EEPRU

Policy Research Unit in Economic Evaluation of Health and Social Care Interventions

Research Report

Title: Economics of Medicines Optimisation.

Authors: Faria R, Barbieri M, Light K, Sculpher M.

Correspondence to: Rita Faria, Centre for Health Economics, University of York, Alcuin A Block, Heslington, YO10 5DD. Email: rita.nevesdefaria@york.ac.uk

No: 016

Date January 2014

The University Of Sheffield.

THE UNIVERSITY of York

The Policy Research Unit in Economic Evaluation of Health and Care interventions is funded by the Department of Health Policy Research Programme. It is a collaboration between researchers from then University of Sheffield and the University of York.

The Department of Health's Policy Research Unit in Economic Evaluation of Health and Care Interventions is a 5 year programme of work that started in January 2011. The unit is led by Professor John Brazier (Director, University of Sheffield) and Professor Mark Sculpher (Deputy Director, University of York) with the aim of assisting policy makers in the Department of Health to improve the allocation of resources in health and social care.

CONTENTS

1. EXECUTIVE SUMMARY

1.1. BACKGROUND

The UK National Health Service (NHS) faces the triple challenge of improving health outcomes while coping with the increasing demand for services and achieving efficiency savings. Medicines use is one of the areas that can offer considerable scope for improving health outcomes and reducing costs. Addressing these various areas of concern in an effective and cost-effective manner requires an understanding of the size and nature of the evidence base. The objectives of this work are, firstly, to undertake a scoping review relating to the suboptimal use of medicines in the NHS, both in terms of the scale, costs and health lost; and, secondly, to review the extent of the evidence on effectiveness and cost-effectiveness of interventions to address suboptimal medicines use.

1.2. METHODS

Systematic searches (up to February 2013) of the NHS Economic Evaluation Database, the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects for systematic reviews on the effectiveness or cost-effectiveness and for primary research on cost-effectiveness of interventions. Studies in written in English set in any country were included.

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1.3. RESULTS

In total, 107 studies were included in the review (29 economic evaluations and 78 systematic reviews) from 646 records identified.

Systematic reviews on effectiveness of interventions

With the exception of insufficient generic prescribing, every one of the aspects of suboptimal medicines use was addressed by the systematic reviews. The majority of the studies (51, 65%) focussed on interventions to improve adherence, either in any disease area (21; 27%) or in specific conditions (30, 38%). Randomised controlled trials (RCTs) were available for all aspects. There appears to be considerable evidence on the different aspects of suboptimal medicines use specific to the UK setting. Most studies report intermediate outcomes: measures of adherence (53, 68%), clinical outcomes (24, 31%) and adverse drug events (16, 21%). No study reports quality-adjusted life years but four (5%) report measures of quality of life.

Economic evaluations

The majority of the studies (16, 55%) examined interventions to improve adherence, followed by prescription errors (8, 28%) and inappropriate prescribing (4, 14%). Six studies (21%) addressed more than one aspect of suboptimal use of medicines. Most studies (19, 66%) conducted a within-trial economic evaluation using data from a single study. Clinical outcome measures were the most frequently used (8, 28%), followed by measures of adherence (6, 21%) and appropriateness of medication (5, 17%). Quality-adjusted life years (QALYs) were used in five studies (17%).

1.4. CONCLUSIONS AND IMPLICATIONS FOR RESEARCH

There is a large body of evidence on the effectiveness of interventions to improve adherence to medication. Most are, however, specific to a particular disease area. Interventions to improve the different aspects of suboptimal prescribing form the second largest body of literature, particularly those to reduce prescription errors and inappropriate prescribing. The evidence on cost-effectiveness follows the same pattern but is much smaller in size.

Interventions to improve suboptimal use of medicines tend to be specific to a particular aspect of the pathway and/or to a particular disease area. Little consideration is made on how to improve medicines use in patients with co-morbidities and poly-medication. The medicines pathway is rarely examined holistically but in a fragmented manner, making it difficult to draw conclusions on which aspect of suboptimal use of medicines should be prioritised. Decision modelling has the potential to address the evidence gaps in the literature by translating intermediate outcomes into health and costs and by integrating the evidence across the full medicines pathway.

