interviewees described processes where editorial groups go through a series of 'decision gates' or steps in deciding where to invest their effort e.g. where there is a good chance that a review will be empty, rapid searches could be run to assess whether a full protocol should be developed. Using this scenario this work could still be recorded by the Cochrane Library, perhaps

with the review title linked to a statement of 'no relevant research evidence available at the time of the search prior to protocol'. It would be important to identify to Cochrane Library users that they are looking at a different product to a protocol for a systematic review. With a scheduled check of these records and where relevant studies or trials are found or added to trial registries then a protocol could be initiated. This approach could be driven inside Cochrane as an efficiency measure and externally by the funder by not (or minimally) financially rewarding empty reviews.

"would like to see more distinction at an earlier stage about the nature of the review required - a shorter process of dialogue and using existing priority setting and contextual information to frame questions, and then rapid searching for what is likely to be out there - and then a common sense decision about where next - avoid empty reviews (and don't reward them)" (22)

3.3 The 'RCT Gold Standard' hierarchy of Evidence Based Health/Medicine

Many interviewees wanted to talk about the type of primary research included in a Cochrane review. Currently the perception (and practice) is to include only high quality Randomized Clinical Trials and this is conceptualised in the 'Hierarchy of Evidence' or 'Gold Standard' model.

Some interviewees felt strongly that this approach limits the usefulness of a Cochrane review in the real NHS world. This is due to factors including; *"the tendency for trials to include participants that don't reflect real world populations" and "use of group mean data", (Int 21). "Cochrane is in danger of applying a reductionist approach to increasingly complex areas of health". (Int 15)*

The solution as interviewees perceive it is to develop Cochrane review methods that can encompass a wider range of primary research including; pragmatic trials and realist evaluations of treatments, qualitative research, cohort studies and large data sets (such as the National Joint Registry). Interviewees recognise the methodological challenges of their suggestions but it all came down to how quality is perceived. If quality is about the purity of the process and the product then Cochrane ticks this box, however if quality is about meeting current evidence needs (especially in health commissioning and policy development) then Cochrane is failing important users and potential users.

3.4 Non directional Cochrane review results

Frustration was expressed about review results that 'sit on the fence' and don't have 'directional' results for decision making. However there was a distinction between here between ambiguity in reporting results and clear results where there is nothing to report.

One Cochrane insider felt that this was legitimate critique *"we are trying hard in our editorial processes to avoid these ambiguity traps and rely on clinicians and patients to tell us if our reviews are usefully reported." (Int 14)*

> *I recognise that review users often want directional or certain results but I think that this is a naive way to look at research" (Int 28)*

This is also part of the 'more research is needed' picture where authors could be much more specific about exactly what is needed in primary research to address the review question. Research recommendations that specify particular interventions, (and good description of these) populations

and patient important outcomes were suggested. Added to this was a plea from review users for more simplicity when communicating results especially effect size where there are very small treatment effects or harms.

Some interviewees were able to accept that there would always be Cochrane reviews where there wasn't much to report.

> *"The thing about Cochrane reviews is that they tell you about the evidence - not what they think about the evidence"* (Int 32).

Equally important and a strength of the Cochrane publishing model is the value of negative results from reviews.

> *" about a 1/3 have 'negative' results and these are important to publish as they can demonstrate evidence of absence of treatment effect, no benefit, or point up research gaps which are important findings in themselves. (Int 28)*

3.5 Review author teams and skill mix

There were indications from Cochrane review producers that there are tensions in the current hybrid volunteer and professional reviewer workforce. Not least the resource needed to support new authors or those with limited skill sets. *"My professional reviewer spends a lot of their time 'holding the hands' of new authors and this is not efficient" (Int 14)*

However the "*use of volunteers as authors of reviews is making the most of NIHR funds - authors get systematic review learning and a publication out of the transaction". (Int 5)*

"One of the strengths of the Cochrane model is the use of 'amateur' reviewers who are far more likely to come from the NHS - they have important links to real life use of reviews" (Int 34)

Another interviewee went further suggesting that author teams should have at least one author who *"has 'feet on the ground' clinically or from a patient perspective" (Int 31),* to keep a sense check on proceedings.

Cochrane producers in this sample seemed clear that there is a 'recipe' for getting good reviews done and this is: author team time, clinical expertise, methodological expertise and being able to respond to editorial comments in a timely and constructive fashion.

3.6 Timeliness and updates of Cochrane reviews

This issue was mentioned in different contexts, from guidance producers fitting in Cochrane reviews to their production timelines, to reviews being used in topical and public debates, to updates when a well known and potentially impactful trial has been published.

The aforementioned hybrid author model may be part of the problem where volunteer authors get busy and aren't able to meet Cochrane ideal editorial timelines and expectations. Or they may not be able to meet updating requirements, or 'let go' of their review so that it can be processed by others.

"What has helped deliver systematic reviews to timelines and quality expectations has been research assistants embedded in the review group (as part of programme grant funds)to get a consistency of quality and focus on key reviews". (Int 5)

However a more fundamental concern from some interviewees is a focus on the need of the user and the pressing nature of the question being considered.

"A good rationale for making decisions about different methods is being flexible and asking; is this the right approach to answer the question? What is the risk of getting it wrong? What is the strength of the primary evidence? Being clear about the approach and limitations in the output. Essentially for some urgent decisions some form of evidence synthesis is better than none, and a dose of pragmatism might not go amiss." (Int 26)

"go for rapid reviews where need is great and a full review where it is an important and impactful question where there is evidence and maybe is not so time critical" (22)

3.7 Setting priorities for Cochrane reviews

This is more a question of clarification, and relates somewhat to theme 1.1 (Relevance of reviews). Interviewees wanted to know how review groups set their priorities for reviews and who and what influenced these decisions (in the UK). They were also interested in whether models like the James Lind Alliance (JLA) was used within Cochrane, or if JLA priorities were reflected in Cochrane review priorities.

"Main issue to increase value of NIHR spend on Cochrane is to have a more transparent and robust process for prioritization and selection of reviews so that they are relevant and useful and the effort it focussed in these areas." (Int 8)

3.8 MECIR standards

The Methodological Expectations of Cochrane Intervention Reviews have been seen as a positive development in helping to drive up quality of Cochrane reviews and interviewees appreciated efforts to summarise findings and describe risk of bias in reviews in clearer terms.

4. Cochrane products and dissemination

4.1 Range of Cochrane review products

What people value about the Cochrane review is that it delivers evidence in a reliable and consistent way - *"it doesn't matter which Cochrane review you read they will all have the same feel and look - I like that"* (Int 32) however therein lies also some problems.

A significant number of interviewees rarely read the full technical review *"reading a Cochrane review kills me!"* (Int 2) and rely on the abstract summary, the Plain Language Summary and the tables and graphs for their information. Some wondered if Cochrane reviews are only read by technical analysts (an important audience, but not the only one). There are an increasing number of summary articles, such as this recent example http://www.cochrane.org/CD011045/PUBHLTH_portion-

package-or-tableware-size-changing-selection-and-consumption-food-alcohol-and-tobacco and these were described as useful but some interviewees weren't aware of these products.

Review users in this sample want Cochrane to consider the derivative products that could help users navigate the key review information and results. Suggestions included; expanded plain English summaries, 'info graphics' and blog shots (these are being trialled by UKCC), and contextualisation of the review.

> "*What would help the NHS (especially commissioners and policy makers) is more clarity about what is helping or not from interventions reviewed as part of Cochrane - in a way that is accessible and relatable to these particular groups - who have ever increasing demands of evidence. They want evidence that is quality assured, robust and defensible...." "So this is about using what Cochrane already has at its fingertips and presenting it in a way that helps decision makers much more by providing a "framework for a conversation" - this need not represent a lot more work - dialogue with policy makers and commissioners could help work out the domains of interest that they have." (Int 30)*

Several interviewees suggested grouping reviews around a topic of interest with values for Number Need to Treat (NNT), Number Needed to Harm (NNH) Quality of Life measures, and economic measures if they are available. Hyperlinks to the original reviews would provide an audit trail. This is not to suggest that Cochrane authors interpret results for commissioners but presents them in a way that makes them relatable and accessible.

> *It is not Cochrane's role to tell people what to do - it is about presenting high quality evidence in a way that is useful for people and organisations (clear picture of where the treatment effect is or isn't) and to accept that is open for interpretation." (Int 5)*

> *"What would increase the value of investment of NIHR funding in Cochrane would not necessarily be to fund more reviews (although there are some big questions in Pre Term Birth e.g. what is the best diet to prevent pre term birth? Not addressed by Cochrane but a very common question from women) but to focus on the different audiences for reviews and tailor the information about the review to their needs - for increased awareness and uptake of the evidence that is available. A good place to start is who will this impact and why?" (Int 31)*

> *"Cochrane review authors have a moral obligation to disseminate their results (be it gaps in research, positive or null results) to the communities that need this information - it is not enough for Cochrane to take a position of 'we just do the reviews and that is our job done'"(Int 29)*

Several interviewees were aware of the recent end of life care publication 'Better Endings' http://www.dc.nihr.ac.uk/highlights-and-reviews/end-of-life-care from the NHS Dissemination Centre which brought together a range of evidence - and thought this a very useful addition to evidence to support decision making and were interested in how much Cochrane would be working with this Centre?

4.2 Cochrane and technology

Technology can offer ways of assessing more effectively who uses Cochrane reviews. Several interviewees asked whether Cochrane tracks Cochrane library users, especially how they are using search engines etc. Others wanted to know if Cochrane

"Can technology be used to help work out who and what people using Cochrane reviews for? Are they being used in training and development as well as clinical decision making and policy development? How do sectors such as care fit in?"(Int 24)

It was also felt that Cochrane should consider offering RSS (Really Simple Syndication) feeds to users, so that they can tailor the feed to their needs - they would receive regular personalised updates of reviews and updates within their scope of interest. Two interviewees also thought that some UK Cochrane Groups were wary of social media and saw it as a one way 'megaphone' to announce reviews, rather than a two way conversation with actual and potential users.

"...would like to see more outreach from Cochrane via feeds with relevant review results - this is achieved by other groups such as NETSCC and NIHR where useful items arrive in my inbox without me having to look for them (assume some sort of algorithm being used?)....I recognise that this may be considered 'lazy' but this is the way of things nowadays!" (Int 12)

"I would appreciate more reaching out from Cochrane about published reviews - and some way of tailoring my needs for reviews in (****) that relate to each other as well? In my condition there are other specific overlapping conditions that will affect what I do with the review". (Int 25)

UKCC seem to be leading the way in efforts to reach out on social media and repackage review results for a much wider audience. Initiatives such as the Evidently Cochrane blog and the most recent developments of 'Everyday Evidence' were also cited as a move in the right direction of adding value to systematic review production in the UK and for the NHS. Whilst some interviewees were wary of Twitter many saw Social Media as the future for dissemination of Cochrane reviews over and above the Cochrane Library and Journals.

Interestingly one interviewee cited a report about mHealth (use of mobile phones in health) which highlighted the tension between the characteristics of mHealth (disruptive, innovative and under evaluated) and the current NIHR/NHS environment (highly regulated, evidence-based and a slow adopter).

"Cochrane is behind the times in terms of social media and should take some responsibility for how it wants it's really important/impactful reviews disseminated - at the moment it is leaving others to do this....but that is taking a chance, which seems strange given its brand. I have found the UKCC new direction refreshing and relevant though" (Int 19)

For some of the sample searching for Cochrane reviews is not straight forward - the search engines in the Cochrane Library (whilst indexing has improved some noted) - don't always help people find what they are looking for, especially where users don't have prior knowledge of medical terminology.

"I find the overly technical language difficult to navigate and understand" (Int 25)

5. Cochrane brand and influence

5.1 Brand awareness and what Cochrane stands for

> This was one of the strongest themes from the interviews, *" CEU (Central Editorial Unit) are doing a great job with the branding" (Int 11)*

From this interview sample the brand was articulated as:

- Trusted source of evidence
- A reliable source of evidence
- A thorough and consistent process used to produce the evidence
- Evidence that addresses bias and conflicts of interest in its processes and results

An improvement suggested by some interviewees was that Cochrane could make more of the fact that it should be the *"first port of call in any evidence review"* (Int 17)

> *"A key message for Cochrane must be that it is the place to start! I know a researcher who read over 100 studies without realising that others had already done work in summarising research in this area - mad!" (Int 16)*

Other suggestions for improvement were (with particular reference to the NHS) "*Don't be preachy about your product"... "ask for review user's suggestions for review topics - there isn't an open portal for review title suggestions I think that there should" (Int 6).*

The brand is not reaching everyone who matters though.....It was suggested by all the charitable organisations interviewed that awareness of Cochrane was probably low in this sector and would benefit from some attention. The Association of Medical Research Charities was approached for this evaluation and didn't have a position on systematic reviews generally, and Cochrane in particular.

5.2 Cochrane's organisational relationships and partnerships

Cochrane's visibility with the NHS workforce was questioned, as was influential and strategic partnerships with groups allied to the NHS and healthcare. Strategic partnerships with influencing agencies and organisations to maximise the impact and reach of Cochrane reviews in the NHS was seen as an important development in Cochrane. Some recognised that UKCC had developed strategy in this area, and wanted to add to that.

Suggestions included:

- Kings Fund
- Nuffield Trust
- Health Foundation
- Royal Colleges and membership organisations (ideally named contacts such as Directors of Research)
- The big four health consultancy companies - KPMG, Capita etc
- Charitable sector
- NHS Management Organisations
- Guideline Developers

- Policy Developers
- Deans of Medical Schools
- Commissioning organisations e.g. NHSCC

Cochrane culture sometimes feels like it is too inward looking, and can be patronising *"academics to the rescue"* (Int 1) rather than "let's work together". The strategic partnership between NICE and Cochrane was mentioned several times as a way of enabling two allied organisations make the most of their respective outputs. Facilitating link people with duality of experience (in this case systematic reviews and clinical guidance) may also help.

A priority area for this work was identified as NHS commissioners and UK policy developers as they would especially benefit from more relationship development, and assessment of their evidence needs. Interestingly there were some subtle points to these discussions as illustrated with the quote below;

"The key issue here is for Cochrane to reach out to this community and listen.....there is an important distinction here between listening to us on our (commissioning and policy) territory and space rather than inviting us into their 'business as usual' Cochrane (and NIHR) way of doing things. Commissioners that have entered this world have not found it helpful as the two ways of working are very different." (Int 18)

5.3 Who are the most important users of Cochrane reviews?

This reflection was voiced in many interviews but there wasn't much consensus about who they were.

Some interviewees suggested that it might be helpful to think in terms of direct and indirect users of Cochrane reviews. Technical analysts (such as guideline producers and commissioned evidence producers) are well served by Cochrane. It was suggested that NHS commissioners and policy developers were important, but possibly low users of Cochrane reviews.

"For guideline developers who are the main Cochrane audience they need the full picture - for everyone else it is highlights" (Int 5)

"if Cochrane says that it is for everyone that tells me they haven't thought enough about who their products are for" (Int 2)

I'm not sure that it is Cochrane's job to translate its' work for such a wide group of users?" (Int 13)

6. Cochrane Structure and ways of working

6.1 Current configuration of review groups

This theme was enthusiastically addressed by Cochrane review producers, but some users also had views about the current structure, and how open it was. There key point was that the medical model of review groups (Airways, etc) does not reflect the population using the NHS, and the evidence needs of organisations organising treatment, services and care.

"UK structure is growing outdated with organ and medical model structure of groups - e.g. no Primary Care GP review group or one for surgery, which might be more helpful? Many of the Coordinating Editors will be coming to the end of their careers and unless the structure is

changed things will continue in the same vein. This is a good time to review the structure and suggest change". (Int 4)

" NIHR should have more stretching expectations of review groups and UKCC - they should be hands off in terms of editorial decisions but as they have the real power (money) they should think more creatively about structure of review groups in the UK and how to get better functioning and efficiencies".(Int 11)

Are Cochrane committees/groups just made up of Cochrane people or are there outsiders allowed in? (Int 24)

Some interviewees were unhappy with lack of progress from recent internal Cochrane structural review - *"feels as if an opportunity might have been missed to make real change?" (Int 14).* The move towards natural pairings of review groups seems sensible and was welcomed by interviewees. More connectivity between CRGs with sharing of experiences and methods as well as administration, back office and shared review production activity were also thought to be important, if piecemeal progress.

" The systematic review market is growing and Cochrane needs to watch the space - commercial providers may be able to meet the payer's needs more as they can be more flexible and focussed on their client's needs" (Int 23)

6.2 Review production and editorial processes

Several of the co-ordinating editors and Cochrane methodologists questioned the nature of the current structure that mixes editorial processes and review production and felt that these should be kept separate.

One perspective was that a review group's role should only concern content development, clinical, patient and stakeholder input and partnerships and author support. Independent 'hubs' (which could be virtual) could support a collection of review groups with skills support specifically; statistical, information science and searching (for example to assess likelihood of an empty review), methodological input, and plain language writing skills.

Another suggestion was to have a proportion of the current NIHR spend given to an independent organisation that can assess NHS evidence needs, triage reviews on a priority basis, undertake rapid appraisal of the evidence and then hand these back to the relevant UK review groups and task them with producing them within a year.

6.3 UKCC training programme

Interviewees (both users and producers of Cochrane reviews) were familiar with the UKCC training offer and had benefited from it (especially from a NHS point of view of it being free at point of access).

6.4 Cochrane meetings

There was mixed feelings about Cochrane sponsored meetings - *"the annual Colloquium seems to be the meeting to be seen at - whereas I have had better experiences and learning at the UK Symposium"* (*Int 1)*

*"I enjoy participating in Colloquia (*interviewee who self funds attendance*) for inspiration, reigniting passion when it (*writing reviews*) feels 'sloggy' I get ideas about my areas of clinical interest but also generic areas of evidence" (Int 20)*

"I caution my review teams to think carefully about attending colloquia - they are expensive and I am not sure that they are the best place for decision making"(Int 3)

Interviewees noted recent and more historical debates within Cochrane about evidence synthesis and they all indicated that a better space was needed for handling challenges and debates and disaffection within Cochrane than in public meetings.

6.5. Central Editorial Unit (CEU)

Some interviewees were not aware of the differences between the CEU and UKCC and this is perhaps not surprising. For those 'in the know' the main feedback point was the rapid growth of the CEU in recent years. For some this meant a more professional, focussed and outward facing picture of Cochrane. The increased growth has led to inevitable centralization of processes and thinking, and this for some is a reasonable trade off.

Others felt that the growth was in fact was impeding creativity and innovation in Cochrane review processes and development, with a sense of risk aversion evident where previously Cochrane had been 'courageous and bold'.

7. NIHR Cochrane funding

7.1 Amount of NIHR funding

When asked to comment on the amount of current funding the most common reaction in interviews was surprise. Many interviewees articulated that £6 million is a modest amount of funding (in relation to the overall NIHR research spend). Cochrane is able to achieve added value because of the harnessed use of volunteers and academic resources to support review production. Interviewees cited examples of very expensive individual research studies that were' in the millions' with questionable impact on health.

" Systematic reviews are very good value for money, much less expensive than primary research and usually the most appropriate unit of knowledge translation - generally far more informative in this respect than a single trial" (Int 26)

The different ways resource is deployed (UKCC, UK review groups and incentive schemes) was welcomed and the combination of a stable infrastructure funding and competitive tendering by parts of that structure is also a strength of the current funding picture.

The incentive schemes were noted as good leverage to encourage review groups to propose important UK/NHS review topics, or take on complex reviews.

7.2 Ring fenced funding

Many interviewees described scenarios where stable funding had led to consistency of purpose and integrity in the Cochrane structure, and sustainable review groups that have developed and built skills and experience. Robust assessment is thought to be entirely proper and should be done in cycles (no consensus about the time scales of this; annual, 3 or 5 year).

A smaller number of interviewees were more cynical about the value of the ring fencing arrangement, describing Cochrane as complacent and not challenged enough to show the value this investment gives back to the NHS.

> *"Cochrane needs to become a bit humble and work on the assumption that no one is interested in what they have.....and work from there" (Int 15)*

7.3 How should Cochrane value be measured?

There were some interesting discussions in interviews about what is meant by 'value'. One interviewee suggested that the last twenty years have focused on measures of cost-effectiveness, but we are now entering an era in which the number of effective and cost effective interventions being produced may be greater than the resources available. This suggests that gradations of value (more than cost effectiveness) of interventions need to be assessed so that reallocation (from low to high value) can occur in a transparent way. Another interviewee saw value of NIHR spend on Cochrane as; relevance of Cochrane reviews in an NHS context and impact the review has in clinical practice and patent benefit.

> *Who is the market for reviews and are their needs being met? This should drive how we perceive value. (22)*

What most interviewees agreed on was the complexity of measuring value, but it was legitimate for NIHR to have achievable and stretching performance indicators for Cochrane.

Suggestions included;

- Citations and downloads of Cochrane Library and in Journals and Guidelines
- Cochrane reviews cited as part an online discussion forum and blogs
- Existence and quality of relationships with review users
- Existence and quality of relationships with health commissioners, policy makers and managers
- Policy and practice changes e.g. NICE Uptake Database https://www.nice.org.uk/about/what-we-do/into-practice/measuring-the-uptake-of-nice-guidance or Quality Outcomes Framework
- Using existing citation trackers such as ORCHID, Research Gate
- Cost benefit analysis of Cochrane reviews
- Audit of citations in clinical guidance, and policy
- Social media 'imprint'
- Numbers of reviews, and updates (but not protocols)*

***** Some interviewees felt that the counting approach to review production and updates encouraged perverse behaviours in review groups such as 'salami slicing' reviews and too many empty reviews.

Some Cochrane review producers were frustrated that current data on performance isn't in the public domain and open for scrutiny.

5. Acknowledgments

- Most thanks goes to the interviewees who gave their time and attention to the interview process, all of them busy people.
- Thanks to the team at NETSCC who undertook the identification and scheduling of the interviews.
- Thanks to the review panel for comments and advice about the structure and reporting.