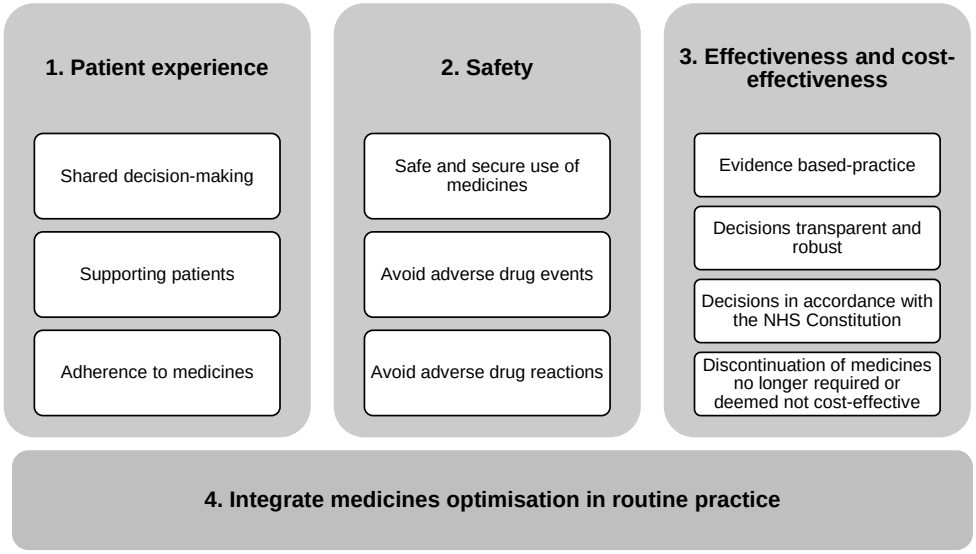
2. BACKGROUND

The UK National Health Service (NHS) faces the triple challenge of improving health outcomes while facing increasing demand for services and achieving efficiency savings in the region of £20 billion by 2014-15 as part of the Quality, Innovation, Productivity and Prevention (QIPP) initiative [2]. QIPP is part of a wider international drive to improve quality of care and health outcomes whilst keeping costs down [3]. Medicines use is considered to be one of the areas that offers considerable scope for improving health outcomes and reducing costs. In the UK, the cost from medicines waste in primary care was estimated at £300 million per year [6]. In secondary care, hospitalisations related with adverse drug reactions may cost up to £466 million per year [7]. Worldwide, medicines optimisation could achieve savings in the region of 8% of total global healthcare costs [8]. The potential for health gains is equally impressive as more than 250,000 hospital admissions per year are attributable to adverse drug events [7] and 16% of medication incidents have resulted in patient harm and 0.9% in death [9].

Medicines optimisation can be seen as the 'low-hanging fruit' in the drive to optimise health care services and ultimately health outcomes. Since market access is conditional on evidence on quality, safety and efficacy, medicines offer a 'standardised' expectation of benefit. Most other types of healthcare resource cannot achieve this level of standardisation due to the involvement of an 'operator', i.e. the healthcare professional diagnosing, advising, treating or operating. As long as the medicine is used appropriately within its marketing authorisation, treatment effectiveness may be expected to fall within the interval observed in the regulatory clinical trials. In this sense, suboptimal use of medicines represents a failed opportunity to improve health for those receiving them.

In practice, the optimal use of medicines involves getting all the steps right in the medicines pathway, namely prescribing, record keeping, dispensing, monitoring and administration. Although a perfect system is impossible, suboptimal use of medicines is often the norm for most patients as only 4%-21% may be getting the maximum benefit from medicines [10].The different aspects of suboptimal medicines use relate to the different steps in the medicines management pathway. Optimal prescribing may be affected by poor compliance with best-practice guidelines, insufficient generic prescribing, inappropriate prescribing (under-, over- and misuse of medicines) and prescription errors. The interface between primary and secondary care is another area affected by suboptimal use of medicines, in particular at admission (medicines reconciliation) and discharge. Other causes of suboptimal medicines use are dispensing errors, administration errors, poor medicines management in care homes, under-monitoring and non-adherence. As a result, optimisation involves not only integration of the different healthcare professionals but also communication with patient and carers. Figure 1 sets out the key elements in medicines optimisation: an understanding of the patient's experience, ensuring that the medicine use is as safe as possible, making decisions guided by evidence on effectiveness and cost-effectiveness and integrating medicines optimisation within routine practice [11-12].

Figure 1 Principles of medicines optimisation [11-12]



Addressing these various areas of concern in an effective and cost-effective manner requires an understanding of the size and nature of the evidence base. The objectives of this work are, firstly, to undertake a scoping review relating to the suboptimal use of medicines in the NHS, both in terms of the scale, costs and health lost; and, secondly, to review the extent of the evidence on effectiveness and cost-effectiveness of interventions to address suboptimal medicines use. This will inform future research on cost-effective strategies to achieve medicines optimisation.