Appendix 12: Value of Cochrane reviews to the UK: a value of implementation analysis [Report]

Hodgson R, Biswas M, Morgan P. *Value of Cochrane reviews to the UK: a value of implementation analysis*. York: Centre for Health Economics; Centre for Reviews and Dissemination; University of York, 2015. 88p.

CONFIDENTIAL UNTIL PUBLISHED

Value of Cochrane reviews to the UK: A value of implementation analysis

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Date completed	14th December 2015

Source of funding

This report was commissioned by the NIHR HTA Programme as project number HTA 15/147/02.

Declared competing interests of the authors

None.

Acknowledgements

We would like to thank Professor Stephen Palmer, Professor of Health Economics at Centre for Health Economics at University of York, for advice throughout the project and comments on the report. We would like to thank Professor Lesley Stewart, Director of the Centre for Reviews and Dissemination at University of York, for comments on the report. We would like to thank Professor Mark Sculpher, Professor of Health Economics at Centre for Health Economics at University of York, for advice on the project.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Hodgson R, Biswas M, Morgan P. Value of Cochrane review to the UK: a value of implementation analysis: CRD and CHE, University of York, 2015

Contributions of authors

Robert Hodgson, Mousumi Biswas and Philip Morgan wrote the report and conducted the economic analyses.

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List of abbreviations

A&E	Accident and emergency
APHO	Association of Public Health Observatories
Anti-VEGF	Anti-vascular endothelial growth factor
BHF	British heart foundation [confirm with Phil]
CG	Clinical guideline
CHD	Coronary heart disease
CRGs	Cochrane Review Groups
CSMO	Clinically significant macular oedema
CVD	Cardiovascular disease
DMO	Diabetic macular oedema
DR	Diabetic retinopathy
IAPT	Improving access to psychological therapies
ICER	Incremental cost-effectiveness ratio
NICE	National institute for health and care excellence
NIHR	National institute for health research
NHS	National health services
NMB	Net monetary benefit
OCT	Optical coherence tomography
ONS	Office of National Statistics
QALY	Quality adjusted life year
RCT	Randomised Controlled Trial
SSAEs	Serious systemic adverse events
TA	Technology appraisal
UK	United Kingdom
VOI	Value information
VOIM	Value of implementation

Abstract

Background

The Cochrane Collaboration is a global independent organisation that aims to provide information about the effects of healthcare interventions. There are 21 Cochrane review groups in the UK producing, updating and disseminating systematic reviews. The infrastructure costs for the 21 UK Cochrane review groups are funded by the National Institute for Health Research (NIHR).

Aims and objectives

This study commission by the NIHR aims to evaluate the value of Cochrane reviews to the UK and specifically to evaluate the value of increased/faster adoption of healthcare interventions in the NHS resulting from the publication of Cochrane reviews.

Methods

To address this research aim this study has estimated the value of implementing four healthcare interventions recommended in four exemplar Cochrane reviews by applying the value of implementation VOIM framework described in Fenwick et al[1]. This framework operates by seeking to assess the value per patient of implementing a healthcare intervention these benefits scaled up to the population level by considering the size of current and future population eligible to receive the intervention.

Results

Using our base-case assumption, the estimated health gains for the four case studies ranged from 116 QALYs from the review of anti-VEGF therapies for DMO to 15,816 QALYs from the review of statins for the primary prevention of CVD. The value in terms of net monetary benefit (NMB) which accounts for the value of the health gains and any additional costs of implementing the intervention ranged from a NMB of approximately £0.9 million for the anti-VEGF review to £0.4 billion in the Statins review.

This study also highlights a number of drivers of value and importance of considering the policy context in which on and in particular the following factors are important when considering the potential value of any review or update:

- The size of the eligible population;
- Current and projected utilisation of the intervention;
- Current and future NICE guidelines and technology appraisals;
- Cost-effectiveness and resource implications of implementing the intervention.

Conclusions

The results of this study, while subject to a number of substantial caveats has shown that there is substantial value from implementing the recommended healthcare interventions both in terms of additional health benefits as well as net value to the NHS. For Cochrane to represent value for money Cochrane would only need to recommend a small number (possibly only 1) cost-effective intervention a year. Further, these reviews can originate from any of Cochrane review groups including those based outside the UK.

The analysis also illustrates some of the challenges of evaluating the value of Cochrane outputs and in particular the difficulty of disentangling the influence of Cochrane from NICE guidance and other implementation activities. Due to these complexities it may be more appropriate for future research to consider how Cochrane is able to optimise their contribution to current processes of evaluation and implementation of interventions.

Plain English summary

The Cochrane Collaboration is a global independent organisation that aims to provide information about the effects of healthcare interventions. There are 21 Cochrane review groups in the UK producing, updating and disseminating systematic reviews. The infrastructure costs for the 21 UK Cochrane review groups are funded by the National Institute for Health Research (NIHR).

This study commission by the NIHR aims to evaluate the value of Cochrane reviews to the UK and specifically to evaluate the value of increased/faster adoption of healthcare interventions in the NHS resulting from the publication of Cochrane reviews. To address this research aim this study has estimated the value of implementing four healthcare interventions recommended in four exemplar Cochrane reviews.

In all four exemplar Cochrane reviews the potential benefits of increased implementation were significant both in terms of health gains and monetary value. These significant benefits were observed assuming relatively modest increases in implementation resulting from the Cochrane reviews. For Cochrane to represent value for money Cochrane would only need to recommend a small number (possibly only 1) cost-effective intervention a year. Further, this recommendation can originate from any of Cochrane review groups including those based outside the UK.

Scientific Summary

Background

The Cochrane Collaboration is a global independent organisation that aims to provide information about the effects of healthcare interventions. It does this primarily by producing, disseminating and promoting systematic reviews of healthcare interventions. Cochrane reviews are produced by Cochrane Review Groups (CRGs), which comprise of people who prepare, maintain and update the Cochrane Reviews and people who support them in this process. There are 52 review groups worldwide with 21 based in the United Kingdom (UK).[2] Each review groups focuses on a specific area of health, though the remit of individual groups varies significantly with some groups having a very specific focus such as the tobacco addiction review group and others much broader remits such as the public health group.

Systematic reviews aim to ascertain and synthesize the available research evidence with regards to a specific question. By bringing all available evidence together systematic reviews can often reduce the uncertainty about the clinical and cost effectiveness of an intervention and are often better placed to make definitive conclusions about the relative effectiveness of interventions than a single primary study. Systematic reviews are therefore particularly helpful in making researchers, policy makers and clinicians aware of the current state of knowledge and informing decision making. Two specific benefits of systematic reviews are therefore that can firstly they help identify the most effective and cost-effective treatments for patients and secondly in doing so promote their use by clinicians and policy makers thereby improving patents outcomes and maximizing value for money.

Aim of the study

The overall aim of this study is to consider the value of Cochrane reviews to the UK and specifically to evaluate the value of increased/faster adoption of healthcare technologies in the NHS resulting from the publication of Cochrane reviews. To address this research aim this study seeks to answer the three research questions listed below by estimating the value of implementing four healthcare interventions recommended in four exemplar Cochrane reviews.

1. What is the value, both terms health and monetary value, of implementing the health care intervention identified as effective I the four Cochrane reviews?
2. Given plausible values for the degree to which a Cochrane review may influence practice what is the value of each of Cochrane reviews both in terms of improved health and economic value?
3. What factors are likely to influence the value of implementing the health care intervention identified as effective?

Selection of the Cochrane review

In this study, four Cochrane reviews were selected for the analysis. The selection of the four reviews was carried out by the funder from a short list of 16 reviews; eight of which were put forward by the funder, and eight of which were put forward by the York team. The reviews selected were chosen as exemplars because they are considered to have had a major impact in either in shaping NICE guidelines or have significant implications in terms of improvements in health.

In order to meaningfully apply the VOIM framework the selected reviews also were required to meet the following three criteria:

- The Cochrane review draws unequivocal conclusions regards the clinical benefits of one or more healthcare interventions;
- An existing UK based assessment of cost-effectiveness study that evaluates one of the recommended interventions and all relevant comparators;
- The recommend intervention is cost-effective at threshold of £30,000 per QALY and reports either incremental QALYs and costs or NMB.

The included four Cochrane reviews were:

- Review of anti-VEGF treatments for diabetic macular oedema (DMO);
- Review of Interventions for preventing falls in older people living in the community;
- Review of statins for the primary prevention of cardiovascular disease (CVD);
- Review of collaborative care for depression and anxiety problems.

Methods of the study

The VOIM framework developed by Fenwick et al[2] was applied to assess the value to the NHS of increased implementation of four interventions identified as clinically effective in four case-study Cochrane reviews. The models developed for all four case studies share a common structure based broadly on the model developed in a previous application of the VOIM framework to B-type natriuretic peptide testing in diagnosing chronic heart failure.[3] The models developed for the four case studies are multiple period models in which the eligible population and utilisation of each the relevant interventions in the eligible population is modelled over time. To assess the impact of the Cochrane review, the model is run assuming an increase in utilisation upon publication of the Cochrane review. This allows the estimation of utilisation both with and without the Cochrane review. To calculate the value of the increased utilisation we consider the additional QALYs generated and their value to the NHS assuming a threshold of £30,000 per QALY (i.e. that we are we willing to spend

£30, 000 for one additional QALY of health). The value of this increase in health is then compared with the cost of carrying out a Cochrane review.

A dynamic model was chosen rather than a static model used in some applications of the VOIM framework, because this allows the benefits of increased implementation to be considered both in the current prevalent population, and also in the future incident populations. The use of a dynamic model also allows the dynamics of the natural diffusion of an intervention to be accounted for in the analysis. We considered a 10 year time horizon for our analysis. The future costs and benefits were discounted at a rate of 3.5%.

Results

Using our base-case assumption, the estimated health gains for the four case studies ranged from 116 QALYs from the review of anti-VEGF therapies for DMO to 15,816 QALYs from the review of statins for the primary prevention of CVD. The value in terms of NMB which accounts for the value of the health gains and any additional costs of implementing the intervention ranged from a NMB of approximately £0.9 million for the anti-VEGF review to £0.4 billion in the Statins review.

Impact of the Cochrane reviews to the NHS

Cochrane reviews	Assuming full implementation		Base-case assumptions of the implementation	
	QALYs gain	Net values	QALYs gain	Net values
Review of anti-VEGF treatments for diabetic macular oedema	5,600	£48,444,564	116	£877,048
Review of Interventions for preventing falls in older people living in the community	23,910	£740,601,295	1,558	£48,139,336
Review of statins for the primary prevention of cardiovascular disease	534,406	£13,832,171,646	15,816	£409,227,452
Review of collaborative care for depression and anxiety problems	58,254	£917,535,903	416	£6,487,256

These significant benefits were observed assuming relatively modest increases in implementation resulting from the Cochrane reviews of just 1% in our base case. In a scenario analyses conducted assuming just a 0.1% increase in utilisation, the value of the realised benefits remained positive in three of the cases (the exception being anti-VEGF therapy for DMO) with estimated health gains ranging between 12 QALYs from the review of anti-VEGF therapies for DMO to 1590 QALYs in the statins review and NMB ranging from -£10,816 for the anti-VEGF review to £41 million in the Statins review.

This study also highlights a number of drivers of value and importance of considering the policy context in which on and in particular the following factors are important when considering the potential value of any review or update:

- The size of the eligible population;
- Current and projected utilisation of the intervention;
- Current and future NICE guidelines and technology appraisals;
- Cost-effectiveness and resource implications of implementing the intervention.

Care should, however, be taken not to over interpret the results of this analysis as there were significant issues in applying the VOIM framework to the four case-study reviews. These stem in part from the lack of appropriate data, particularly relating to current and past utilisation. As consequence the models developed make a number of simplify assumptions, particularly regarding the impact Cochrane reviews have on utilisation. The results of this analysis should therefore be considered indicative of the potential magnitude of any benefits given the assumed increases in implementation. It is not possible to assess from our analysis whether the estimated benefits have been/will be realised.

Conclusions

The results of this study, while subject to a number of substantial caveats has shown that there is substantial value from implementing the recommended healthcare interventions both in terms of additional health benefits as well as net value to the NHS. The analysis also illustrates some of the challenges of evaluating the value of Cochrane outputs and in particular the difficulty of disentangling the influence of Cochrane from NICE guidance and other implementation activities. Due to these complexities it may be more appropriate for future research to consider how Cochrane is able to optimise their contribution to current processes of evaluation and implementation of interventions.

1 Background

The Cochrane Collaboration is a global independent organisation that aims to provide information about the effects of healthcare interventions. It does this primarily by producing, disseminating and promoting systematic reviews of healthcare interventions. Cochrane reviews are produced by Cochrane Review Groups (CRGs), which comprise of people who prepare, maintain and update the Cochrane Reviews and people who support them in this process. There are 52 review groups worldwide with 21 based in the United Kingdom (UK).[2] Each review groups focuses on a specific area of health, though the remit of individual groups varies significantly with some groups having a very specific focus such as the tobacco addiction review group and others much broader remits such as the public health group.

Each review groups has an editorial base consisting of a small team led by coordinating editor. The editorial team carry out a number of functions including providing methodological and editorial support to review authors and coordinating the peer review process that all reviews must undergo before being published in the Cochrane database of systematic reviews.

Cochrane review authors are based all round the world and consist mainly of academic researchers and health professionals who contribute their time on a voluntary basis. Approximately 34% of review authors are based in the UK. [2]

1.1 Funding of Cochrane

Funding for the Cochrane collaboration comes from a variety of sources including international governmental and non-governmental organizations, national governments and universities. The collaboration does not accept funding from commercial organizations such as pharmaceutical companies. This is to ensure that the conclusions of Cochrane reviews are not influenced by commercial interests. In the UK the National institute for health research (NIHR) funds the infrastructure costs of the 21 Cochrane review groups based in the UK and is the single largest of the Cochrane Collaboration.[2] Currently the NIHR's funding for systematic reviews including those produced and published by Cochrane is £15.5 million[3] of which approximately £6 million[4] per year funds Cochrane UK. This contribution does not directly fund Cochrane reviews other than the editorial support described above, and many Cochrane reviews are carried out without formal funding, with some receiving informal support of author time from host institutions. Some Cochrane reviews, however, do receive formal funding from organizations such as the NIHR, for example through the Cochrane Programme grant scheme. The Cochrane collaboration also receives revenue from the publication of the Cochrane library the majority of which goes to support the central executive and central initiatives. [5]

1.2 Impact and value of Cochrane outputs

Systematic reviews aim to ascertain and synthesize the available research evidence pertaining to a specific question. By bringing together all available evidence, systematic reviews can often reduce the uncertainty about the clinical and cost effectiveness of an intervention, and are therefore generally better placed to provide best evidence about the relative effectiveness of interventions than a single primary study. They are helpful in raising awareness of the current state of knowledge and informing decision making. Systematic reviews help identify the most effective and cost-effective treatments for patients and in doing so promote use by clinicians and policy makers; thereby improving patents' outcomes and maximizing value for money. One way to measure the value of the systematic reviews produced and published by Cochrane is to consider the value of the reduction in uncertainty attributable to the systemic review and its impact on practice in terms optimizing the use of effective and cost-effective interventions.

Systematic reviews may also generate value in a number of other ways. For example, systematic reviews often identify uncertainties about the most appropriate treatments, for example where insufficient reliable evidence exists to recommend one treatment over another. The identification of such uncertainties can promote and direct future research to reduce decision uncertainty. This identification of uncertainty is valuable in of itself.

1.3 Aims and research questions

The overall aim of this study is to consider the value of Cochrane reviews to the UK and specifically to evaluate the value of increased/faster adoption of healthcare technologies in the NHS resulting from the publication of Cochrane reviews. To address this research aim this study seeks to answer the three research questions listed below by estimating the value of implementing four healthcare interventions recommended in four exemplar Cochrane reviews.

1. What is the value, both terms health and monetary value, of implementing the health care intervention identified as effective I the four Cochrane reviews?
2. Given plausible values for the degree to which a Cochrane review may influence practice what is the value of each of Cochrane reviews both in terms of improved health and economic value?
3. What factors are likely to influence the value of implementing the health care intervention identified as effective?

As described above systematic reviews may generate value in a number ways, the current study, however, focuses on only a single aspect of value. The decision to focus on a single aspect of value is in part driven by the limited time available for this study, but also by our approach discussed in Section 2 below. In interpreting the findings of this study it should remembered that there are other ways in which systematic reviews generate value and therefore the estimates generated in this study

may be underestimate the true benefits of Cochrane reviews. The focus of this study on the impact of Cochrane reviews on the adoption effective healthcare interventions, however reflect one of the most significant impacts of Cochrane reviews and is consistent with the principal aims of Cochrane to inform clinical practitioners of the most effective health care interventions.

1.4 Structure of the report

This report is structured as follows. Section 2 describes the conceptual framework adopted in this study and the approach taken to valuing Cochrane outputs. Section 3 provides an overview of the methods used and the models constructed to evaluate the potential value of exemplar reviews. Sections 4 to 7 describe the details of the inputs and methods used for each case study, and the results of analysis. Section 8 summarises the findings and discusses their implications, including a discussion of the strengths and limitations of this study.

2 Conceptual framework and our approach

2.1 Previous Evaluations of the impact of Cochrane reviews

A number of studies have addressed the impact of research on clinical practice and health policy[6-11], however, very few of these have sought to assess either the impact of systematic reviews or more specifically Cochrane reviews. Two studies that have are Palmer et al.[12] and Bunn et al.[13]. The Palmer study published in celebration of 20 years of the Cochrane Collaboration, looks back over some of the achievements of Cochrane in the area of nephrology as well as presenting a discussion of some of challenges of working in this area. The study highlights a number of reviews that potential changed practice by resolving uncertainty about the effectiveness of interventions, but prevents no formal evaluation of the magnitude of the benefits from these reviews. In contrast, the Bunn et al.[13] study presents a much more comprehensive evaluation of the impact of Cochrane reviews. The study applies mixed methods approach informed by the Buxton and Hanney framework[6, 14] for evaluating research impact. The Buxton and Haney framework incorporates a broad range of potential avenues of research impact including knowledge production, research targeting, informing policy development and impact on practice/services, thereby allowing for a more rigorous evaluation of the impact of Cochrane reviews. In line with the mixed methods approach the Bunn evaluation consists of a number of separate work packages consisting of questionnaires, document analysis, bibliometric analysis, and interviews with important stakeholders. It identified three broad areas of impact for Cochrane reviews:

- That Cochrane reviews have contributed to the creation of new knowledge, played a role in identifying gaps in the evidence base and influenced the conduct of new research;
- That Cochrane reviews have informed policy, contributing to the development of a large number of clinical guidelines and were heavily used at all stages of guideline development including assessing the strength of the evidence at the scoping stage and later in the process as part of the evidence review;
- That Cochrane reviews had potentially influenced practice and the utilisation of effective treatments, however the authors commented that it was difficult assess whether these changes were directly as a result of the Cochrane Reviews or the result of subsequent clinical guidelines.

Other reflections on the impact of Cochrane reviews by Cochrane themselves have tended to use metrics as measures of impact similar to those used in the Bunn study. For example, the latest annual report for Cochrane UK[15] presents figures on the number of times Cochrane reviews produced by UK Cochrane review groups have been cited in NICE guidelines and NHS patient decision aids.

These studies suggest that Cochrane reviews may indeed impact upon practice in some cases. However, the approach taken is insufficient for current needs because it does not seek to quantify the

benefits of any impact, or provide a way of evaluating whether the resources invested in producing and updating Cochrane reviews represent value for money.

2.1 Payback models

The payback framework was originally developed by Buxton and Hanney (1996)[14], and has since been developed and adapted in a variety of studies. The general aim of the framework is to measure the value of research in decision making generated through improved information.[16] The methodology allows for the value of specific research to be measured and a way to prioritise competing research projects. The framework assumes that research is an investment in information, and the quality of that information contributes to the extent that the technology is adopted.[1] Improved information reduces uncertainty around whether the adoption of a technology is the optimal decision, and it encourages, or discourages implementation of the technology by increasing the evidence for its effectiveness or ineffectiveness.

In the payback approach the costs and benefits of conducting and implementing research are evaluated. The majority of studies consider two states of the world: one where the research takes place and the counterfactual where the research does not take place. The net benefits of conducting the research are calculated by finding the difference between the costs and health benefits of the two scenarios for the populations of interest.[17] Buxton and Hanney present a broader approach, identifying five different categories of potential benefits from health services research which include: knowledge benefits, benefits to future research, political and administrative benefits and broader economic benefits.[14]

2.2 Value of information and implementation

Fenwick et al[1] in their seminal paper describe the role of decisions makers such as NICE to be to:

- Identify and issue guidance about cost-effective interventions;
- To issue identify the need for research evaluating the effectiveness of interventions;
- To promote the implementation of guidance an uptake of cost-effective interventions.

Health economics provides two vehicles via which the value of investing in each of these activities can be assessed. The first is value of implementation (VOIM) which seeks to evaluate the value of investing in implementing interventions into practice. The second is value information (VOI) which allows an assessment of resolving decision uncertainty by investing in further research e.g. carrying out a new trial. The Fenwick study provides a single unified framework via which these two separate, but related activities can be evaluated.

2.2.1 Net monetary benefit

Central to the framework developed in Fenwick et al[1] is the concept of net benefit. Net monetary benefit (NMB) is related to the more commonly known incremental cost effectiveness ratio or ICER. The ICER assumes that new health care interventions are considered valuable if they provide more overall health than is lost as a result of displacing other health care interventions used elsewhere in the health system. NICE assumes that the value of displaced treatments is between £20,000 and £30,000 per quality adjusted life year (QALY). Therefore a new intervention is considered value for money if it provides incremental QALYs over current standard care at less than £20,000 to £30,000 per QALY. The calculation of the ICER is show in Equation 3.1.

Equation 0.1 $$\boldsymbol{ICER = \frac{C_A - C_B}{H_A - H_B} = \frac{\Delta C_{AB}}{\Delta H_{AB}}}$$

Where, $\boldsymbol{\Delta C_{AB}}$ is the incremental cost of the new intervention compared to standard care and $\boldsymbol{\Delta H_{AB}}$ the incremental effect of the new intervention compared to standard care.

Net monetary benefit is alternative, but equivalent way of representing value and rearranges the above equation into a measure of the monetary value of the intervention to the NHS. The NMB statistic is calculated as shown in Equation 2.

Equation 0.2 $$\boldsymbol{NMB = \lambda * \Delta H_{AB} - \Delta C_{AB}}$$

Where, $\boldsymbol{NMB}$ net monetary benefit, $\boldsymbol{\lambda}$ the cost effectiveness threshold, $\boldsymbol{\Delta C_{AB}}$ the incremental cost of the new intervention compared to standard care and $\boldsymbol{\Delta H_{AB}}$ the incremental effect of the new intervention compared to standard care.

Net monetary benefit captures the monetary value of health gains to the NHS and compares them to the loss from any interventions displaced elsewhere within the NHS to fund the new intervention. A new healthcare intervention is cost-effective if its NMB is positive. The greater the NMB of a new intervention the greater the value of the intervention to the NHS for each patient treated.

2.2.2 Value of Implementation

As described above the value to the NHS of any new intervention can be summarised by NMB, which represents the value of treating an additional patient with a new healthcare technology instead of current standard care. Assuming NMB is positive then increasing the utilisation rate of the new health technology will be of positive value to the NHS. An implementation initiative that increases the utilisation of a technology with a positive NMB is therefore of potential value to the NHS provided that the cost of implementing the initiative is lower than the potential gains of increased utilisation. The VOIM framework allows for the estimation of the maximum possible value to the NHS of

implementing any technology, and therefore the cost at which an implementation strategy would not be worthwhile. So for example if there are a total of 1000 eligible patients, of whom 20% are currently receiving the new intervention then there are potentially 800 additional patients who could also receive it. Given a NMB of £1,000 increasing the utilisation rate to 100% would be worth £800,000 (800 patients x £1,000 NMB) to NHS.

Given the cost of an implementation initiative, the framework also allows for the estimation of the minimum increase in the utilisation rate that would be required to make an implementation strategy worthwhile. So for example, if a Cochrane review costs £100,000, then the Cochrane review would need to raise the utilisation rate by 10% or more ((£100,000 cost/£1,000 NMB)/1000 eligible patients) to be of positive economic value.

2.2.3 Value of Information

Clinical decisions about which treatments are most effective are often made without full and complete information about the relative effectiveness of all the possible treatment options. In such cases treatments will be administered to patients where there is the possibility that the treatment is ineffective or in some cases will do harm. In such cases further information about treatment or intervention is most effective is of value. Consider a simple example in which patients on standard care have a 50% risk of dying. Assume the incidence of this disease is 1000 people per year such that the number of deaths on standard care is 500 per year (50% mortality x 1000 incidence). Now consider a new treatment is available that can potentially reduce mortality. There is however a degree of uncertainty as to whether it is truly effective and on the basis of current evidence there is 75% chance that the new treatment reduces mortality by 20% i.e. relative risk of 0.8 and equally a 25% chance 20% that it increases in mortality i.e. a relative risk of 1.2. If the treatment does not work mortality will increase by 20% and there will be 100 additional deaths per a year (0.2 increased mortality risk x 50% mortality x 1000 incidence). Given that the treatment has 25% chance of being ineffective, then the expected number of excess deaths due per year due to uncertainty would be 25 per year (100 extra deaths x 25% of treatment not working). This represents the total benefit of resolving the uncertainty surrounding the effectiveness of the treatment. Using NMB we can also place a monetary value on resolving this uncertainty. If we assume that we have further information that tells us that the NMB per surviving patient is £100,000, then avoiding 25 deaths is worth £2.5 million (25 deaths x £100,000 NMB). This is the value to the NHS of resolving the uncertainty surrounding the effectiveness of the treatment.

Given the cost of further data collection, the framework allows for the estimation of whether further data collection is warranted. So for example, if a systematic review could be carried out to resolve the uncertainty and this costs £100,000 then it would be worth carrying out as the net value to the NHS would be £2.4 million (2.5 million benefit of resolving uncertainty - £100,000 cost of review). If,

however a new trial was required instead and the cost of this trial is £3 million then would not be worth undertaking as the net value would be minus £500,000 (2.5 million benefit of resolving uncertainty - £3 million cost of trial). The value of information while distinct from the value of implementation is intrinsically linked as it assumes full implementation of the intervention.

2.2.4 Our approach

The approach taken in this study is to use the framework described in Fenwick et al.[1] and use it to assess the impact of Cochrane reviews in terms of the increase in implementation that may result from resolving uncertainty in effectiveness. This study does not seek to apply the VOI element of the framework described in Fenwick et al as this is not possible in the 8 week time frame for completing this study.[1] Cochrane reviews may, however, generate value in this way as by synthesising all available evidence they can reduce uncertainty regarding the relative effectiveness of interventions. A potential extension to this work outlined in Section 8 would the therefore to consider the value of Cochrane reviews in terms of resolving uncertainty.

The framework developed by Fenwick et al.[1] has two specific advantages over alternative approaches. Firstly, unlike payback methodologies that seek to measure the cost-effectiveness or value of further research by assessing its likely impact on clinical practice the Fenwick approach is able to distinguish between value generated by resolving uncertainty and value generated by changing practice. Secondly, by assessing value using NMB the framework acknowledges that funding for the provision of health care and expenditure on research come from a shared budget and that therefore resources invested in research must compete against investment in healthcare provision. Further by using NMB to assess value this allows for an evaluation of the value of research in manner consistent with the way in which NICE evaluates the cost-effectiveness of new health technologies.

3 Methods

In order to gauge the potential value of Cochrane reviews influence on clinical practice the framework outlined above was applied to four case studies Cochrane reviews with the aim of assessing the value of increased implementation of interventions identified in the reviews as effective. The number of case studies considered was dictated by the timeframe and resources of this project.

3.1 Selection of case studies

Selection of the four reviews was carried by the funder choosing from a short list of sixteen reviews; eight that they put forward, and eight put forward the York team. A list of the 16 short listed reviews is reported in the appendix. The reviews selected as exemplars were chosen because they are considered to have had a major impact either in shaping NICE guidelines, or have generated significant independent improvements in health. In order to allow meaningful application of the VOIM framework outlined above, selected reviews also had to meet the following criteria:

1. That the Cochrane review drew unequivocal conclusions about the clinical benefits of one or more healthcare technologies;
2. Existence of a UK based assessment of cost-effectiveness evaluating one of the recommended technologies and all relevant comparators;
3. That the intervention recommend in the Cochrane review is cost-effective at threshold of £30,000 per QALY and reports either incremental QALYs and costs or NMB.

3.1.1 Selected reviews

The four selected reviews are listed in Table 3.1. Table 3.1 also lists previous Cochrane reviews addressing these topics, as in three cases the selected reviews were updates of existing Cochrane reviews. These previous iterations are relevant to the policy context and our interpretation of the identified reviews and are used in the VOIM analysis. Case study 1 is the review of treatments for diabetic macular oedema (DMO); case study 2 is the review of interventions for falls prevention in older people living in the community; case study 3 is the review of statin for the primary prevention of cardio vascular disease (CVD); and, case study 4 is the review of collaborative care for the treatment of depression and anxiety.

Table 0.1: Selected Cochrane reviews

Case study 1: - Virgili G, Parravano M, Menchini F, Evans J. Anti-vascular endothelial growth factor for diabetic macular oedema. Cochrane Database of Systematic Review 2014.[18]
Associated reviews: - Parravano M, Menchini F, Virgili G. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for diabetic macular oedema. Cochrane Database of Systematic Review 2009.[19] - Virgili G, Parravano M, Menchini F, Brunetti M. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for diabetic macular oedema. Cochrane Database of Systematic Review 2012.[20]
Case study 2: - Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. Cochrane Database of Systematic Review 2012.[21]
Associated reviews: - Gillespie L, Gillespie W, Cumming R, Lamb S, Rowe B. Interventions for preventing falls in the elderly. Cochrane database of systematic reviews (Online) 2000:CD000340.[22] - Gillespie L, Gillespie W, Robertson M, Lamb S, Cumming R, Rowe B. Interventions for preventing falls in elderly people. Cochrane database of systematic reviews (Online) 2001:CD000340.[23] - Gillespie L, Gillespie W, Robertson M, Lamb S, Cumming R, Rowe B. Interventions for preventing falls in elderly people. Cochrane database of systematic reviews (Online) 2003:CD000340.[24] - Gillespie LD, Robertson MC, Gillespie WJ, Lamb SE, Gates S, Cumming RG, et al. Interventions for preventing falls in older people living in the community. Cochrane database of systematic reviews 2009.[25]
Case study 3: - Taylor F, Huffman MD, Macedo AF, Moore THM, Burke M, Smith GD, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Review 2013.[26]
Associated reviews: - Taylor F, Ward K, Moore THM, Burke M, Smith GD, Casas JP, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Review 2011.[27]
Case study 4: - Archer J, Bower P, Gilbody S, Lovell K, Richards D, Gask L, et al. Collaborative care for depression and anxiety problems. Cochrane database of systematic reviews 2012.[28]

3.1.2 Challenges of identifying appropriate reviews and representativeness of sample

Identifying four reviews that met the strict selection criteria was challenging as many Cochrane reviews do not consider the available evidence compelling enough to make an unequivocal recommendation about the relative effectiveness of the included interventions. Linking reviews that do draw unequivocal conclusions with appropriate cost-effectiveness analyses was similarly

problematic; in part because Cochrane reviews focus on clinical effectiveness and rarely consider cost-effectiveness. This meant that we had to search separately for cost-effectiveness evidence and in many cases we not able to identify any appropriate UK perspective cost-effectiveness analysis. Thus, the four Cochrane reviews selected cannot be considered representative of all Cochrane reviews, and therefore no generalisations about the total value of all Cochrane reviews cannot be drawn from this sample. The case studies instead should be interpreted as being illustrative of the potential value of high impact systematic reviews, and are used as a vehicle to highlight specific considerations and factors that may influence the value of any particular review in terms of both health outcomes and value for money.

3.2 Overview of structure of VOIM models developed

The model developed for all four case studies share a common structure based broadly on the model developed in a previous application of the VOIM framework to assess the value of implementing B-type natriuretic peptide testing in diagnosing chronic heart failure.[29] The models developed for the four case studies are multiple period models in which the eligible population and utilisation of each the relevant interventions in the eligible population is modelled overtime. To assess the impact of the Cochrane review the model is run assuming an increase in utilisation upon publication of the Cochrane review, see Section 3.2.2 for detail on the magnitude of this increase. This allows the estimation of utilisation both with a without the Cochrane review. To calculate the value of the increased utilisation we consider the additional QALYs generated and their value to the NHS assuming a threshold of £30,000 per QALY (i.e. that we are we willing to spend £30, 000 for additional QALY of health) due to the increased utilisation. The value of this increase in health is all compared with the cost of carrying out a Cochrane review.

A dynamic model was chosen rather than a static model used in some applications of the VOIM framework, because this allows the benefits of increased implementation to be considered both in the current prevalent population, but also in the future incident populations. The use of a dynamic model also allows the dynamics of the natural diffusion of an intervention to be accounted for in the analysis.

Additional, aspects of the modelling relating to the estimation of the cost of Cochrane review, magnitude of implementation effect, discounting of benefits and costs and time horizon relevant to all four case studies are described in the remainder of this Sub-Section. All other inputs specifically relevant to the individual case studies are described in Sections 4 through 7.

3.2.1 Cost of implementing the Cochrane review

To assess the NMB of the four identified Cochrane reviews is necessary to weigh up any benefits against the costs of carrying out the review. Calculating the costs of each of the four case study reviews is however not straight forward for a number of reasons. Firstly, the funding model that

Cochrane adopts makes significant use of volunteers some of whom will be working on their own time while others will be working during employment hours. Secondly, three of the four reviews are updates of previous reviews and therefore one should also arguably consider the cost of each of the previous iterations of the reviews. One simplistic way of assessing the average cost of each Cochrane review is take the total funding for Cochrane by the NIHR and divide by the number of reviews published by UK Cochrane centres in a year. This approach, however ignores the fact that many Cochrane reviews are carried out by researchers and clinicians within work hours and are therefore displacing some other activity they could be carrying out. An alternative way to consider the costs of carrying out a review is therefore to consider the time necessary to carry out a review and place a value on this time. To estimate the time taken to carry out each of the four case-study reviews, we use a formula developed in Allen and Olkin[30]. To account for the updates we consider each iteration of the review as a separate review and summed the cost of doing all iterations of the review. Table 3.2 summaries the predicted time to complete each of the four case study reviews including all updates.

Table 0.2: Estimated time to complete each review

Case study	**Estimated time**
Anti-VEGF for Diabetic Macula oedema	2805 Hours
Statins for primary prevention of cardio vascular disease	3304 Hours
Fall prevention for older people living in the community	3172 Hours
Collaborative care for treating depression and anxiety	1439 Hours

To calculate the cost of a reviewer's time we assume that the full economic cost per reviewer is £70,000 per annum. Assuming 37.5 hour week and 46 weeks worked per year (taking into account holidays) the cost per hour of a reviewer is estimated to be £40.58. Table 3.3 summarises the cost of carrying out each review based on this hourly rate. For the purpose of our analysis we use these values to account for the costs of carrying out the reviews. Consideration is, however, also given to the total £6 million funding by the NIHR when considering the NMBs of the reviews.

Table 0.3: Estimated cost of carrying out each review

Case study	Estimated Cost
Anti-VEGF for Diabetic Macula oedema	£113,817
Statins for primary prevention of cardio vascular disease	£134,091
Fall prevention for older people living in the community	£128,753
Collaborative care for treating depression and anxiety	£58,414

Note we have been purposely pessimistic in valuation of the costs of carrying out a review and these should be considered conservative values. It is acknowledged that these values do not consider that some Cochrane reviewers are conduct on an entirely voluntary basis.

3.2.2 Impact of Cochrane reviews on implementation

To assess the value of a Cochrane reviews impact on implementation it is necessary to understand the magnitude of any increase in implementation resulting from Cochrane reviews. The only significant previous evaluation of the impact of Cochrane reviews is Bunn et al[13], the Bunn et al[13] study, however, drew only cautious conclusions about the impact of Cochrane reviews on clinical practice. Furthermore, the study did not seek to quantify any impact with respect to any particular intervention. There is therefore no direct evidence of the impact of Cochrane reviews on clinical practice. On alternative would to analyse the utilisation data for all four of the recommended interventions and examine whether there was significant change in the adoption rate around the time of the publication of the Cochrane review. A similar approach has been carried using econometric techniques with respect to NICE clinical guidelines in a number of previous studies.[31] This kind of analysis, however, requires a regular time series data on the utilisation of a healthcare technology and was not available to us with timeframe and resources for this study.

The studies analysing the impact of NICE guidance do, however, give us some hint as to what the potential impact of Cochrane reviews might be, particularly as the influence of a Cochrane review may not be direct, but rather through subsequent clinical guidelines. The studies analysing the impact

of NICE guidance, however, offer up heterogeneous results with a number of studies finding significant changes in practice following the publication of NICE guidance[31]and others finding no evidence of any impact[31]. This heterogeneity is exemplified in a study by Sheldon et al[31]which examines the impact of NICE guideline in twelve sets of guidance finding mixed results regarding the impact of NICE guidelines.

Given the lack of evidence we assume in three of the four case studies that the Cochrane review resulted in a 1% increase in utilisation. The true impact of the Cochrane reviews in these cases is likely to have been different, but by choosing a common value it allows the illustration of the relative benefits of increasing the utilisation of each of the interventions recommend in the Cochrane reviews. The 1% increase while somewhat arbitrary is in part justified by limited utilisation data that we were able to access, which show only modest increases in utilisation some years after the publication of the relevant Cochrane reviews. Along with the base case value we also present a number of additional analyses considering a 0.1% increase which consider as a pessimistic scenario and a 3% increase which we consider as an optimistic scenario. Further to this, we also present an additional analysis estimating the number of patients that must be treated for each review to cover the estimated costs of carrying out the relevant review. In the fourth Cochrane review of collaborative care for depression and anxiety we take an alternative approach to evaluating the impact of Cochrane and assume that the review is able to accelerate the publication of NICE guidance. This approach is taken as there is clear evidence of impact of this review on the updating of NICE guidance in this area. For this review we assume in the base case that the publication of the Cochrane review means that NICE guidance is published three months sooner. As with the other reviews we also present additional analyses considering a pessimistic and optimistic scenario's. For the pessimistic scenario we assume that NICE guidance is published one month sooner and in the optimistic scenario we assume that it is 12 months sooner.

3.2.3 Discounting

In line with the NICE methods guide future costs and benefits were discounted at a rate of 3.5% .[32]

3.2.4 Time horizon

As described above multi-period analysis is undertaken for each case study. When calculating the value of information and implementation. We therefore need to consider the total horizon of which wish to assess value. There are various views for determining the total time period of interest. The most typical view in economic evaluation is any period over which value could be expected to differ between the alternative options.[33] Other alternatives could be the lifetime of the technology or the length until implementation strategies achieve the same utilisation.[34] Phillips et al. (2008)[35] have discussed the benefits of alternative approaches to time horizons for valuing research decisions and the benefits of modelling future changes in technologies, prices and evidence in which the highlight

the difficulties in establishing an appropriate time horizon. Given the lack of consensus and difficulties in establishing the appropriate time horizon we followed a previous application of the VOIM framework Whyte et al.[29] and used a 10 year time horizon. We considered this to be a reasonable period of time over which we would expect any specific research activity to payback on any initial investment.

4 Case study 1 – Anti-VEGF treatments for diabetic macular oedema

Diabetic macular oedema (DMO) is a disease of the retina whereby extracellular fluid and proteins accumulate on or under the macula of the eye[18, 36] causing it to thicken and swell. This swelling can lead to a distortion of the macula resulting in a loss of central vision. Diabetic macular oedema affects approximately 7% of diabetic patients, with over 160,000 individuals estimated to be affected in England alone.[37] Of these approximately 40%[37] are affected by clinically significant macular oedema (CSMO), which implies significant sight loss. Costs to the NHS of screening, rehabilitation and care exceed £100 million pounds in England alone.[37] Historically, treatment for CSMO consisted of laser photocoagulation. More recently, anti-vascular endothelial growth factors (anti-VEGF) have been developed as potential alternative treatment.

4.1 The review and recommendations

The anti-vascular endothelial growth factor for diabetic macular oedema (Review)[19] which was published by the Cochrane Eyes and Vision Group in October 2009, and later updated in December 2012[20] and October 2014[18], evaluates treatments for DMO. The original review, along with the updates, evaluated anti-VEGF drugs for the treatment of CSMO, comparing anti-VEGF treatments with laser photocoagulation and sham therapy. The original 2009 review concluded that there was not enough evidence to recommend the use of anti-VEGF treatments for DMO. In the 2012 update this conclusion was revised and a cautious recommendation was made regarding the effectiveness of anti-VEGF therapy. The 2014 update concurred with the conclusion of the 2012 review, but was less cautious in its recommendation due to the availability of additional RCT evidence. Neither the original review nor any updates compared different anti-VEGF treatments due to a lack of head to head trial data, and did not distinguish between the different anti-VEGF drugs in their recommendations.

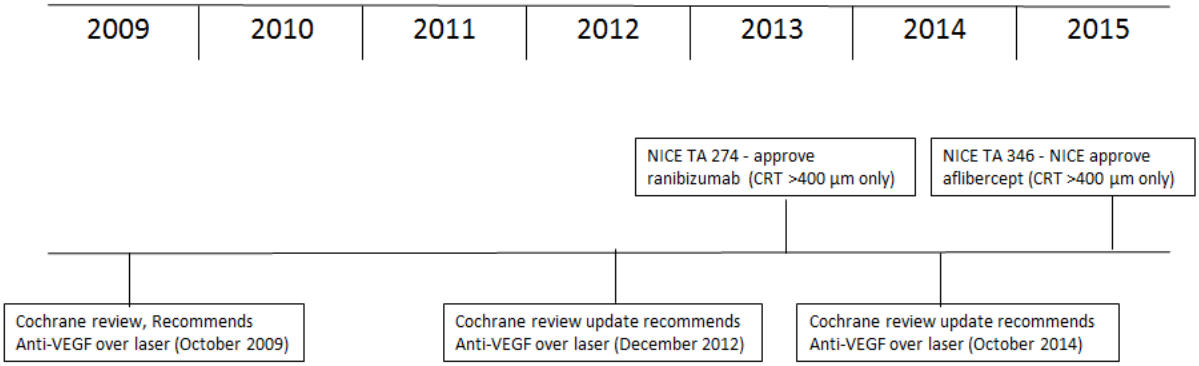
4.2 Current NICE Guidance and policy context

There are three principal anti-VEGF therapies available ranibizumab, aflibercept and bevacizumab. Ranibizumab, aflibercept have been assessed by NICE in a number of technology appraisals, while bevacizumab is used off licence. Ranibizumab was initially assessed in TA237[38] and later in TA274[39]. In both appraisals ranibizumab was approved as a treatment option for patients with CSMO, but only for patients with a central retinal thickness of 400 micrometres or more. Aflibercept was assessed in TA346[40], and like ranibizumab was approved for treating CSMO in the same sub-group.

The NICE TA's are likely to have had a significant impact in the uptake of anti-VEGF therapy and therefore represent a significant part of the policy context within which any review published by Cochrane would operate. Figure 4.1 presents a timeline showing when each of the Cochrane reviews and the NICE TA's were published. The timeline highlights that the first review was published nearly

two years before ranibizumab was approved by NICE. The conclusions of the Cochrane reviews published in 2009 and 2012 therefore stand in tension with the ability of clinicians in England to prescribe anti-VEGF therapies on the NHS. The influence of the first two reviews is therefore difficult to interpret in the context of increased implementation, and is not easily accommodated in the framework developed. The latest review published in 2014 after NICE's partial approval of ranibizumab is easier to interpret. Therefore, the analysis assumes that only the 2014 Cochrane review has an impact on the utilisation of anti-VEGF therapy. This is not to suggest that the initial reviews had no impact on implementation but was made as a simplifying assumption given our limited understanding of how Cochrane reviews influence implementation and the limited data available.