1.1. SCALE AND BURDEN OF SUBOPTIMAL MEDICINES USE IN THE UK

Table 2 summarises the recent literature on the scale and burden of suboptimal use of medicines. Suboptimal prescribing, for example, can occur from poor compliance with guidelines, inappropriate prescribing, low use of generic medication or prescription errors. It is difficult to disentangle these different issues. Poor compliance with guidelines not only can be an issue on its own, but also result in inappropriate prescribing, such as in the case of antibiotics [13], antipsychotics [14] or non-steroid anti-inflammatory medication [15], or insufficient use of generics, as in statins and renin-angiotensin drugs [13].

Prescription errors are another aspect of suboptimal prescribing. Errors are relatively frequent in general practice, but most are unlikely to have adverse consequences [16]. A similar pattern emerges from secondary care, with error rates from 8.4% to 10.3% depending on the grades of doctor considered. However, almost all errors ~~were~~ are intercepted by pharmacists before reaching the patient [17]. Errors can also occur at the interface between secondary and primary care, i.e. at admission to hospital and at discharge [18]. Such errors relate with difficulties in obtaining the patient history and in the communication of changes in medication from the hospital to the GP [18-19]. Dispensing errors appear to be less frequent than prescription errors, both in community pharmacy and in the hospital setting [20-22]. The picture is somewhat different in care homes, with dispensing errors at 9.8% [23]. The difference is related with the repackaging of tablets in monitored dosage systems in the pharmacy. The most frequent cause of errors in care homes is in monitoring, which was also the

type of error most likely to cause harm [23]. Monitoring errors in the community, where 1 in 7 patients may be at risk, are in same order of magnitude as in care homes [24]. Deficient record keeping is an aspect of suboptimal use of medicines that can result in prescription errors, in issues in medicines reconciliation and discharge, dispensing errors, administration errors and monitoring errors. However, no studies were found on the prevalence or burden due to deficient record keeping. The final and most important hurdle for medicines optimisation is adherence. Overall, between 30%-60% of all medicines are not taken as prescribed [25]. Non-adherence is a complex issue [26]. Non-adherence may be non-intentional, i.e. the patient forgets to take the medication, or intentional, whereby there is a rational decision process in which the individual compares the benefits and risks from the medication. In any case, non-adherence can have a substantial impact on both costs and health outcomes. Non-adherence has been estimated to cost between £36-£196 million per year in direct costs to the NHS (2006-07 prices) [27]. The consequences in terms of health loss are more difficult to estimate, but there is evidence that non-adherence is associated with poorer outcomes in cardiovascular disease [28], diabetes [29], osteoporosis [30] and asthma [31].

Table 1 Overview of the recent literature of the scale and the burden of suboptimal use of medicines in the UK

Aspect of suboptimal use	Scale of the problem	Costs and health lost
Poor compliance with guidelines	• Evidence of unwarranted variation of prescription rates of recommended drugs: o Prescribing rates for anti-dementia drugs varied 25-fold across Primary Care Trusts in England during 2010-11, between 0.1-1.3 per age- and sex- weighted population, a variation that is unlikely to be fully explained by differences in prevalence[32]. o Prescribing rates for Parkinson's disease drugs across Primary Care Trusts in England during 2010-11 varied from 2.0-6.9 per age-weighted population, a variation that is unlikely to be fully explained by differences in prevalence[32]. o Prescribing rates of hypnotics drugs per weighted population varied fourfold across Primary Care Trusts in England during 2010-11[32].	• Not following the guidelines in the prescription of statins, renin-angiotensin drugs, proton-pump inhibitors and clopidogrel account for £227 million over one year [13]. • Insulin total net ingredient cost per patient varied from £79 to £176 in 2010-11 across Primary Care Trusts in England but this variation does not correlate with patient outcomes[32]. • Non-insulin anti-diabetic drugs total net ingredient cost per patient varied from £65 to £180 in 2010-11 across Primary Care Trusts in England, but this variation does not correlate with patient outcomes [32].
Insufficient generic prescribing	• Prescribing rates in 2006 for statins prescribed as simvastatin (recommended) varied across Primary Care Trusts from around 25% to 85% [13].	• Not following the guidelines in the prescription of statins, renin-angiotensin drugs, proton-pump inhibitors and clopidogrel account for £227 million over one year [13].
Inappropriate use of antibiotics	• 58% of patients referred to hospital with sore throat were prescribed an inadequate dose or an inappropriate antibiotic in primary care. Hospital doctors prescribed antibiotics contrary to guidelines in 39% of patients [33]. • There is a threefold variation in prescribing rates of Quinolones across Primary Care Trusts, an antibiotic that should be reserved for resistant infections [14].	
Inappropriate prescribing	• An evaluation of the quality of prescribing in 102 hospitals across England found that 47% were not on the appropriate anti-thrombotic prophylaxis and that 51% were inappropriately prescribed benzodiazepines [34]. • A review of the use of antipsychotic medication in people with dementia found that 80% of patients are unlikely to derive any benefit from these drugs [35]. • An analysis of UK patient records in 2003 found that 32.2% of elderly patients were prescribed potentially inappropriate medication and 20.5% ~~were~~ received a potential high risk drug [36].	• The inappropriate use of antipsychotic medication in patients with dementia is likely to be associated with an additional 1,800 deaths and 1,620 cerebrovascular events per year [35]. • Inappropriate prescribing of non-steroid anti-inflammatory drugs has been estimated to be associated with 3,500 hospitalisations and 400 deaths per year in patients over 60 years of age [15].
Prescription errors	• A retrospective study in 15 general practices in England (the PRACtICe study) reviewed the records of 1,777 patients (6,048 prescription items) and found 247 (4.08%) prescribing errors, 55 (0.91%) monitoring errors, 427 (7.06%) of suboptimal prescribing and 8 legal problems. Overall, 12% of all patients and	