Figure 0.1: Timeline for the NICE clinical guidelines and the Cochrane reviews



4.3 Cost-effectiveness studies conducted from UK NHS and/or social perspective

The cost-effectiveness of the two anti-VGEF therapies ranibizumab and aflibercept have been respectively assessed in TAs 274[39] and TA 346[40]. As stated in Section 4.2 both anti-VEGF drugs were only recommended in a subgroup and therefore the relevant ICER considered represents the cost-effectiveness of these interventions in this subpopulation. Table 4.1 presents the cost-effectiveness estimates for the anti-VEGF therapies. Due to their being considered commercial in confidence, we were unable to obtain incremental QALYS, incremental costs, and consequently were unable to calculate NMB for ranibizumab. In the model we therefore assume that the cost-effectiveness of anti-VEGF therapy generally is based on the estimated incremental QALYS and incremental costs for aflibercept. This is probably a reasonable assumption given the two treatments share many similarities and produce similar ICER values.

Table 0.4: Cost effectiveness of anti-VEGF therapies

	ICER	Incremental QALYS	Incremental costs	Net monetary benefit
Aflibercept	£21,422	0.59	£12,639	£5,061.00
Ranibizumab	£21,418	NA	NA	NA

4.4 Methods of analysis and identification of inputs

To apply the VOIM framework it is necessary define the size of the population eligible for treatment, the diffusion of the therapy in to practice over time, and how relevant Cochrane reviews may have influenced utilisation. This section describes the inputs and methods used for the model, and any assumptions made in order to conduct the analysis.

4.4.1 Population size

The value of implementation of any particular technology will depend on the size of the population eligible to receive it. The scope of the current work is to establish the value of Cochrane to the UK and therefore a UK-wide perspective is taken. The population considered in the analysis are those with CSMO with a retinal thickness of greater than 400µm in line with NICE guidance.

Only the incident population with newly developed CSMO were included in the analysis rather than the prevalent population who currently have the disease. This was because newly diagnosed patients are the most likely to start receiving DMO and we have no way of estimating the proportion of the prevalent population that would switch to DMO from laser photocoagulation. This assumption is a conservative one and is likely to lead an underestimation the eligible population, and therefore the value of the Cochrane review.

Our estimate of the incidence of patients with CSMO who have a retinal thickness of greater than 400µm is based upon the values used in the costing analysis presented as part of TA346[41]. This analysis assumes that a fixed proportion of the diabetic population will become eligible for treatment each year. The population consists of diabetic patients who develop CSMO and have a retinal thickness of greater than 400µm, as well as prevalent patients with CSMO who have a prior central retinal thickness of less than 400µm that subsequently increases to greater than 400µm.

The costing analysis assumes that 0.25% of the diabetic population will develop CSMO macular oedema each year based on the values in used TA274[42] and that 26% of these patients will have central retinal thickness greater than 400µm. The prevalence of CSMO is assumed to be 2.77% of

diabetic patients of which 74% (100% - 26%) are assumed to have a central retinal thickness of less than 400µm. This gives the proportion of prevalent patients with central retinal thickness of less than 400µm. Of these it is assumed 8.5% will experience an increase in central retinal thickness such that their central retinal thickness exceeds 400µm and become eligible for treatment.

To calculate the size of the diabetic population we used data from the Association of Public Health Observatories (APHO) diabetes prevalence model to estimate the past, present and future prevalence.[43] The AHPO model presents predictions for the prevalence of diabetes from 2010 going forward to 2030. The AHPO estimates are not available on UK wide basis but are estimated for England, Scotland and Wales separately. Estimates of the prevalence of diabetes in Northern Ireland are also not available from the AHPO model. Estimates of the prevalence of diabetes the each year for England, Scotland and Wales were therefore made using AHPO data which was linearly interpolated to fill in missing values where data was not available. Estimates of the prevalence of diabetes in Northern Ireland were obtained from Diabetes UK[44] for the year 2013, and the growth rate of diabetes in Scotland applied to account for future increases in prevalence. The diabetic population for each nation is presented along with the interpolated values in Table 4.2.

Table 0.5: Estimates of total diabetes prevalence, 2014-2024

Year	England	Scotland	Wales	N. Ireland	UK
2014	3,321,750	301,806	261,392	79,072	3,964,019
2015	3,394,948	304,076	263,662	79,667	4,042,352
2016	3,466,662	313,695	241,973	82,187	4,104,516
2017	3,537,915	319,371	246,576	83,674	4,187,536
2018	3,609,169	325,046	251,179	85,161	4,270,555
2019	3,680,423	330,722	255,782	86,648	4,353,574
2020	3,751,676	336,397	260,384	88,135	4,436,593
2021	3,822,930	342,073	264,987	89,622	4,519,612
2022	3,896,190	347,920	269,576	91,154	4,604,839
2023	3,969,449	353,768	274,164	92,686	4,690,067
2024	4,042,709	359,615	278,752	94,218	4,775,294

4.4.2 Current and future utilisation

To model the impact of the Cochrane review on the utilisation of anti-VEGF therapies it is necessary to estimate the utilisation of the technology over time. Data on utilisation tends to be sparse, and for the purposes of this analysis it is necessary to evaluate utilisation both historical and going forward into the future. To do this we have used data from the NICE costing tools present in TA 274[42] and TA 346[41] which estimate that from 2013 till 2015 the utilisation of anti-VEGF therapy rose from 0% to around 80%. .

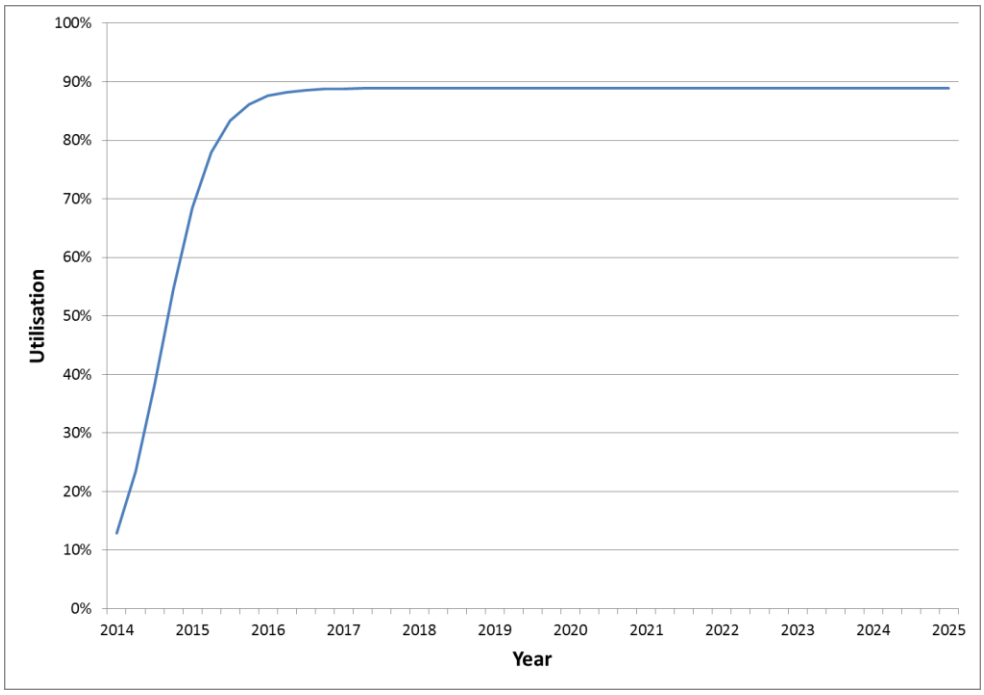
The costing reports show that a small proportion of patients receive both laser treatment and one of the anti-VEGF therapies. As a simplifying assumption for the purpose of this analysis, we assume that

these patients are receiving anti-VEGF therapy alone, which is likely to have minimal impact on the results. As none of the Cochrane reviews drew any conclusions regarding the use of combination therapy, these review are unlikely to have influenced the uptake of this therapy combination, and therefore are unlikely to have an impact on the resulting analysis. The NICE costing template also shows that around 10% of patients chose to receive no active treatment. For the purpose of the analysis it is therefore assumed that 10% of patients do not receive any active treatment.

To model the utilisation of anti-VEGF therapies we follow a previous application of the implementation framework[29] and assume that a S-shaped utilisation curve is most appropriate to represent total cumulative utilisation over time. This is drawn from diffusion theory and suggests that adoption of a technology tends grow exponentially in the early period following its launch, before levelling off and even declining in later periods.

Similar to previous applications of the VOIM framework we fit a parametric curve of the form f(t) =0. 9/(1+exp(-at+k))+(1-0.9) to the available utilisation data, where *t* is time and *a* and *b* are constants. This curve was fitted using nonlinear regression analysis and is presented in figure 4.2. It was assumed that at time zero utilisation of anti-VEGF therapy was 0% (i.e. it was not in use in the NHS) and that after 39 months was being used to treat 85% of patients. Although it was estimated that anti-VEGF utilisation was 0% prior to the publication of TA 274 it likely that a chance that some patients with DMO received bevacizumab, a drug licensed to treat a variety of cancers. Based on the costing template we also assumed that laser photocoagulation would remain a preferred therapy for a limited number of patients and therefore set an upper limit on the proportion of patients receiving anti-VEGF of 90% (i.e. 10% of treated patients continue to receive laser therapy).

Figure 0.2: **The utilisation curve for Anti-VEGF in the >400µm sub-group**



4.5 Results

4.5.1 What is the value of full implementation?

Table 4.3 presents the expected value of perfect implementation of anti-VEGF therapy for DMO patients and estimates the value to the NHS of all eligible patients receiving anti-VEGF therapy i.e. 100% utilisation. The expected value of perfect implementation can be understood as the maximum amount the NHS could invest in implementing anti-VEGF therapy without incurring a negative return on their investment. The expected value of perfect implementation is approximately £53 million and results in a total QALYs gain of 6,179.

Table 0.6: Value of full implementation

	Net monetary benefit	**QALY gain**
Full implementation	£48,444,564	5660

4.5.2 What are expected health gains from the Cochrane review of anti-VEGF therapy?

As discussed in Section 1, the central aim of Cochrane collaboration is to support clinicians and policy makers by providing up to date, high quality information about the relative effects of health technologies. We therefore examined the potential impact of Cochrane in terms of health gained by considering the incremental QALYs gained due to the increase in utilisation of anti-VEGF therapy. Table 4.4 presents the results of our analysis for the base case 1% increase in utilisation and for two further scenarios that present a 0.1% increase and a 3% increase. The results show that a 1% increase

in utilisation results in a gain of 115.51 QALYs. This falls to just 12.08 QALYs with a 0.1% increase and rises to 316.32 QALYs with a 3% increase in utilisation. The results demonstrate that there are modest health gains to be had from relatively small increases in utilisation.

Table 0.7: Estimated Health gains from Anti-VEGF review

Impact of Cochrane review of utilisation	QALY gain
Base case (1% increase)	115.51
Pessimistic scenario (0.1% increase)	12.08
Optimistic scenario (3% increase)	316.32

4.5.3 What is the expected net value the Cochrane review of anti-VEGF therapy?

The potential health gains outlined in Table 4.4 do not come without costs and must be weighed up against the cost of implementing anti-VEGF therapy, as well as the costs of carrying out the review. Table 4.5 presents the additional costs incurred due to the increased utilisation of anti-VEGF therapy and from carrying out the Cochrane review. The total additional costs from a 1%, 0.1% and 3% increase in utilisation are respectively £2.59 million, £373,694 and £6.89 million.

Table 0.8: Estimated additional costs for Anti-VEGF review

Impact of Cochrane review of utilisation	Additional implementation cost	Cost of review	Total costs
Base case (1% increase)	£2,474,520	£113,817	£2,588,337
Pessimistic scenario (0.1% increase)	£258,877	£113,817	£372,694
Optimistic scenario (3% increase)	£6,776,162	£113,817	£6,889,979

To estimate the net value of implementing the review we set these additional costs against the heath gains. To do this we need to assign a value to the QALYs gained through additional implementation.

As outlined in Section 3.2, we assume that each additional QALY is worth £30,000 to the NHS. Table 4.6 presents the estimated expected value of the increased implementation resulting from the Cochrane review.

Table 0.9: Estimated net value of Cochrane review of anti-VEGF therapy

Impact of Cochrane review of utilisation	Value of additional health	Total Additional costs	Net value of Cochrane review
Base case (1% increase)	£3,465,385	£2,588,337	£877,048
Pessimistic scenario (0.1% increase)	£362,539	£372,694	£-10,155
Optimistic scenario (3% increase)	£9,489,522	£6,889,979	£2,599,543

The estimated net value of the Cochrane review in the base line model assuming a 1% increase in utilisation following publication of the review was approximately £0.9 million. Under the pessimistic scenario the Cochrane review fails to recover its costs with an estimated net value of -£10,155. In the optimistic scenario assuming a 3% increase in utilisation the net value rises to approximate £2.6 million

4.6 Discussion

4.6.1 Summary of the results

- The expected value of perfect implementation is approximately £48 million and results in a total QALY gain of 5,660 QALYs.
- The result shows that a 1% increase in utilisation results in a gain of 116 QALYs. This falls to 12 QALYs with a 0.1% increase and rises to 316 QALYs with 3% increase in utilisation. The results demonstrate that there are modest health gains to be had from a relatively small increase in utilisation.
- The additional costs of implementing the review from a 1%, 0.1%, 3% and 100% increase in utilisation are £2.5 million, £372,694 and £6.9million, respectively.
- The estimated net value of the Cochrane review in the base case model assuming a 1% increase in utilisation following the review is approximately £0.9 million; assuming a 0.1% increase in utilisation is -£10,155 and assuming a 3% increase in utilisation the net value is

approximately £2.6 million. Under the pessimistic scenario the Cochrane review fails to recover its costs.

4.6.2 Limitations

There are several limitations with the presented analysis resulting from lack of data and uncertainty in how the published Cochrane reviews may have impacted on practice. The data issue mostly stems from difficulty in accessing past and future utilisation data and we relied on NICE forecasting regarding the use of anti-VEGF therapies. A further issue related to lack of access to the complete ERG report from TA 274 that meant we had to lump together all anti-VEGF therapies. The most significant potential limitation is our interpretation of the impact of Cochrane. The publication of the two Cochrane reviews prior to the approval of anti-VEGS was difficult to interpret in the context of the TA's published a number of years later and our simplifying assumption assumed no impacts of these Cochrane reviews. The 2009 and 2012 reviews may have had a significant impact on the use of anti-VEGF therapy, in particularly the use of bevacizumab an off licence treatment for DMO. Given that the effectiveness of bevacizumab is similar to other anti-VEGF therapies and has significantly lower costs than either ranibizumab or aflibercept the use of bevacizumab by clinicians may have resulted in potentially significant gains in terms of health and NMB. It was however, not possible to capture these potential benefits because we found no data on the utilisation of bevacizumab for the treatment of DMO.

5 Case study 2 – Interventions for preventing falls in older people living in the community

Falls and fall-related injuries are a common and serious problem amongst the elderly. For instance, in 2013/14, there were 201,122 emergency hospital admissions for injuries caused by falls in people aged 65 and over in England, equivalent to more than 2% of the corresponding population.[45] The incidence of recorded falls amongst the elderly population aged 60 years old and above is about 3.6% in UK primary care, and recurrent recorded falls is approximately 0.7%.[46] The incidence rates are higher for older age groups (≥80 years), women, and the least advantaged social groups.[46] Mortality for recurrent fallers is about twice that of the general population.[46]

Since November 2004, NICE guidelines for the prevention of falls have been put into practice across England.[47, 48] these include a range of recommendations that aim to reduce or modify factors which increase the risk of falling (or risk of injury from falling) among older people, both within the community and within residential care settings.

5.1 The review and recommendation

The interventions for preventing falls in older people living in the community (Review)[21, 25] was published by the Cochrane Bone, Joint and Muscle Trauma Group in April 2009[25], and later updated in September 2012[21]. The review evaluates the effectiveness of interventions aimed at reducing the incidence of falls amongst older people living in the community. The review included randomised trials of interventions to reduce falls of older people living in the community, and the primary outcomes were the rate of falls and risk of falling.

The results of the initial review[25] included 111 trials and a total of 55,303 participants. It mainly recommended multiple-component group exercise, Tai Chi, individually prescribed multiple-component home-based exercise (which reduce rate of falls and risk of falling); and assessment and multifactorial intervention (which reduces rate of falls, but not risk of falling). The original review also recommended home safety interventions which are effective in people with severe visual impairment and in others at higher risk of falling, an anti-slip shoe device which reduced rate of falls in icy conditions and gradual withdrawal of psychotropic medication. Further recommendations included a prescribing modification programme for primary care physicians, pacemakers (which reduce rate of falls in people with carotid sinus hypersensitivity); and first eye cataract surgery.

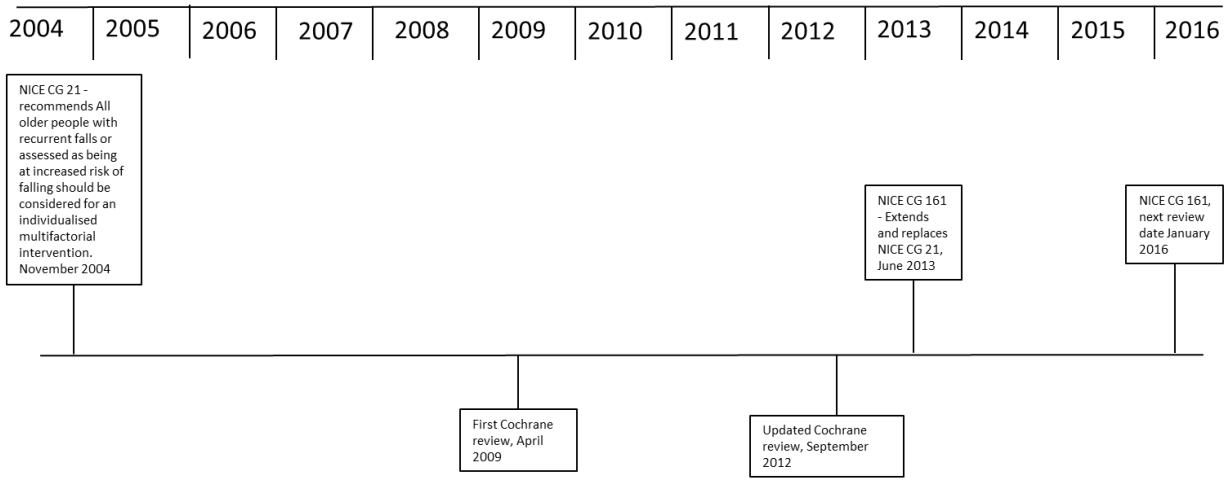
The updated review[21] included 159 randomised controlled trials with 79,193 participants. The new evidence presented in the review supported all of the previous recommendations and presented more precise results. In the updated review, footwear assessment, customised insoles, foot and ankle exercises, and regular podiatry were also recommended.

5.2 Current NICE Guidance and policy context

The assessment and prevention of falls in older people has been assessed twice by NICE. The first NICE CG21[47], for the assessment and prevention of falls in older people, was published on November 2004. NICE CG21[47] was replaced by CG161[48]. The NICE CG161 extended the remit of previous guidance to include assessing and preventing falls in older people during a hospital stay (inpatients). However, the recommendations made for older people in community remain unchanged. In NICE CG161[48], the key recommendation is for the older people who present for medical attention because of a fall, or report recurrent falls in the past year, or demonstrate abnormalities of gait and/or balance. The guidance recommends that these patients should be offered a multifactorial falls risk assessment which should be performed by a skilled and experienced healthcare professional. This assessment should be part of an individualised, multifactorial intervention.

NICE CG21[47] and CG161[48] are likely to have had significant impact in the uptake of the multifactorial assessment and intervention programme in UK practice. Figure 5.1 presents a timeline which shows when each of the Cochrane reviews and NICE CG's were published. The timeline shows that the first NICE guideline was published nearly five years before Cochrane reviews were published. Therefore, it is highly unlikely that the Cochrane review increased the uptake/utilisation of the multifactorial assessment and intervention programme. However, this is not to suggest that the initial review had no impact on utilisation. The current utilisation might have been influenced by both the NICE CGs and the Cochrane reviews. Giving our limited understanding of how Cochrane reviews influence utilisation and the limited data available, it is not plausible to quantify the impact of the Cochrane reviews using the current utilisation data. Therefore, we assume a small additional increase in utilisation due to the first Cochrane reviews published in 2009. In the scenario analysis, we also explore an additional increase in utilisation after the updated review was published in September 2012.

Figure 0.3: Timeline for the NICE clinical guidelines and the Cochrane reviews



5.3 The cost-effectiveness studies conducted from UK NHS and/or social perspective

The cost effectiveness analyses of two falls prevention strategies: exercise programmes for at risk individuals dwelling in the community and multifactorial assessment and intervention programmes for at risk individuals dwelling in the community were assessed in NICE CG161 (Section 2.3.11)[48]. The economic analysis estimated costs and QALYs over a life time horizon. Both interventions were found to be cost-effective compared to the control which is doing nothing. The estimated total cost of the control was £14,431, while the total costs for the multifactorial assessment and interventions programme, and the exercise programmes were £14,285 and £15,645 respectively. The multifactorial assessment and interventions programme was dominant among the two interventions as it was less costly and resulted in a higher QALY gain compared to the control. The ICER for the multifactorial assessment and interventions programmes was estimated to be -£980 resulting from negative incremental costs and positive incremental QALYs (Negative ICERs were as reported in CG161). Table 5.1 presents the ICER, incremental QALYs, and incremental costs reported for each of the strategies.

Table 0.10: Cost effectiveness of two falls prevention strategies

	ICER (95% CI)	Incremental QALYs	Incremental costs	Net monetary benefit
Multifactorial intervention	- £980 (-£19,533 to +£75,270)	0.149	- £146	£4,616
Exercise intervention	£9,559 (-£184,828 to +£187,149)	0.127	£ 1,214	£2,596

However, the 95% confidence interval of the ICERs were large and showed that there is great uncertainty surrounding the estimate of effect, and costs of providing the interventions and treating fall related injuries.

5.4 Choice of intervention

The Cochrane review recommended a range of interventions for fall prevention amongst older people in the community (Section 5.1). However, the identified cost-effectiveness model evaluated only two of those recommended interventions in a UK healthcare setting: exercise programmes and

multifactorial assessment and intervention programmes for at risk individuals dwelling in the community. To model the impact of the Cochrane review on utilisation, it is necessary to model utilisation over time. There is limited data on the utilisation of the exercise programmes over the time. Considering this limitation, we evaluate the impact of the Cochrane review solely on multifactorial assessment and intervention programmes. This assumption is conservative and one of the major limitations of this case study.

5.5 Methods of analysis and identification of inputs

As stated in the method section, to apply the VOIM framework, it is necessary to define the size of the population eligible for treatment, the diffusion of the therapy into practice overtime and how any relevant Cochrane review may have influenced this. This section describes the inputs and methods used to model each of these parameter inputs.

5.5.1 Population size

The value of implementation of any technology will depend on the size of the population eligible to receive the technology. The scope of the current work is establishing the value of Cochrane to the UK and therefore a UK wide perspective is taken. The population eligible for the multifactorial assessment and intervention programme includes those aged 65 and older who: present for medical attention because of a fall, or have reported recurrent falls in the past year, or demonstrate abnormalities of gait and/or balance. It is very difficult to estimate the true size of the eligible population nationally. There are few studies that have looked at the incidence rate of falls amongst older people.

The study by Scuffham et al[49], estimated the number of accident and emergency (A&E) attendances, and admissions to hospital due to falls in older people in the UK. The study estimated, for the four age groups (60–64, 65–69, 70–74, and >75), A&E attendance rates per 100 population were 2.74, 2.87, 3.68, and 9.45, and hospital admission rates per 100 population were 0.35, 0.52, 0.92, and 3.69, respectively. However, the incidence rates were estimated using secondary care data, meaning a number of less severe fall injury cases that were treated in primary care may excluded. As a result, this study might be underestimating the incidence rates.

A more recent study by Gribbin et al[46] estimated the incidence of falls amongst older people in UK primary care. The study estimated that the crude incidence of recorded falls was 3.58 per 100 person-years. For the four age groups (60–64, 65–69, 70–74, and >75), the crude incidence rates per 100 person-years were 0.94, 1.62, 2.65, and 7.17, respectively. The major limitation of this study was the reliability of recorded falls as a measure of falls seen in primary care. A comprehensive set of codes were used to identify recorded falls, however, it is likely that the estimates do not include some of the fall cases attending primary care.

It is unlikely that any of the above studies captured the true incidence rates of the elderly population who seek medical attention because of a fall. After careful consideration of the limitations of the studies, we assume that the results from the Scuffham et al[49] study are the most appropriate to estimate the eligible population.

The Scuffham et al[49] study estimated two sets of incidence rates; one is the rate of accident and emergency (A&E) attendances, and the other is the rate of admissions to hospital due to falls amongst the elderly population. In this case study, the identified uptake data is based on data collected from the elderly people who were admitted to hospital due to a fall. Therefore, we consider this population to be more appropriate for the VOIM model while estimating impact of the Cochrane review. However, in the scenario analysis we explore the impact of the eligible population estimated from the incidence of accident and emergency (A&E) attendances.

The number of falls have increased over the time as the number of older adults has risen in UK, although, the incidence of falls[46] or emergency hospital admissions for injuries caused by falls[45] has remained constant over the time. Therefore, we estimate the eligible population by combining a constant incidence of hospital admission with the Office of National Statistics (ONS) population estimates for those aged 65 and above. We have used the ONS mid-year population estimates from 2009 to 2014[50-52] and ONS population projections from 2015-2020[53] to reflect the increasing number of falls cases over the 10 year time horizon (Table 5.2).

Table 0.11: Estimated eligible population per year (2009 to 2020)

Year	Eligible population (based on hospital admission rate per year)	Eligible population (based on incidence of A&E attendance per year)
2009	213,463	623,592
2010	216,882	634,116
2011	220,310	644,746
2012	225,184	661,730
2013	229,521	675,942
2014	234,816	691,854
2015	238,217	702,546
2016	241,936	714,111
2017	247,353	728,968
2018	253,852	746,347

2019	260,955	765,046
2020	267,704	782,880

5.5.2 Current and future utilisation

To model the impact of Cochrane review on the utilisation of the multifactorial assessment and intervention programme it is necessary to model the uptake over time. Data on utilisation tends to be sparse, and for the purposes of this analysis it will be necessary to evaluate utilisation both historically and going forward into the future. To do this, we have used uptake data for the recommendation 1.1.2.1 of the NICE CG161: Falls: assessment and prevention of falls in older people.[54] Table 5.3 shows the utilisation of the multifactorial assessment from 2011 to 2014, which shows an upward trend over time. The uptake data is based on the National Hip Fracture database reports which include people with hip fracture who receive a falls assessment prior to discharge. The data were collected from those in the high risk of falling group during their hospital stay. There might be a possibility of overestimating utilisation if we use this data, however, considering the limited utilisation data available, we assume it to be a fair estimation of the uptake of the multifactorial assessment and intervention programme.

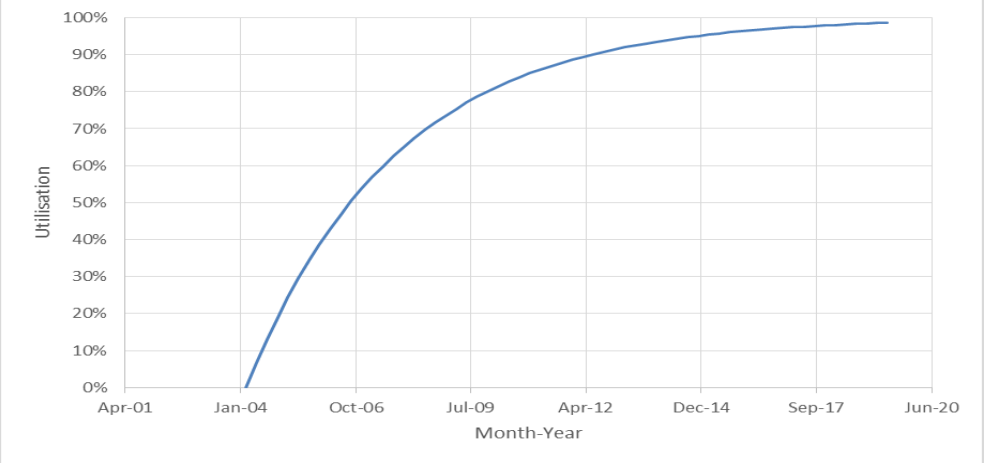
Table 0.12: Uptake data for NICE CG161 recommendation 1.1.2.1 [data from National Hip Fracture Database Reports][54]

Month-Year	Uptake
March 2011	81%
March 2012	92%
March 2013	94%
December 2013	94.6%
December 2014	96.1%

To model the utilisation of the multifactorial assessment and intervention programme, we follow previous applications of the implementation framework and assume a non-linear utilisation curve which is estimated from the uptake data from NICE CG161. We fit a parametric curve of the form $f(t)=(1-exp(-1*a*t))*b$ to the available utilisation data, where t is time and a and b are constants. The

constant values were estimated from observed uptake data using nonlinear regression analysis. We assume that the uptake of the multifactorial assessment and intervention programme is zero before the publication of NICE CG21. We have estimated utilisation on a quarterly basis. It is estimated that the uptake of the intervention is 75% in the first quarter of the year 2009 just before the first review was published. The utilisation curve for the Multifactorial assessment and intervention programme is presented in Figure 5.2. The additional increase in utilisation is added after the first quarter of the year 2009 to reflect the impact of the Cochrane review. In the analysis, we have used a 1%, 0.1% and 3% additional increase in utilisation to represent the potential impact of the review. In the scenario analysis, an additional 1% increase of utilisation is assumed when the updated Cochrane review was published (September 2012). In the VOIM model, we estimate the value of implementation starting from the first quarter of the year 2009 over a 10 year period.

Figure 0.4: The utilisation curve for Multifactorial assessment and intervention programme using uptake data from NICE CG161



5.5.3 Scenario analysis

We have conducted the following scenario analyses:

- Impact of increased utilisation due to the initial Cochrane review: we assume a 1% increase in utilisation in the base case; and present a further two scenarios: a pessimistic assumption of a 0.1% increase in utilisation, and an optimistic assumption of a 3% increase in utilisation
- Impact of alternative utilisation assumption on the additional costs of implementing the Cochrane review
- Impact of the updated Cochrane review (2012) assuming a 1% increase in utilisation to reflect its impact
- Using an alternative eligible population based on the incidence of accident and emergency (A&E) attendances from the Scuffham et al. study[49]

5.6 Results

5.6.1 What is the value of full implementation?

Table 5.4 presents the expected value of perfect implementation of multifactorial assessment and intervention programme. The expected value of perfect implementation is approximately £741 million and results in a total QALY gain of 23,910 QALYs.

Table 0.13: Value of full implementation

	Net monetary benefit	QALY gain
Full implementation	£740,601,295	23,910

5.6.2 What are expected health gains from the Cochrane review of Interventions for preventing falls in older people living in the community?

Table 5.5 presents the QALY gains for a 1%, 0.1% and 3% increase in utilisation. The results show that a 1% increase in utilisation results in a gain of 1,558 QALYs. This falls to just 158 QALYs with a 0.1% increase and rises to 4,540 QALYs with 3% increase in utilisation. The results demonstrate that there are modest health gains to be had from relatively small increases in utilisation.

Table 0.14: Estimated health gains from the Interventions for preventing falls in older people living in the community review

Impact of initial Cochrane review (2009) on utilisation	QALY gain
1% increase of utilisation	1,558
0.1% increase of utilisation	158
3% increase of utilisation	4,540

5.6.3 What is the expected net value the Cochrane review of Interventions for preventing falls in older people living in the community?

Table 5.6 presents the additional costs incurred due to the increased utilisation of the multifactorial assessment and intervention programme and resulting from carrying out the Cochrane review. The additional costs of implementing the review for a 1%, 0.1% and 3% increase in utilisation are -£1.5 million, -£154,497 and -£4.4 million, respectively. The negative additional implementation cost indicates that implementing the review is actually cost saving for the NHS.

Table 0.15: Estimated additional costs for the Cochrane review of Interventions for preventing falls in older people living in the community

Impact of initial Cochrane review (2009) on utilisation	Cost of review	Additional implementation cost	Total costs
1% increase of utilisation	£128,753	-£1,526,677	-£1,397,924
0.1% increase of utilisation	£128,753	-£154,497	-£25,744
3% increase of utilisation	£128,753	-£4,448,237	-£4,319,484

Table 5.7 presents estimated expected value of the increased implementation resulting from the Cochrane review of interventions for preventing falls in older people living in the community.

Table 0.16: Estimated net value of the Cochrane review of Interventions for preventing falls in older people living in the community

Impact of initial Cochrane review (2009) on utilisation	Value of additional health	Total Additional costs	Net value of Cochrane review
1% increase of utilisation	£46,741,412	-£1,397,924	£48,139,336
0.1% increase of utilisation	£4,730,148	-£25,744	£4,755,892
3% increase of utilisation	£136,189,178	-£4,319,484	£140,508,662

The estimated net value of the Cochrane review in the base case model assuming a 1% increase in utilisation following the review is approximately £48 million. Under the pessimistic scenario assuming a 0.1% increase in utilisation the net value falls to approximately £4.8 million. In the optimistic scenario assuming a 3% increase in utilisation the net value rises to approximate £140.5 million.

5.6.4 Scenario analysis

5.6.4.1 Impact of the alternative utilisation assumption on additional costs of implementing the Cochrane review

This scenario analysis demonstrates the magnitude of increased utilisation on the additional costs of implementing the Cochrane review. Table 5.8 presents the additional costs incurred due to the increased utilisation of the multifactorial assessment and intervention programme caused by the Cochrane review. The additional costs of implementing the review for a 1%, 0.1%, 3% and 100% increase in utilisation are -£1.5 million, -£154,497, -£4.4 million and -£23.4 million, respectively. The negative additional implementation cost indicates that implementing the review is actually cost saving for the NHS. The results show it is cost saving even in the pessimistic scenario of a 0.1% increase in utilisation.

Table 0.17: Estimated additional implementation costs for the Cochrane review of Interventions for preventing falls in older people living in the community

Impact of Cochrane review on utilisation	Additional implementation cost
1% increase of utilisation	-£1,526,677
0.1% increase of utilisation	-£154,497
3% increase of utilisation	-£4,448,237
100% increase of utilisation	-£23,428,637

5.6.4.2 Impact of the updated Cochrane review

We assume a 1% increase in utilisation to reflect the impact of the updated Cochrane review (2012). The estimated net value of the Cochrane review assuming a 1% increase in utilisation following the initial review and a 1% increase of utilisation following the updated review is approximately £70 million. Under the pessimistic scenario assuming a 0.1% increase in utilisation following the review and a 1% increase of utilisation following the updated review, the net value falls to approximately £27 million. In the optimistic scenario assuming a 3% increase in utilisation following the review and 1% increase of utilisation following the updated review, the net value rises to approximate £161 million (Table 5.9).

Table 0.18: Impact of the updated Cochrane review on estimated net value

Impact of Cochrane review of utilisation	QALYs gain	Value of additional health	Total Additional costs	Net value of Cochrane review
1% increase of utilisation due to initial review plus 1% increase of utilisation due to updated review	2,257	£67,710,681	-£2,082,826	£69,793,507
0.1% increase of utilisation due to initial review plus 1% increase of utilisation due to updated review	877	£26,304,325	-£730,404	£27,034,729
3% increase of utilisation due to initial review plus 1% increase of utilisation due to updated review	5,193	£155,792,126	-£4,959,759	£160,751,885

5.6.4.3 Alternative eligible population based on the incidence of accident and emergency (A&E) attendances

Calculating the size of the eligible population from the incidence of accident and emergency (A&E) attendances, the estimated net values of the Cochrane review assuming a 1%, 0.1% and 3% increase in utilisation are approximately £142 million, £14 million, and £413 million, respectively. The eligible population based on the incidence of accident and emergency (A&E) attendances is approximately three times larger than our base-case eligible population. The resulting net value of the Cochrane review is therefore commensurately higher (Table 5.10).

Table 0.19: Estimated net value of the Cochrane review using eligible population based on the incidence of accident and emergency (A&E) attendances

Impact of Cochrane review on utilisation	QALYs gain	Value of additional health	Total Additional costs	Net value of Cochrane review
1% increase of utilisation	4,573	£137,179,511	-£4,351,831	£141,531,341
0.1% increase of utilisation	463	£13,882,756	-£324,688	£14,207,445
3% increase of utilisation	1,3322	£399,667,733	-£12,925,271	£412,593,004

5.7 Discussion

5.7.1 Summary of the results

- The expected value of perfect implementation is approximately £741 million and results in a total QALY gain of 23,910 QALYs.
- The result shows that a 1% increase in utilisation results in a gain of 1,558 QALYs. This falls to 158 QALYs with a 0.1% increase and rises to 4,540 QALYs with 3% increase in utilisation. The results demonstrate that there are significant health gains to be had from a relatively small increase in utilisation.
- The additional costs of implementing the review from a 1%, 0.1%, 3% and 100% increase in utilisation are -£1.5 million, -£154,497, -£4.4 million and -£23.4 million, respectively. The negative additional implementation costs indicate that implementing the review is actually cost saving for the NHS.
- The estimated net value of the Cochrane review in the base case model assuming a 1% increase in utilisation following the review is approximately £48 million; assuming a 0.1% increase in utilisation is approximately £4.8 million and assuming a 3% increase in utilisation the net value is approximately £140.5 million.
- The estimated net values of the updated Cochrane review are approximately £70 million (1% increase), approximately £27 million (0.1% increase) and approximately £161 million (3% increase).

- Using an alternative eligible population, the estimated net values of the Cochrane review assuming a 1%, 0.1% and 3% increase in utilisation are approximately £142 million, £14 million, and £413 million, respectively. The eligible population based on the incidence of accident and emergency (A&E) attendances is approximately three times larger than the base-case eligible population resulting in a greater net value of the Cochrane review.

5.7.2 Limitations

This case study shows that a small increase of utilisation has a huge impact on the net value of the Cochrane review. However, it is uncertain what magnitude of the impact of the Cochrane review had on utilisation given NICE guidance had been in place for a substantial period of time before the Cochrane reviews was published. Even if we assume that there is an influence on utilisation, we are not able to estimate the true impact value as it is not clear exactly how Cochrane reviews influence the utilisation.

One of the major limitations of this case study is that we evaluated the impact of the Cochrane review based on one recommendation. This assumption is conservative and does not capture the impact of the Cochrane review if all recommendations were implemented. However, we are restricted to one recommendation due to lack of UK based cost-effectiveness studies and the limited time and resource available to complete this study.

Another major limitation is the cost-effectiveness study. In the identified study, the multifactorial assessment and interventions programmes was dominant as it was less costly and had a higher QALY gain than the control. The ICER was estimated to be -£980 as a result of negative incremental costs and positive incremental QALYs. However, in the sensitivity analysis, the 95% confidence interval of the ICER was -£19,533 to +£75,270 per QALY gain. This result showed that there is great uncertainty surrounding the evidence of the effect, and costs of providing the interventions and treating fall related injuries.

Another major limitation of the case study is the utilisation data. We have used utilisation data based on the National Hip Fracture database reports that include people with hip fracture who received a falls assessment prior to discharge. Using this data, there might be a possibility that the utilisation is overestimated.

A major challenge in this case study is to define the eligible population. The Cochrane reviews recommended some of the interventions for fall prevention to all elderly people living in the community and others in particular subgroups. However, the identified cost-effectiveness study recommended interventions for elderly people who are at risk of falling, and the identified utilisation

data is for people who were admitted to hospital due to a fall. Considering these facts, we have defined the base case eligible population as elderly people who were admitted to hospital due to a fall.

6 Case study 3 – Statins for the prevention of cardiovascular disease

Cardiovascular disease (CVD) covers a range of conditions including: coronary artery disease, cerebrovascular disease and hypertension[55]. In 2014 28% of all UK deaths were attributed to CVD, making it the second main cause of death. Treatments for CVD cost NHS England £6.8 billion in 2012/13[56]. In addition, further research has estimated that in 2009 the cost of informal care for people with CVD was around £3.8 billion in the UK[57], and production losses due to mortality and morbidity associated with CVD cost over £6 billion. A major risk factor of CVD is high cholesterol; statins have been identified as a potentially effective measure to reduce cholesterol levels in the blood. Previously little has been offered routinely on the NHS for the primary prevention of CVD events, but in the last decade or so statins have been increasingly offered across the UK.

6.1 The review and recommendation

The review 'Statins for the primary prevention of cardiovascular disease', was published by the Cochrane Heart Group on 19 January 2011[27], with an updated review published 31 January 2013[26]. The most current review published in 2013 included eighteen randomised control trials, with fourteen of those recruiting patients with specific conditions such as diabetes and hypertension. All trials compared statins with placebo, with nine testing pravastatin, two atorvastatin, two fluvastatin, two lovastatin, two rosuvastatin and two simvastatin. Statins were found to lower all-cause mortality, combined fatal and non-fatal CVD events, CHD and stroke events, and revascularisation rates. The review pooled all published adverse events and found no difference between the intervention and control groups in terms of the number of events. The Cochrane review found a small increase in the risk of type 2 diabetes but these findings were driven by the outcomes of one trial.

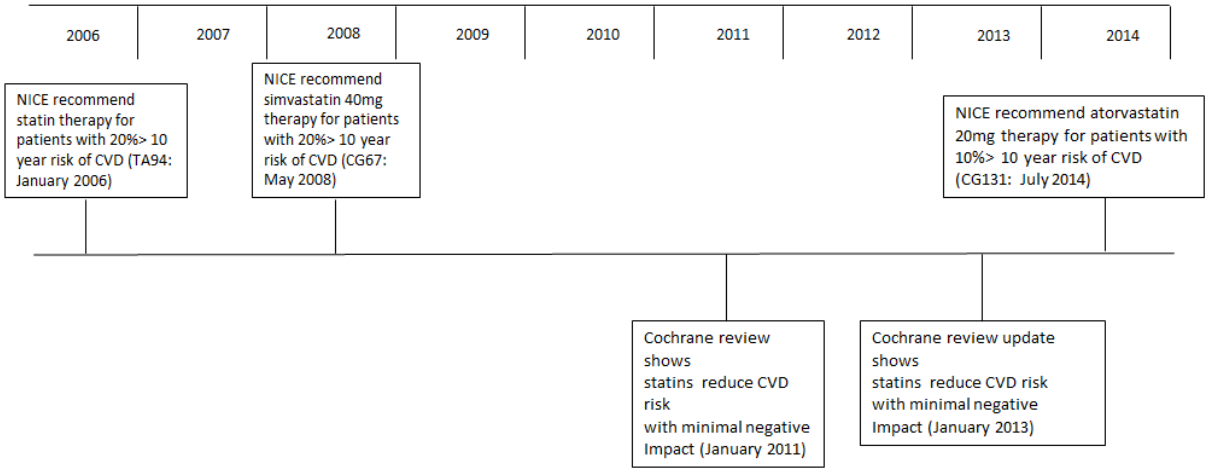
The first review published in 2011 included fourteen randomised controlled trials and also concluded that statins were effective, without increasing the risk of adverse events. However, the results had wider confidence intervals, resulting in greater uncertainty. However, the review found several issues with the published trials which were mostly resolved in the updated review and therefore, concluded that caution should be taken in offering statins for primary prevention to those at low risk of a CVD event. After incorporating new trial data, the updated review concluded with more confidence, that there was minimal association between statins and adverse events. The updated review also concluded that statins are likely to be cost-effective due to reduced treatment costs, and potential improvements in quality of life, even amongst patients with low CVD risks.

Due to a lack of trial data the review was unable to distinguish between different statin drugs in their recommendation. The review was also limited to comparing statins with placebo, rather than with alternative lipid-lowering therapies such as ezetimibe. However, these alternatives are not recommended by NICE and have been shown to be far less effective than statins for the primary prevention of CVD[58].

6.2 Current NICE Guidance and policy context

Statins were initially assessed in TA 94[59] and CG 67[60], which recommended simvastatin 40mg for those identified as having a 20% or greater 10-year risk of developing a CVD event. Due to improved evidence the guidance was updated in 2014 (CG 181) to recommend statins for patients with a 10% or greater 10-year risk. Figure 6.1 presents a timeline showing when each of the Cochrane reviews and NICE recommendations were published. It is likely that the NICE TA and subsequent guidance had significant impact on the uptake of statins, but it is difficult to assess the timing and impact of the Cochrane reviews, especially as statins were recommended prior to the publication of either review. A further difficulty is that although the reviews suggest that statins are an effective preventative measure, they failed to make specific policy recommendations, making the interpretation of any Cochrane effect difficult.

Figure 0.5: Timeline for the NICE clinical guidelines and the Cochrane reviews



Due to the timing of the reviews and the clinical guidelines, we assume for the analysis that Cochrane had an impact on two different patient groups. Firstly, the initial review which made cautious recommendations for the use of statin's, is assumed to have an impact in increasing the number of people with a 20% or greater 10-year risk who receive treatment. The second review, which makes a more confident assertion about the effectiveness and safety of statins, is then assumed to have an impact in increasing the number of patients with a 10-20% risk who receive treatment after the publication of CG181[58].

6.3 The cost-effectiveness studies conducted from UK NHS and/or social perspective

Three cost-effectiveness studies were identified from a NHS perspective. McConnachie et al. (2013)[61] conducted an analysis from the perspective of primary care facilities in Scotland. The study investigated the cost-effectiveness of Pravastatin 40mg daily and found that it dominated placebo. However, the analysis is limited as it only considers one type of statin and does not conduct a sub-group analysis for different risk groups. Two cost-effectiveness studies were also developed for TA

94[59] and CG 181[58]. Both adopted a UK-wide perspective and investigated the cost-effectiveness of a range of statins for primary prevention versus no treatment.

Ward et al. (2005)[62] report on an analysis developed for TA 94. The cost-effectiveness analysis stratified the primary prevention population by annual risk of coronary heart disease events, providing the equivalent CVD risk as well. The study found that statins were cost-effective for men aged 65 with a 10 year risk of 10% or greater at a cost-effectiveness threshold of £20,000 per QALY. However, since this study the price of statins has fallen due to patent expiries, limiting the applicability of the findings.

The most current cost-effectiveness study was developed for CG181[58] and reported incremental costs and QALYs for different CVD risk groups and for different statins, incorporating the impact of the patent expiry of atorvastatin. Atorvastatin 20mg generated the highest net health benefit for primary prevention, producing an ICER of £4,125 for those with a 10% or greater 10-year CVD risk, and an ICER of £1,416 for those with a 20% or greater risk. As it is the most current study, these ICERs were considered the most relevant.[58]

As statins were recommended for a sub-group in both clinical guidelines we used the ICER value for the relevant sub-group. To run the analysis we separately modelled the effect of Cochrane on the 20% 10-year risk group, and then the effect on those with a risk of between 10-20%. However, there was no access to an ICER for the 10-20% risk group, therefore, we were unable to use two separate ICER values. For simplicity we took the ICER for those with a 10% or greater risk and applied it to all patients considered in the model. This value is larger than the ICER for the 20% group, and therefore will lead to a more conservative estimate of the value of the Cochrane review.

Although there are five different statins currently prescribed by the NHS, each with different dosages, for simplicity we took the ICER value for Atorvastatin 20mg and applied it to the entire statin population. This is because Atorvastatin 20mg is now recommended for primary prevention in the most recent NICE guidance, and because there is very little difference between the costs and QALYs for each statin type. For example the ICER for atorvastatin 20mg compared to no treatment is around £4,125, whereas for simvastatin 20mg it is around £4,175. Using this ICER however may slightly over-estimate the value of Cochrane as Atorvastatin 20mg is marginally more cost-effective compared to other treatments.

Another issue is that the cost-effectiveness analysis assumes that the most relevant comparator to statins is no treatment. There are other treatments that can be used for primary prevention such as ezetimibe and fibrates, however, their effectiveness is unclear and they are not recommended by

NICE. Table 6.1 presents the ICER, incremental QALYs, incremental costs and NMB reported for statins.

Table 0.20: Cost-effectiveness of statin therapy

	ICER	Incremental QALYS	Incremental costs	Net monetary benefit
Atorvastatin 20mg	£4,116.50	0.31	£1,272	£7,998

6.4 Methods of analysis and identification of inputs

6.4.1 Population size

The population considered for the first analysis was anyone with a 10 year CVD risk of 20% or above, and for the second analysis the population includes anyone with a risk of 10-20%. Estimates for these populations were obtained from the NICE costing tool developed for CG 181[63], which calculates the financial impact of lowering the risk threshold for statin eligibility. The calculation was based on findings from Collins and Altman (2012)[64], who estimated the proportion of people aged between 30 to 84 years old who were at risk of a CVD event. The study used a large database of 2,0844,445 patients and followed them over time to identify how many suffered a CVD event. This allowed them to calculate the average CVD risk of the population, and also establish the proportion of patients who had a CVD risk greater than 10% or 20%. The costing tool then used population data to estimate the proportion of people aged 30 to 84 in the UK, allowing for the number per 100,000 people with at least a 20% or 10% 10-year risk of a CVD event to be calculated.

ONS mid-year population estimates were then obtained for 2011 to 2023[52, 53, 65, 66] and multiplied by the proportions calculated in the costing report to provide an estimate of the eligible population for each year.

Although we were able to incorporate population increases over time into the analysis, we were unable to take into account changing CVD risks over time. As CVD risk is heavily linked to factors such as age, diet and smoking status then the number at high risk of a CVD event[67], and therefore eligible for statin use will change over time as the severity of these risk factors change. As there are multiple risk factors it is unclear whether overall CVD risk would rise or fall over time; and also unclear how future risk levels could be accurately predicted. However, as the population size is so

large, this is unlikely to have a significant impact on the results. The eligible primary prevention population is presented in Table 6.2.

Table 0.21: Estimates of total CVD risk population, 2011-2023

Year	Number with a >20% risk	Number with a 10-20% risk
2011	4,572,352	5,148,247
2012	4,602,688	5,182,404
2013	4,631,634	5,214,995
2014	4,667,115	5,254,946
2015	4,703,265	5,295,649
2016	4,737,607	5,334,315
2017	4,770,662	5,371,535
2018	4,803,673	5,408,703
2019	4,835,531	5,444,574
2020	4,866,734	5,479,707
2021	4,897,213	5,514,025
2022	4,927,656	5,548,302
2023	4,957,932	5,582,391

As the population of interest is a prevalent population who receive treatment over their lifetime rather than an incident population, the population over time was modelled in a different way to the other case studies. It was assumed that when the Cochrane review was published the lifetime costs and

QALYs for all people receiving statins at that moment were accrued at that point in time. Costs and QALYs gained in subsequent years were from new patients who received statins due to increased utilisation. This simplification means that we do not consider the incident population, meaning we may under-estimate the eligible population, and therefore, the effect of the Cochrane review. However, this simplification will also impact how the costs and QALYs are discounted and therefore may marginally over-estimate the value of the Cochrane review as most of the costs and QALYs are assumed to not fall in the future.

As we are focussing on a sub-group of the population for our analysis whereas the Cochrane review conducts an analysis and makes recommendations for the entire population, it becomes difficult to interpret correctly the impact of Cochrane. There is also potential for the Cochrane reviews to have a negative effect if they encourage clinicians to prescribe statins to patients with a 10-year risk of less than 10% as they are not considered cost-effective at such low levels of risk.

6.4.2 Current and future utilisation

The impact of the Cochrane review on the 20% > risk group and the 10-20% group were modelled separately. The impact was investigated from 2011 till 2021 for the 20%> risk group, and from 2014 till 2024 for the 10-20% risk group. 2014 was used as the start date for the updated review as this was the year that the clinical guidelines were updated, recommending statins for the lower risk group.

To model statin utilisation for the 20% > risk group we used data from three studies, which calculated the proportion of the eligible population who were being prescribed statins. The studies report data from: 1993-2006[68], 2008-2010[69], and 2013-2014[70] providing three utilisation values. For the 10-20% risk group one study reported utilisation for 2013-2014[70], but no other estimates were available for previous years. The NICE costing tool for CG 181 projected that statin use for the sub-group would reach 80% within five years of the guidance being introduced, based on the assumption that there will be full utilisation but 20% of people who are prescribed statins will not take them. The basis of this assumption is unclear and does not seem feasible considering that we have yet to see full utilisation in the 20% > risk group. Due to potential adverse events there has been reluctance among many clinicians to prescribe statins for primary prevention to the 10-20% risk group, meaning an assumption of full utilisation after five years does not appear to be reasonable[71]. Rather than setting such a high utilisation value we looked at how utilisation had changed over time for the 20%> risk group and decided that, based on this data, a utilisation value of 50% 10 years after the publication of CG 181 was a more reasonable estimate. Using a lower utilisation value is potentially conservative but is likely to have minimal impact on the results as we are interested in the difference between the world with the Cochrane review and world without it, rather than the absolute utilisation values.

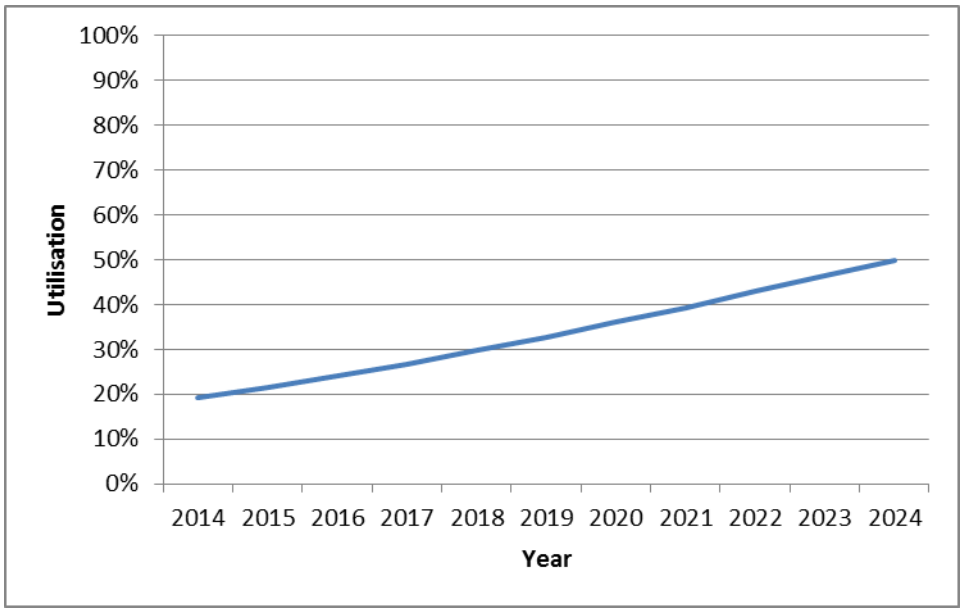
The utilisation data used for both risk groups is summarised in Table 6.3. A small number of the patients receive statins in combination with another treatment such as ezetimibe, but we assume that these patients are receiving statins alone to simplify the analysis.

Table 0.22: Statin utilisation data

Year	>20% uptake	10-20% uptake
1993-2006	7.0%	NR
2008-2010	39.8%	NR
2013-14	49.7%	19.2%

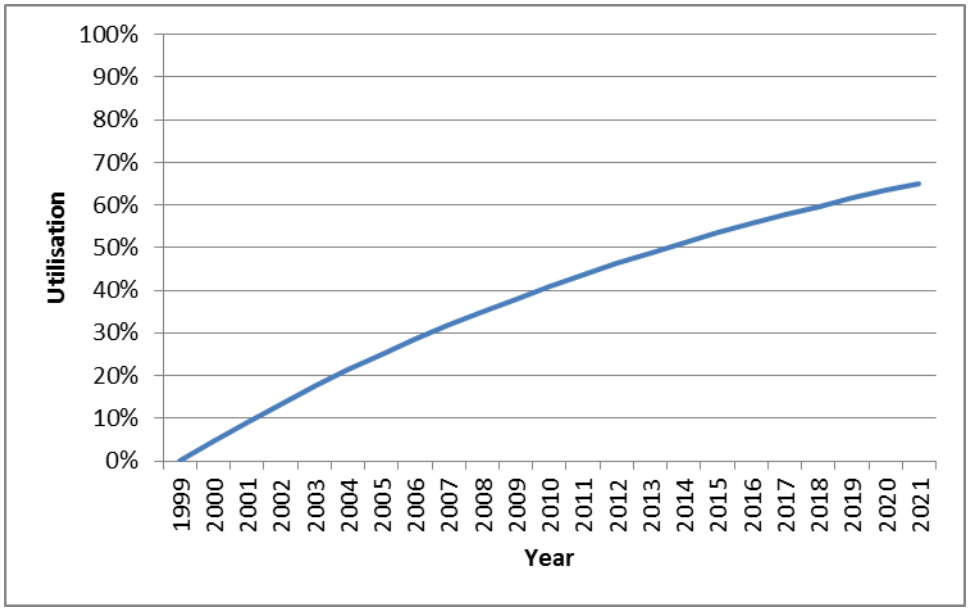
To model the utilisation of the 10-20% group we followed previous applications of the implementation framework and assumed an S-shaped utilisation curve as the most appropriate to represent total cumulative utilisation over a period of time. We fit a parametric curve of the form $f(t)=1/1+exp(-at+b))$ to the available utilisation data, where t is time and a and b are constants. This curve was fitted using nonlinear regression analysis based on the two data points. The diffusion curve for the 10-20% risk group is presented in Figure 6.2.

Figure 0.6: The utilisation curve for the 10-20% risk group



For the 20% > risk group we fitted a parametric curve of the form *f(t) = 1-exp(-a*t)*, where *t* is time and *a* is constant. This function was used instead of an S-shaped curve due to its better fit of the data. The function allows for utilisation levels to rise more slowly into the future rather than approach full utilisation which is not feasible based on the observed data. However, the drawback of the function is that it assumes that the Cochrane effect remains constant rather than increasing, or decreasing over time, which might not be an accurate representation of reality. To fit this curve the three data points were used to extrapolate utilisation values into the future. The diffusion curve for the >20% risk group is presented in Figure 6.3.

Figure 0.7: The utilisation curve for the 10-20% risk group



6.5 Results

6.5.1 What is the value of full implementation?

Table 6.4 presents the expected value of full implementation for the >20% 10-year CVD risk group, and Table 6.5 the value for the 10-20% 10-year group. The expected value of perfect implementation for the >20% risk group is approximately £14 billion, and results in a total QALY gain of 534,406.

Table 0.23: Value of full implementation of 20%> risk group

	Net monetary benefit	QALY gain
Full implementation	£13,832,171,645.65	534,406

For the 10-20% risk group the expected value of perfect implementation is approximately £23 billion, and results in a total QALY gain of 893,061 QALYs.

Table 0.24: Value of full implementation of 10-20% risk group

	Net monetary benefit	QALY gain
Full implementation	£23,115,415,218.42	893,061

6.5.2 What are expected health gains from the Cochrane review of statins?

Table's 6.6 and 6.7 present the QALY gains for the base case 1% increase in utilisation attributed to the 2011 review and the 2013 review respectively, and further present two scenarios for a 0.1% and a 3% increase in utilisation. The results for the 2011 review show that a 1% increase in utilisation results in a gain of 15,816 QALYs. This falls to 1,590 with a 0.1% increase and rises to 46,831 with a 3% increase in utilisation.

Table 0.25: Estimated Health gains from 2011 statins review

Impact of Cochrane review of utilisation	QALY gain
Base case (1% increase)	15,816
Pessimistic scenario (0.1% increase)	1,590
Optimistic scenario (3% increase)	46,831

The results for the 2013 review show that a 1% increase in utilisation results in a gain of 13,661 QALYs. This falls to 1,365 with a 0.1% increase and rises to 41,039 with a 3% increase in utilisation. The results highlight that even relatively small increases in utilisation can result in large health gains.

Table 0.26: Estimated Health gains from 2013 statins review

Impact of Cochrane review of utilisation	QALY gain
Base case (1% increase)	13,661
Pessimistic scenario (0.1% increase)	1,365

Optimistic scenario (3% increase)	41,039

6.5.3 What is the expected net value the Cochrane review of statins?

Table 6.8 and 6.9 present the additional costs incurred due to the increased utilisation of statins and resulting from carrying out the 2011 and 2013 Cochrane review respectively. For the 2011 review the additional costs from a 1%, 0.1% and 3% increase in utilisation are £65.1 million, £6.5 million and £192.8 million respectively.

Table 0.27: Estimated additional costs for Statins 2011 review

Impact of Cochrane review of utilisation	Additional implementation cost	Cost of review	Total costs
Base case (1% increase)	£65,104,762	£134,091	£65,238,853
Pessimistic scenario (0.1% increase)	£6,543,393	£134,091	£6,677,484
Optimistic scenario (3% increase)	£192,780,555	£134,091	£192,914,646

For the 2013 review the additional costs from a 1%, 0.1% and 3% increase in utilisation are £56.2 million, £5.6 million and £168.9 million respectively.

Table 0.28: Estimated additional costs for Statins 2013 review

Impact of Cochrane review of utilisation	Additional implementation cost	Cost of review	Total costs
Base case (1% increase)	£56,237,247	£134,091	£56,371,338

Pessimistic scenario (0.1% increase)	£5,620,636	£134,091	£5,754,727
Optimistic scenario (3% increase)	£168,936,213	£134,091	£169,070,304

Table's 6.10 and 6.11 present estimates of the expected net value of the increased implementation resulting from the 2011 and 2013 Cochrane reviews respectively. For the 2011 review the estimated net value in the base case model assuming a 1% increase in utilisation is approximately £410 million. Under the pessimistic scenario the net value is £41 million and for the optimistic scenario the net value is £1.2 billion.

Table 0.29: Estimated net value of 2011 Cochrane review of statins

Impact of Cochrane review of utilisation	Value of additional health	Total Additional costs	Net value of Cochrane review
Base case (1% increase)	£474,466,305	£65,238,853	£409,227,452
Pessimistic scenario (0.1% increase)	£47,686,520	£6,677,484	£41,009,036
Optimistic scenario (3% increase)	£1,404,933,759	£192,914,646	£1,212,019,114

For the updated review the estimated net value of the Cochrane review in the base case model is £353 million. Under the pessimistic scenario the net value is £35 million and for the optimistic scenario the net value is £1.1 billion.

Table 0.30: Estimated net value of 2013 Cochrane review of statins

Impact of Cochrane review of utilisation	Value of additional health	Total Additional costs	Net value of Cochrane review
Base case (1% increase)	£409,842,202	£56,371,338	£353,470,865

Pessimistic scenario (0.1% increase)	£40,961,707	£5,754,727	£35,206,981
Optimistic scenario (3% increase)	£1,231,162,496	£169,070,304	£1,062,092,192

6.6 Discussion

6.6.1 Summary of Results

- The value of full implementation in NMB is approximately £14 billion for the 2011 review and £23 billion for the 2013 review.
- The health gains from the 2011 review for a 0.1-3.0% Cochrane review effect range from 1,590-46,831 QALYs and for the 2013 review range from 1,365-41,039 QALYs.
- The net value of the 2011 review for a 0.1-3.0% Cochrane effect ranges from approximately £41 million-£1.2 billion and for the 2013 review ranges from approximately £35 million-£1.1 billion.
- The results highlight that the value of additional health benefits from increased utilisation far outweigh the costs of the review and of additional implementation.
- Conservative estimates were used in the analysis whenever possible making the results fairly robust.
- The figures are so large for such a small increase in utilisation due to the large eligible population, the low initial levels of implementation and the large net benefit attributed to statins.

6.6.2 Limitations

There are several limitations with the analysis due to a lack of data, resulting in the use of limiting assumptions. Neither of the two Cochrane reviews made recommendations specific to the sub-groups we investigated, making the effect of Cochrane difficult to interpret. The analysis compared statins to no treatment rather than with potential comparators, meaning the NMB of statins may be over-estimated. However, for simplicity in the analysis we also applied the ICER for the 10% > risk group to both populations of interest, leading to an under-estimation of the NMB of statins.

Assumptions were also made in relation to the timing of the effect the Cochrane reviews had. In reality the largest effect could occur immediately after the publication of the review, or the impact could increase over time. However, as no prior research has been conducted on the impact of Cochrane then this was not possible to incorporate. The lack of utilisation data restricted the analysis

as future predicted utilisation values were extrapolated from minimal data on past values, and fitted to future values based on assumptions about future utilisation.

7 Case study 4 – Collaborative care for depression and anxiety

Mixed anxiety and depression is the most common mental disorder in United Kingdom. In 2012/13, it is estimated that of 18.3% of the adult UK population had some evidence of depression and anxiety, and the proportion is much higher for women (21.5%) than men (14.8%).[72] Anxiety and depression impose a huge economic burden on the UK NHS. In England alone, costs of mental illness was £21.3 billion a year, through health and social care.[73] The costs to health and social care are expected to be higher in the coming decade.

In England, NICE recommended use of the framework of a stepped-care model to organise the provision of services, and support patients with anxiety and depression, their families, carers and physicians in identifying and accessing the most effective interventions.[74-76]

7.1 The review and recommendation

The Collaborative care for depression and anxiety problems (Review) was published by the Cochrane Depression, Anxiety and Neurosis Group in October 2012.[28] The review evaluates the effectiveness of collaborative care for depression and anxiety. Collaborative care is a complex system intervention and its definition has changed since it was first introduced by Katon et al. (1995)[77]. The Cochrane review used a widely accepted definition of collaborative care, which includes the four key criteria of a multi-professional approach to patient care, structured management plan, scheduled patient follow-ups and enhanced inter-professional communication.

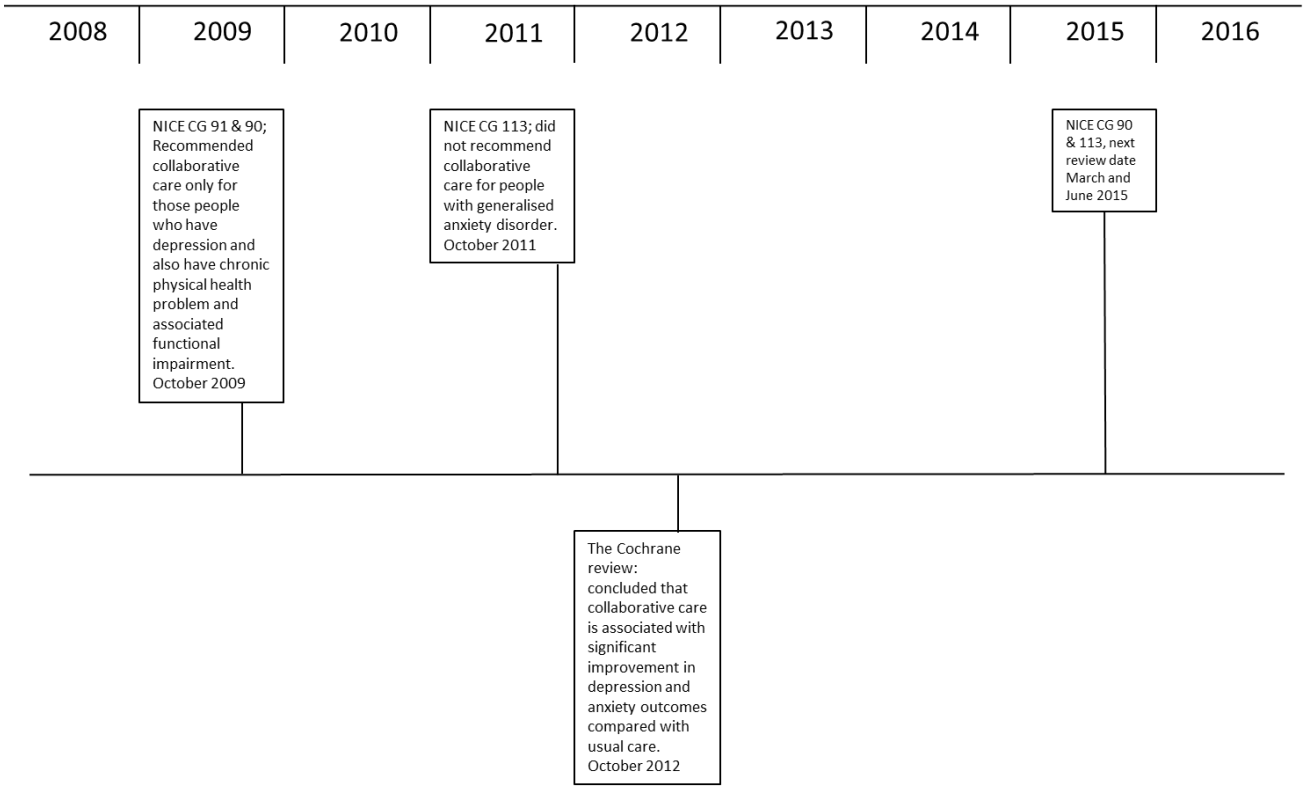
The primary outcome of the review was the change in depression or anxiety, as measured by an observer or patient self-report. The result of the review included 71 trials and a total of 24,308 participants. The review concluded that collaborative care is associated with significant improvement in depression and anxiety outcomes compared with usual care.[28]

7.2 Current NICE Guidance and policy context

Collaborative care for the people with depression and anxiety has been assessed by NICE in a number of clinical guidelines. In current practice, collaborative care is imbedded within the stepped-care model for treatment and care of depression. NICE CG90 and CG91 recommended collaborative care for the sub-group of people who have depression and chronic physical health problem with associated functional impairment.[74, 75] It is not recommended for people with generalised anxiety disorders.[76] Figure 7.1 presents a timeline which shows when each of the NICE CG's and the Cochrane review were published. It shows that the NICE guidelines (CG90 and CG91) on depression were published three years before Cochrane review was published recommending treatment for a sub-group of people. The Cochrane review, published in 2012, concluded that collaborative care significantly improved depression and anxiety outcomes. The review reported that there was no substantial difference in the findings of the review when studies in patients with long-term physical conditions

were excluded.[28] In addition to this, the Cochrane review was referred several times in the surveillance report for NICE CG90,[78] indicating that the results found in the review have encouraged NICE to update clinical guidance, and to potentially update them sooner more urgently. Therefore, it is highly likely that the Cochrane review has significant influence on the NICE clinical guidelines update and that may in turn influence the utilisation of collaborative care.

Figure 0.8: Timeline for the NICE clinical guidelines and the Cochrane review



7.3 The cost-effectiveness studies conducted from UK NHS and/or social perspective

An economic evaluation conducted alongside a multi-centre cluster randomised controlled trial was identified.[79] This compared collaborative care with usual primary care for adults with depression. It calculated costs and QALYs from a total of 581 participants over a 12-month follow-up, from the perspective of the UK NHS and Personal Social Services (i.e. Third Party Payer). The study concluded that collaborative care was cost-effective compared to usual primary care. The ICER for collaborative care was estimated to be £14,248 per QALY gain. Table 7.1 presents the ICER, incremental QALYs, and incremental costs for collaborative care. The study indicated that collaborative care has 65% of probability of being cost-effective at willingness to pay of £30,000 per QALY.

Table 0.31: Cost effectiveness of collaborative care

	ICER	Incremental QALYs (95% CI)	Incremental costs (95% CI)	Net monetary benefit
Collaborative care	£14,248	0.019 (-0.019 to 0.06)	£270.72 (-202.98 to +886.04)	£301.25

7.3.1 Methods of analysis and identification of inputs

7.3.2 Population size

In this case study, we have considered the adult population aged ≥16 years old diagnosed with moderate or severe depression in the UK. Although, the Cochrane review focussed on both depression and anxiety, our analysis only focuses on depression, as both the cost-effectiveness study and the NICE clinical guidance made recommendations for depression alone. Therefore the impact of the Cochrane review may be underestimated as we do not factor an additional NMB gains from those with anxiety (considering collaborative care is cost effective for those with anxiety).

The incidence of depression is taken from the study by Rait et al. (2009).[80] We use 16 years as the cut-off age for the adult population keeping the age group consistent with the study used data from 298 UK general practices and collected data for two or more years from January 1996 till March 2006. A total of 4,986,111 patients' data were included and every patient had a minimum of 1-year follow-up data. The combined incidence over the study period was 24.8 per 1,000 person years at risk, which was equivalent to a mean annual incidence rate of around 2.5%. In this case study, we have adopted a monthly cycle length for the model. Hence, the annual incidence is converted into a monthly incidence, giving us a rate per cycle for the number of people who develop depression.

We chose to investigate only the incident population rather than the prevalent population who currently have depression. This is because newly diagnosed patients are the most likely to start receiving collaborative care and we have no way of estimating the proportion of the prevalent population who would switch to collaborative care from their current treatment. Hence, we may be underestimating the population size as well as the impact of the Cochrane review.

The proportion of those with depression who are diagnosed with a moderate or severe condition is then calculated. An estimate of this proportion is taken from the costing tool prepared for NICE CG23 (which has been updated and replaced by NICE CG90).[74] The estimate is based solely on expert opinion making its reliability uncertain, however, it is the most relevant estimate found in the literature. In the costing tool, it was assumed that 20% of people with depression have a moderate condition, and 10% have severe depression.

UK population estimates are taken from the ONS mid-year 2013 population study[52] and the number of people aged ≥16 years old is estimated to be approximately 52 million. This population estimate is then multiplied by the monthly incidence rate of moderate to severe depression and this gives us the eligible population for each month.

7.3.3 Current and future utilisation

Collaborative care is currently not offered widely in the UK; hence, it is difficult to predict future utilisation rates. It is similarly difficult to predict the shape and scale of the utilisation curve over time. Due to lack of data, this case study is considered more an illustrative example of the effect that the Cochrane review could have. However, it still allows us to demonstrate the magnitude of effect the Cochrane review could potentially have, and the key drivers of the results.

In 2013/14, a total of 8,499 collaborative care appointments were made thorough the Improving Access to Psychological Therapies (IAPT) services, which makes up less than 1% of total appointments.[81] IAPT is an NHS programme that is rolling out services across England offering interventions approved by NICE for treating people with depression and anxiety disorders.

We therefore assume that the proportion of people currently receiving collaborative care is approximately 1%, which is used as our starting utilisation value. As there are no projections for future utilisation available the uptake is modelled using three different scenarios in the world where the Cochrane review is assumed to have an effect. In the base case, we assume that utilisation reaches 30% after 10 years. In addition to this, we have illustrated two alternative scenarios assuming utilisation reaches 10% and 50% after 10 years.

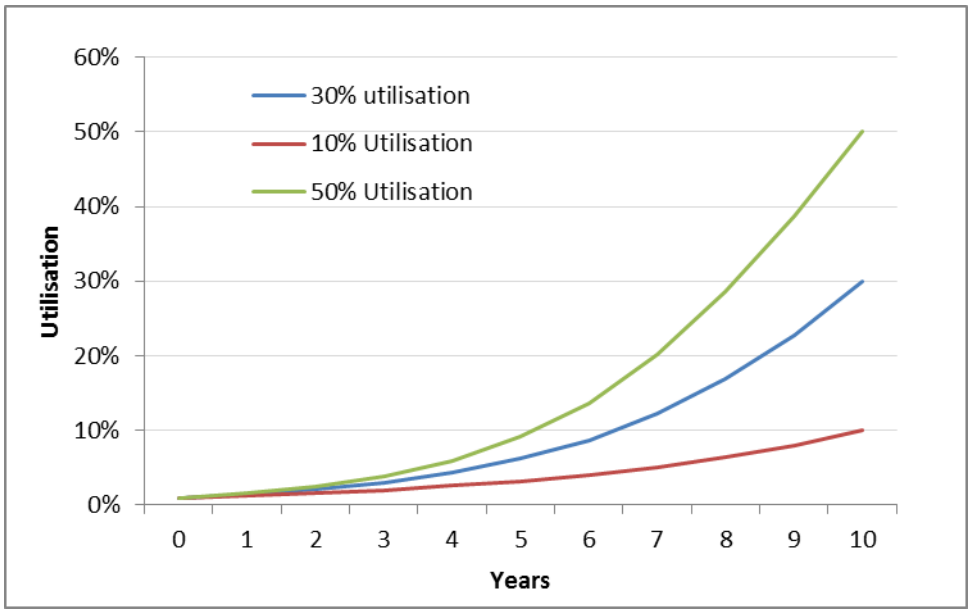
We have adopted a different approach than the other case studies to model the effect of the Cochrane review. Rather than modelling the effect of the Cochrane review as a percentage increase in utilisation over time, we instead assume that the Cochrane review brought forward the NICE guidance update on collaborative care. As the Cochrane review found collaborative care to be an effective way of treating depression, it is assumed these findings would encourage NICE to develop guidance. In the surveillance review for NICE CG90[82] the Cochrane review is referenced several times, indicating that

the results found in the review have encouraged NICE to update the previous clinical guidance, and to potentially update them sooner more urgently.

As the base-case, we assume that the Cochrane review brought forward NICE guidance by three months, and present two further scenarios where the review brought forward guidance by one month and 12 months. We assume that utilisation remains at 1% until the guidance is published and then begins to rise over time. This alternative approach is adopted as we believe this is a potentially more feasible way by which to demonstrate impact of the Cochrane review had an impact, and also to demonstrate a different approach to modelling the effect of the review. If guidance brought forward, in theory, more patients will receive the treatment in the short-term, resulting in additional NMB being gained.

To model utilisation over time, we fit a parametric curve of the form $f(t) = 1/1+exp(at+b))$ to the utilisation data, where t is time and a and b are constants. This curve was fitted using nonlinear regression analysis based on the data points for each scenario. The three diffusion curves are presented in Figure 7.2. The curves show that utilisation increases slowly in the beginning but increases more rapidly in later years. This is based on the fact that collaborative care involves a number of health professionals working with a patient, meaning it will likely take time to re-organise the way depression is treated. However, this assumption is not informed by data, meaning that the way in which utilisation is modelled may be incorrect. However, the impact on the results is like to be minimal.

Figure 0.9: Diffusion curves for the Collaborative care utilisation



7.4 Results

7.4.1 What is the value of full implementation?

Table 7.2 presents the expected value of perfect implementation of collaborative care. The expected value of perfect implementation is approximately £918 million and results in a total QALY gain of 58,254 QALYs.

Table 0.32: Value of full implementation using base case

	Net monetary benefit	QALY gain
Full implementation	£917,535,903	58,254

7.4.2 What are expected health gains from the Collaborative care for depression and anxiety problems review?

Table 7.3 presents the QALY gains for utilisation expects to reach 30%, 10% and 50% after 10 years. The results show that there is a 416 QALYs gain using the base case assumption of utilisation which reaches 30% after 10 years. This falls to 131 QALYs using pessimistic assumption of utilisation which reaches 10% after 10 years. This rises to 703 QALYs using optimistic assumption of utilisation which reaches 50% after 10 years.

Comparing with the QALYs gain assuming the Cochrane review brought forward the NICE guidance update by 3 months, the QALY gain falls when the review brought forward guidance update by 1 months and raises when review brought forward guidance update by 12 months. The results demonstrate that there is a significant impact of the Cochrane review on QALYs gain if the Cochrane review influences the NICE guidance update. (Table 7.3)

Table 0.33: Estimated health gains from the Cochrane review of collaborative care for depression and anxiety problems

Impact of Cochrane review	QALY gain		
	Base case: utilisation reaches 30% after 10 years	Pessimistic: utilisation reaches 10% after 10 years	Optimistic: Utilisation reaches 50% after 10 years
Review brought forward guidance update by 3 months	416	131	703
Review brought forward guidance update by 1 month	142	45	239
Review brought forward guidance update by 12 months	1,495	480	2,554

7.4.3 What is the expected net value the Cochrane review of collaborative care for depression and anxiety problems?

Table 7.4 presents the additional costs incurred due to the increased 30% utilisation of collaborative care after 10 years and resulting from carrying out the Cochrane review. Under the base case assumption that utilisation reaches 30% at 10 years, the additional costs from the review brought forward guidance update by 3, 1 and 12 months are £6 million, £2.1 million and £21.4 million respectively. The estimated NMBs from the review brought forward guidance update by 3, 1 and 12 months, are £6.5 million, £2.2 million and £23.5 million, respectively. (Table 7.4)

Table 0.34: Estimated net value of the Cochrane review assuming the utilisation will reach 30% at 10 years

Impact of initial Cochrane review:	Value of additional health	Additional implementation cost	Total Additional costs	Net value of Cochrane review
Review brought forward guidance update by 3 months	£12,466,650	£5,920,980	£5,979,394	£6,487,256
Review brought forward guidance update by 1 month	£4,253,547	£2,020,203	£2,078,617	£2,174,930
Review brought forward guidance update by 12 months	£44,855,971	£21,304,143	£21,362,557	£23,493,414

Table 7.5 presents the additional costs incurred due to the increased 10% utilisation of collaborative care after 10 years and resulting from carrying out the Cochrane review. Under the pessimistic assumption that utilisation reaches 10% at 10 years, the additional costs from the review brought forward guidance update by 3, 1 and 12 months are £1.9 million, £0.6 million and £6.8 million respectively. The estimated NMBs from the review brought forward guidance update by 3, 1 and 12 months, are £2 million, £0.6 million and £7.5 million, respectively. (Table 7.5)

Table 0.35: Estimated net value of the Cochrane review assuming the utilisation will reach 10% at 10 years

Impact of initial Cochrane review:	Value of additional health	Additional implementation cost	Total Additional costs	Net value of Cochrane review
Review brought forward guidance update by 3 months	£3,944,689	£1,873,512	£1,931,926	£2,012,763
Review brought forward guidance update by 1 month	£1,342,206	£637,475	£695,889	£646,317
Review brought forward guidance update by 12 months	£14,391,265	£6,835,067	£6,893,481	£7,497,784

Table 7.6 presents the additional costs incurred due to the increased 50% utilisation of collaborative care after 10 years and resulting from carrying out the Cochrane review. Under the optimistic assumption that utilisation reaches 50% at 10 years, the additional costs from the review brought forward guidance update by 3, 1 and 12 months are £10.1 million, £3.5 million and £36.4 million respectively. The estimated NMBs from the review brought forward guidance update by 3, 1 and 12 months, are £11 million, £3.7 million and £40.1 million, respectively (Table 7.6).

Table 0.36: Estimated net value of the Cochrane review assuming the utilisation will reach 50% at 10 years

Impact of initial Cochrane review:	Value of additional health	Additional implementation cost	Total Additional costs	Net value of Cochrane review
Review brought forward guidance update by 3 months	£21,102,390	£10,022,486	£10,080,900	£11,021,490
Review brought forward guidance update by 1 month	£7,181,238	£3,410,697	£3,469,111	£3,712,127
Review brought forward guidance update by 12 months	£76,611,821	£36,386,442	£36,444,856	£40,166,965

7.5 Discussion

7.5.1 Summary of the results

- The expected value of perfect implementation of collaborative care is approximately £918 million and results in a total QALY gain of 58,254 QALYs.
- Under the base case assumption that utilisation reaches 30% at 10 years, the estimated NMBs from the review brought forward guidance update by 3, 1 and 12 months, are £6.5 million, £2.2 million and £23.5 million, respectively.
- Under the pessimistic assumption that utilisation reaches 10% at 10 years, the estimated NMBs from the review brought forward guidance update by 3, 1 and 12 months, are £2 million, £0.6 million and £7.5 million, respectively.
- Under the optimistic assumption that utilisation reaches 50% at 10 years, the estimated NMBs from the review brought forward guidance update by 3, 1 and 12 months, are £11 million, £3.7 million and £40.1 million, respectively.

7.5.2 Limitations

This case study shows that there is a significant impact on the net value of the Cochrane review if the review influences the NICE guidance update.

One of the major limitations of the case study is the utilisation data. Collaborative care is currently not offered widely in the UK, hence, it is difficult to predict future utilisation rates. Due to lack of data, this case study is considered more an illustrative example of the effect that the Cochrane review could have. However, it still allows us to demonstrate the magnitude of effect the Cochrane review could potentially have, and the key drivers of the results.

Another major limitation of this case study, is that our analysis only focuses on depression. The Cochrane review effect may be underestimated by not including those with anxiety as we do not factor an additional NMB gains from those with anxiety.

We chose to only investigate the incident population rather than the prevalent population who currently have depression. Therefore, we may be underestimating the population size as well as the impact of the Cochrane review.

8 Discussion and Conclusions

8.1 Summary of findings

There are 21 Cochrane review groups in the UK producing, updating and disseminating systematic reviews. The infrastructure costs for the 21 UK Cochrane review groups are funded by the NIHR. This study commissioned by the NIHR seeks to assess the value to the UK of Cochrane outputs.

The impact and hence value of systemic reviews produced by Cochrane is likely to be multidimensional and include identification of uncertainty and future research priorities, impact on policy decisions clinical guideline development and impact on clinical practice the utilisation of effective treatments through the identification of effective and ineffective interventions.

This study however focuses on just a single aspect of value focusing on the value of increasing the utilisation of interventions identified as clinically effective. To estimate the value of increased implementation the VOIM framework described in Fenwick et al[1] is applied to four exemplar Cochrane reviews. This framework operates by seeking to assess the value per patient of implementing a healthcare intervention these benefits scaled up to the population level by considering the size of current and future population eligible to receive the intervention.

In all four exemplar Cochrane reviews the potential benefits of increased implementation were significant both in terms of health gains and NMB. The magnitude of the estimated health gains ranged from 116 QALYs from the review of anti-VEGF therapies for DMO to 15,816 QALYs from the review of statins for the primary prevention of CVD. The value in terms of NMB which accounts for the value of the health gains and any additional costs of implementing the intervention ranged from a NMB of approximately £0.9 million for the anti-VEGF review to £.04 billion in the Statins review assuming a per QALY threshold of £30,000 per QALY. These significant benefits were observed assuming relatively modest increases in implementation resulting from the Cochrane reviews of just 1% in our base case. In a scenario analyses conducted assuming just a 0.1% increase in utilisation, the value of the realised benefits remained positive in three of the cases (the exception being anti-VEGF therapy for DMO) with estimated health gains ranging between 12 QALYs from the review of anti-VEGF therapies for DMO to 1590 QALYs in the statins review and NMB ranging from -£10,816 for the anti-VEGF review to £41million in the Statins review.

In three of the four reviews evaluated, the estimated net monetary value based on the base case analysis for that single review exceeded the NIHR's total annual contribution to funding Cochrane's infrastructure in the UK. To the extent that Cochrane reviews are able to influence uptake of cost-effective practice, this analysis suggests that the benefits of supporting Cochrane are likely exceed costs and represent a value for money.

Care should, however, be taken not to over interpret the results of this analysis as there were significant issues in applying the VOIM framework to the four case-study reviews. These issues, considered further in Section 8.4 below, stem in part from the lack of appropriate data, particularly relating to current and past utilisation. As consequence the models developed make a number of simplify assumptions, particularly regarding the impact Cochrane reviews have on utilisation. The results of this analysis should therefore be considered indicative of the potential magnitude of any benefits given the assumed increases in implementation. It is not possible to assess from our analysis whether the estimated benefits have been/will be realised. As discussed further below, a formal quantification of the impact of Cochrane reviews on clinical practice is likely to be exceptionally difficult due to the multiple avenues via which Cochrane reviews may influence practice. Further to the above, the four case-study reviews analysed were clearly not representative of all Cochrane reviews and therefore no attempt should be made to extrapolate the results of this analysis to all Cochrane reviews.

Despite the caveats outlined above the magnitude of the benefits demonstrated in the four exemplar reviews demonstrate how small increase in implementation can generate significant benefits both in terms of health gains and net monetary benefits and these benefits far exceed current investment in Cochrane in the UK. For Cochrane to represent value for money Cochrane would only need to recommend a small number (possibly only 1) cost-effective intervention a year. Further, this recommendation can originate from any of Cochrane review groups including those based outside the UK.

8.2 Key drivers of results and implications for practice

The scenario and sensitivity analysis carried out for each of the four case-studies together with comparisons of estimated benefits across the four reviews allows the identification of the key drivers of the value of implementation. These drivers are likely to be generalizable to all Cochrane reviews and therefore highlight factors that may be appropriate to consider when prioritising which reviews and updates to should be completed.

The size of the population eligible to receive each of the four recommended interventions clearly had a very substantial impact on the potential value of the implementation. The size of the eligible population has two components. The first is the absolute eligible population i.e. the total number of people who if the intervention was implemented fully by the NHS would receive it. This point is exemplified when comparing the estimated benefits of implementing statins for primary prevention of CVD with anti-VEGF drugs for DMO. The per patient NMB from implementing each of these interventions was circa £6000 per patient, but there is a significant difference in the eligible populations. In the case of statins the eligible population was many millions of people compared with just a few thousand eligible patients for anti-VEGF therapy. As such the estimated benefits of

increasing the implementation of statins was many times that of implementing anti-VEGF therapy. The second component of the size of the population is the number of people who currently do not receive the intervention. The two risk groups in the statins case-study illustrate this point. The value of full implementation was considerably higher for the 10% to 20% risk group compared with the 20% above group because utilisation of the statins was already widespread in the >20% group. The review of falls also illustrates this point. Utilisation of multifactorial risk assessments was already very high when the Cochrane review was published and therefore there were smaller potential gains to be realised from increasing utilisation to 100%.

Related to the above is the speed with which a technology is likely to diffuse. In the DMO example the adoption of anti-VEGF drugs was projected by NICE to reach near full adoption in a relatively short time frame. This is likely due to the limited alternative treatment options available. In such cases the opportunities and value of influencing practice are likely to be considerably smaller than for an intervention that, for whatever reason, does not diffuse as quickly. Timing of the publication of any review in such cases is likely to be particularly important as the window in which the review is able to influence practice is likely to be limited. Delays are likely to have substantial impact on the realised gains both in terms of health and NMB.

Timing of the publication of the review was an important issue in all four of the case study reviews and not just an issue when diffusion is likely to be particularly rapid. In the DMO case-study the first two editions of the review (in contrast with the third) were published before NICE had approved any anti-VEGF therapy. Therefore the impact of these reviews on clinical practice in the UK may have been limited as the recommended intervention was not available to UK clinicians. The review of collaborative care for depression also illustrates the importance of timing. Here the approach to modelling influence was somewhat different to the others in that it was assumed that the impact of the review was not direct, but through subsequent NICE CG. Assuming that that the Cochrane review brought forward the publication of any subsequent CG developed by NICE. This case-study showed that bringing forward recommendations by just a few months can have significant value in terms of both health and NMB.

One common thread when considering the impact of population size, speed of diffusion and timing is that the policy context is very important when seeking to maximise the value of any review or update. Cochrane reviews do not operate in a vacuum, but stand among a number of other elements that will influence clinical practice decisions. Amongst the most important is inevitability NICE who through TA and CG play a significant role in shaping clinical practice in the UK. It is clear that in many cases Cochrane reviews have a significant influence on CG production in the UK as evidenced by the falls preventions and collaborative case-studies and the significant number of citations Cochrane reviews receive in NICE guidance.[13, 15] This relationship with CG is undoubtedly an important avenue via

which Cochrane reviews can influence practice. Indeed disentangling Cochrane's influence on CG is one the most significant challenges in a project such as this seeking to evaluate the value of Cochrane's outputs. To this extent attempts to evaluate Cochrane reviews in isolation of the other elements fails to account for the fact that Cochrane reviews are only part of larger process of assessment and implementation efforts. A more appropriate assessment for future research to undertake may therefore be of the adequacy of current efforts to implement effective and cost-effective technologies in the UK, and with respect to Cochrane reviews and how Cochrane is best placed to contribute this process. Optimisation of the value Cochrane reviews to the UK is therefore likely to be in part about the degree to which decisions on undertaking and updating of reviews are aligned with and integrated into other elements of evidence assessments and implementation activities. Further, as McKenna et al[83] set out, significant value can be generated by resolving uncertainty over the effectiveness of interventions and these benefits are distinct, though related to, any benefits resulting from changes in implementation. To the extent that systematic reviews and meta-analysis able to resolve such uncertainty, Cochrane's Outputs may provide further additional benefits particularly where there is clinical equipoise regarding the relative effectiveness of treatment options.

8.3 Strengths

Previous studies have attempted to evaluate the impact of Cochrane [Bunn et al and other], however to our knowledge this is the only study to attempt to formally quantify the economic value of Cochrane outputs. To do this we applied the VOIM framework to four case studies, and demonstrate how the VOIM framework can help in quantifying and understanding the value of investing resources in resolving decision uncertainty and promoting the utilisation of cost-effective interventions. One of the particular advantages of this approach is that it is consistent with the value assessment of new interventions conducted by NICE and therefore builds upon current methodologies for evaluating new interventions.

Our estimates, while based on limited data and making a number of simplifying assumptions, are able to illustrate the potential value of increasing implementation of the interventions recommended in the four Cochrane reviews. Furthermore, scenario and sensitivity allow us to illustrate important drivers of benefit and factors that it may appropriate to consider when assessing whether to undertake or update a review.

A further strength of our analysis is that in all four case-studies we have been able to construct either a fully dynamic or partially dynamic model. This has the advantage of reflecting gains from both the prevalent and incident population allowing for more accurate estimates of the value of implementation and also illustrating important dynamic factors that influence the value of any increase in implementation resulting from Cochrane reviews.

8.4 Limitations

This study has highlighted a number of challenges in assessing the value of Cochrane outputs and the difficulty with applying the VOIM framework in this context. These difficulties occurred at three levels.

The first is an issue of data availability, data on many of the inputs used in the presented analysis were very limited, particularly utilisation data which was sparse and potentially subject to significant error. Other parameter inputs were also an issue, such as the availability of reliable and fully reported estimates of cost-effectiveness. This issue arose partly as consequence of problems within the cost-effectiveness analysis that had been carried out (note these were not part of the Cochrane reviews, but separate studies). For example, the cost-effectiveness evidence for multi-factorial risk assessments for the prevention of falls was very uncertain and as such the value of implementing this intervention is subject to similar uncertainty. In normal circumstances, this uncertainty would be modelled within our analysis; however, reporting issues and lack of access to the executable models meant such analysis was not possible. The estimates of the value of implementation presented in this study are therefore are subject to significant uncertainty and as described above, the estimates presented should be considered as indicative of the magnitude of the value of implementation for the four interventions considered, rather as precise estimates.

The second issue relates to the requirements of the VOIM framework and its application to evaluating the value of Cochrane reviews. As discussed, Cochrane reviews foremost aim is to evaluate clinical effectiveness and Cochrane reviews rarely formally consider cost-effectiveness. As such the application of a framework that largely hinges cost-effectiveness and value for money may create tension between the framework and the aims of Cochrane. This has implications for the interpretation of our results, given that the positive value of implementing for the four exemplar interventions was in part a result of the design of the study, which as perquisite required that the intervention recommended by the Cochrane review be cost-effective. Furthermore, the value of implementation framework adopted assumes that a review will make some recommendations regarding the use of an intervention. However, a significant proportion of Cochrane reviews do not draw unequivocal conclusions about the relative effectiveness of the evaluated interventions due to the lack of reliable evidence. Clearly reviews that do not draw clear conclusions about the relative effectiveness of interventions are much less likely to influence clinical practice at least short run. The short run value of these Cochrane reviews in terms of implementation is therefore likely to be limited. Such reviews may, however, add value in the long term, for example, by highlighting decision uncertainty and the need for further research which might lead to further research and ultimately to uptake of the intervention. The VOIM analysis presented in this study, however, does not recognise this potential

source of value. A clear extension to this study therefore may to incorporate alternative sources of value such as the value of identifying uncertainty.

The third issue relates to the ability to link Cochrane reviews to changes in practice. Within this study we have made a number of simplifying assumptions about the impact that Cochrane reviews have on utilisation. The scenario analysis presented for each exemplar shows how different assumptions about the magnitude of the changes in utilisation resulting from the reviews impacts upon estimated benefits. The assumed change in practice had a very significant impact on the estimated value of the review. Reliable and frequently measured utilisation data would have potentially allowed for an evaluation of any direct impact of Cochrane reviews on practice using techniques similar to those used in Sheldon et al. However, even this would have had limitations as the impact of Cochrane reviews on practice may not always be direct, but though other mediums such as clinical guidance/guidelines. As such, evaluating Cochrane in isolation of other levers on practice that Cochrane reviews may feed into is a key issue. A more appropriate question for future research may be the degree to which Cochrane reviews are maximising their value in terms of efficiently linking to these other parts of the process of assessment and implementation. There is a further issue of interpreting the value of multiple reviews. Cochrane reviews are not static pieces of research and are updated regularly, untangling the impact of each of these versions of the review is a significant challenge and one that within this analysis we have largely sidestepped.

8.5 Extensions and future research

As discussed in 3 the framework developed by Fenwick et al[1] incorporates two aspects of value namely VOI and VOIM of implementation. This study focused on the later aspect of implementation, but a clear extension to the current work would be to consider benefits of Cochrane reviews generated in terms of VOI. There are number of ways in which Cochrane reviews may generate benefit in terms resolving decision uncertainty. The first is via the identification of uncertainty and the need for research. Where Cochrane identifies uncertainties in the clinical effectiveness of interventions it may lead to further trials being carried and ultimately to implementation of an intervention. Under this scenario the value generated by reducing uncertainty and implementing the intervention would be in part attributable to the Cochrane review. However, because value generated through a process of further primary research and possibly also further systematic review this study it would be that the evaluation be framed with respect evaluating the process of evaluation and implementation of intervention, as attempting to attribute value individual elements is likely to be very difficult. An alternative, way in which VOI could be applied to systematic reviews is consider the added value systematic review by synthesizing all available evidence. For example, systematic reviews are generally better placed to provide best evidence about the relative effectiveness of interventions than a single primary study as such can resolve uncertainty regards the effectiveness of interventions in way

that single studies cannot. However, interpretation of the contribution of Cochrane added value needs to be considered carefully, as systematic review do not generate new evidence, but more accurately summarise the available evidence and allow the value of the information generated by primary studies to be realised. Therefore as in the first scenario we must consider Cochrane reviews as part of system of evaluation and implementation and not in isolation.

8.6 Conclusions

In this study we have sought to estimate the economic value of Cochrane outputs to the UK. To do this we have applied a value of implementation framework developed by Fenwick et al[1] to four case study Cochrane reviews. Our analysis, while subject to a number of substantial caveats has shown that there is substantial value from implementing the recommended healthcare interventions both in terms of additional health benefits as well as net value to the NHS. Furthermore, our analysis has demonstrated that even small increases in implementation that may have resulted from the publication of the four case study reviews are likely to result in substantial benefits that exceed the NIHR's financial contribution to the Cochrane collaboration.

This study also highlights a number of drivers of that are likely to be important when considering the potential value of any review or update:

- The size of the eligible population;
- Current and projected utilisation of the intervention;
- Current and future NICE guidelines and technology appraisals;
- Cost-effectiveness and resource implications of implementing the intervention.

Our analysis also illustrates some of the challenges of evaluating the value of Cochrane outputs. In part this related to lack of access to reliable data particularly utilisation and estimates of cost-effectiveness. Future studies with more time may be better placed to overcome these issues. Even with improved access to data, evaluating the value of Cochrane outputs face substantial challenges due to the complexity of disentangling the influence of Cochrane from NICE guidance and other implementation activities. Due to these complexities it may be more appropriate for future research to consider how Cochrane is able to optimise their contribution to current processes of evaluation and implementation of interventions.

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10 Appendix

The following Cochrane reviews were initially short listed for evaluation:

Cochrane reviews	Put forward by	Included in the analysis of the study
1. Allen VB, Gurusamy KS, Takwoingi Y, Kalia A, Davidson BR. Diagnostic accuracy of laparoscopy following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. Cochrane Database of Systematic Reviews 2013, Issue 11.	York team	No
2. Andabaka T, Nickerson JW, Rojas-Reyes MX, Rueda JD, Bacic Vrca V, Barsic B. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. The Cochrane database of systematic reviews 2013, Issue 4.	York team	No
3. Archer J, Bower P, Gilbody S, Lovell K, Richards D, Gask L, et al. Collaborative care for depression and anxiety problems. Cochrane Database of Systematic Reviews 2012, Issue 10.	York team	Yes
4. Best L, Simmonds P, Baughan C, Buchanan R, Davis C, et al. Palliative chemotherapy for advanced or metastatic colorectal cancer. Colorectal Meta-analysis Collaboration. Cochrane database of systematic reviews 2000, Issue 1.	York team	No
5. Chong J, Karner C, Poole P. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2012, Issue 9.	Funder	No
6. Cooney GM, Dwan K, Greig CA, Lawlor DA, Rimer J, Waugh FR, et al. Exercise for depression. Cochrane Database of Systematic Reviews 2013, Issue 9.	Funder	No
7. Cosford PA, Leng GC. Screening for abdominal aortic aneurysm (Review). Cochrane Database of Systematic Reviews 2007, Issue 2.	York team	No
8. Dodd JM, Crowther CA, Grivell RM, Deussen AR. Elective repeat caesarean section versus induction of labour for women with a previous caesarean birth. Cochrane Database of Systematic Reviews 2014, Issue 12.	Funder	No
9. Dodd JM, Crowther CA, Huertas E, Guise J-M, Horey D. Planned elective repeat caesarean section versus planned vaginal birth for women with a previous caesarean birth. Cochrane Database of Systematic Reviews 2013, Issue 12.	Funder	No

10. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, et al. Interventions for preventing falls in older people living in the community. Cochrane Database of Systematic Reviews 2012, Issue 9.	Funder	Yes
11. Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. The Cochrane database of systematic reviews 2003, Issue 1.	York team	No
12. Mugford M, Elbourne D, Field D. Extracorporeal membrane oxygenation for severe respiratory failure in new born infants. Cochrane Database of Systematic Reviews 2008, Issue 3.	York team	No
13. Nussbaum AM, Stroup TS. Paliperidone palmitate for schizophrenia. Cochrane Database of Systematic Reviews 2012, Issue 6.	Funder	No
14. Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJS, Dalal H, et al. Exercise-based rehabilitation for heart failure. Cochrane Database of Systematic Reviews 2014, Issue 4.	Funder	No
15. Taylor F, Huffman MD, Macedo AF, Moore THM, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2013, Issue 1.	Funder	Yes
16. Virgili G, Parravano M, Menchini F, Evans JR. Anti-vascular endothelial growth factor for diabetic macular oedema. Cochrane Database of Systematic Reviews 2014, Issue 10.	York team	Yes

Appendix 13: Conflicts of Interest declarations

Committee members:

- Professor Jos Kleijnen (Chair)
- Dr Philip Alderson
- Dr Jane Aubin
- Professor John Cairns
- Sally Crowe
- Professor Paul Garner

Report writing:

- Kate Misso

REPORTING CONFLICTS OF INTEREST

Project Title:	Evaluation of NIHR Investment in Cochrane
Duration:	September 2015 – April 2016
Aim:	The aim of this study is to assess the value of NIHR investment in systematic reviews in general and Cochrane in more detail over the period 2005-2014 (10 completed years), looking at their health and economic impact and other impacts on policy, practice and research.

Name:	Jos Kleijnen
Institution/Organisation:	Professor of Systematic Reviews in Health Care, School for Public Health and Primary Care (CAPHRI), Maastricht University, The Netherlands Director, Kleijnen Systematic Reviews Ltd (KSR), York, UK
Description of Conflict:	I was director of the Dutch Cochrane Centre I was a member of the Cochrane Collaboration Steering Group I was director of the Collaboration Trading Company I am an editor of the Vascular Review Group I am an author of a number of Cochrane Reviews I am a member of a number of Cochrane Methods Groups I am team leader of an NIHR TAR Group doing work for NICE I prepare systematic reviews in a commercial setting within KSR. A proportion of these are for pharmaceutical and other industry. I am not in receipt of any funding from Cochrane or related to Cochrane.

REPORTING CONFLICTS OF INTEREST

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Name:	Philip Alderson
Institution/Organisation:	NICE
Description of Conflict:	10% of my time is funded by a NIHR Cochrane Programme Grant held by the University Hospitals of Morecambe Bay NHS Trust. My work on this is directly concerned with the preparation of Cochrane reviews. My employment at NICE includes some involvement in the commissioning, preparation and quality assurance of systematic reviews, including the direct use of Cochrane reviews. I was employed at the UK Cochrane Centre from 1998 to 2004. I have published views on the usefulness of Cochrane reviews in guidelines, and the impact of Cochrane reviews.

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Name:	Sally Crowe
Institution/Organisation:	Crowe Associates Ltd
Description of Conflict:	• Crowe Associates Ltd has received funding (2014 - 2015) from UK Cochrane Centre for a project on outcomes working with three UK based Cochrane Review Groups • Crowe Associates has a small contract with EPOC Cochrane Group for Public and Patient Involvement Consultancy (2014 - 2017) but Sally Crowe has not worked with EPOC during the period of the evaluation (Oct 15 - March 16) • Crowe Associates conducted a set of stakeholder interviews and summarised findings in a report to augment the evidence for the review and was paid to do this • Sally Crowe is a member of the Systematic Programme Review Advisory Group on behalf of the consumer perspective and receives an honorarium for this work • Sally Crowe is a member of the Cochrane Consumer Network and a Co Convenor or the Cochrane Prioritization Methods Group and does this in a voluntary capacity

Evaluation, Trials and Studies Coordinating Centre

NHS National Institute for Health Research

REPORTING CONFLICTS OF INTEREST

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Name:	John Cairns
Institution/Organisation:	London School of Hygiene & Tropical Medicine
Description of Conflict:	I have no conflicts of interest to declare.

John Cairns

1st April 2016

Evaluation, Trials and Studies Coordinating Centre

NHS National Institute for Health Research

REPORTING CONFLICTS OF INTEREST

Project Title:	Evaluation of NIHR Investment in Cochrane
Duration:	September 2015 – April 2016
Aim:	The aim of this study is to assess the value of NIHR investment in systematic reviews in general and Cochrane in more detail over the period 2005-2014 (10 completed years), looking at their health and economic impact and other impacts on policy, practice and research.

Name:	Paul Garner
Institution/Organisation:	Liverpool School of Tropical Medicine
Description of Conflict:	I run a Research Programme Consortium funded by UKAid that aims to improve decisions made using reliable evidence from systematic reviews. I am coordinating editor of the Cochrane Infectious Diseases Group which is part of Cochrane. As a member of the coordinating editors' executive until 2013, I highlighted the need for Cochrane to prioritise the reviews and focus on improving quality. I do not receive any funds from NIHR. 

REPORTING CONFLICTS OF INTEREST

Project Title:	Evaluation of NIHR Investment in Cochrane
Duration:	September 2015 – April 2016
Aim:	The aim of this study is to assess the value of NIHR investment in systematic reviews in general and Cochrane in more detail over the period 2005-2014 (10 completed years), looking at their health and economic impact and other impacts on policy, practice and research.

Name:	Dr. Jane E. Aubin, Chief Scientific Officer and Vice-President, Research, Knowledge Translation and Ethics
Institution/Organisation:	Canadian Institutes of Health Research
Description of Conflict:	- No direct conflict of interest - However, I make strategic direction recommendations and decisions, and funding recommendations based on peer review, that relate to systematic reviews and organizations, including Cochrane Canada

REPORTING CONFLICTS OF INTEREST

Project Title:	Evaluation of NIHR Investment in Cochrane
Duration:	September 2015 – April 2016
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Name:	Kate Misso
Institution/Organisation:	Information Specialist Manager, Kleijnen Systematic Reviews Ltd (KSR), York, UK
Description of Conflict:	I am a member of the Cochrane Information Retrieval Methods Group I am a member of an NIHR TAR Group doing work for NICE I am a member of the InterTASC Information Specialists' Sub-Group (ISSG) I prepare systematic reviews in a commercial setting within KSR. A proportion of these are for pharmaceutical and other industry. I am not in receipt of any funding from Cochrane or related to Cochrane.

Appendix 14: Acknowledgements

The Committee is grateful for the help of many people, who made this report possible.

Special thanks go to Sally Bailey and Ria Osborne from NIHR, and their colleagues from NETSCC, who provided a lot of the information, organised and participated in Committee meetings, wrote the minutes, and commented on drafts of the report.

Alison Bourgon (Canada) for comments on drafts of the report.

David Tovey, Mark Wilson, Martin Burton, Therese Docherty and other colleagues from Cochrane who provided the Committee with information for the report.

The NIHR Dissemination Centre (NDC) and their College of Raters for assessing the relevance to the NHS of a sample of Cochrane reviews.

Sally Crowe Associates for the stakeholder interviews project, and all participants of stakeholder interviews.

Kay Pattison, Tony Williams and Kathy Mann from DH as observers and hosts of the Committee meetings.

Robert Hodgson, Mousumi Biswas, and Philip Morgan from the Centre for Reviews and Dissemination at the University of York for their report on the economic value of Cochrane reviews.

Steven Duffy, Shelley de Kock, Janine Ross, Lisa Stirk, Sohan Deshpande and Jeanette Kleijnen (all from Kleijnen Systematic Reviews Ltd) for information, content and editorial support.