	4.9% of all prescriptions included prescription or monitoring errors. A total of 302 errors were assessed for severity. The mean severity score was 3.5 and the median 3.3 (IQR 2.2-4.4). The 55 monitoring errors had a median score of 3.8; the 247 prescribing errors had a lower median score of 3.0; 0.18% of all prescriptions had a severe error [16]. • The mean prescription error rate by first year foundation trainee doctors is 8.4% per medication order, but most do not reach the patient [17]. • A study in three NHS hospitals found that 14.7% of prescription orders had an error; 16.3% in medical admission wards and 12.2% on surgical wards [37]. • A study evaluating the effectiveness of an intervention to reduce prescription or monitoring errors (the PINCER trial) found that 3% of patients were at risk of at least one prescription problem [24].	
Medicines reconciliation and discharge	• 24% of GPs do not systematically provide information on co-morbidities, allergies and drug reactions to hospital. 53% of GP practices reported that discharge summaries were received in time to be useful either "all" or "most" of the time. Only 27% of GP practices reported that discharge summaries were "hardly ever" or "never" inaccurate or incomplete; and 81% of practices reported that details of prescribed medicines were incomplete or inaccurate on discharge summaries "all" or "most" of the time [19]. • A UK study in 42 NHS Trusts found 25% to 31% of discrepancies in the patient's medication history at admission [38]. • Another UK study investigated the severity of discrepancies at the time to admission and following discharge. Discrepancies occurred in 69% of the admissions and 43% of the discharges [18].	• An economic evaluation on interventions to reduce medication errors at discharge estimated that medication errors costed £4,092 per 1,000 prescription orders to the NHS [39].
Dispensing	• A systematic review indicated that the dispensing error rate in hospital pharmacies is between 0.008% to 0.02% [20]. • A study in 20 NHS hospitals in Wales estimated an overall incident rate of 0.016 per 100 items dispensed, 24% of which the wrong strength, 17% the wrong drug, 13% the wrong form and 11% the wrong instructions [21]. • An observational study in 11 UK pharmacies found a content error in 1.7% of dispensed items and a labelling error in 1.6%; 67% of errors were unlikely to have adverse consequences [22].	•
Administration errors	• An observational study in older people wards in four hospitals in East Anglia found that 38.4% of doses were given incorrectly to patients [40]. This study also included a review of the literature, which indicated that medication administration errors in the UK ranged between 3-8%.	•
Medicines management in care homes	• A pivotal study evaluating the prevalence, types and causes of medication errors (prescribing, monitoring, dispensing and administration) in the care home setting found that 65.9% of residents had been subject to a medication error: prescribing 8.3%, monitoring 14.7% (for relevant medicines), dispensing 9.8% and administration 8.4%. The mean harm (and range) from the errors for each type of error was prescribing 2.6 (0.2-5.8), monitoring 3.7 (2.8-5.2), dispensing	•

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	2.0 (0.2-6.6) and administration 2.1 (0.1-5.8) [23].	
Adherence	• A longitudinal survey of patients found that 30% of patients are non-adherent to a new medication for a chronic condition at 10 days after initiation and 25% are non-adherent at 4 weeks [41]. • A review of the literature found that 5%-20% of all prescriptions are not dispensed and 10% of repeat medications are not refilled. Overall, 30% to 60% of medicines are not taken as prescribed [25].	• A recent report estimated that the gross annual cost of NHS primary and community care prescription medicines wastage in England for 2009 is currently in the order of £300 million per year, including £90 million of unused prescription medicines in individuals' homes, £110 million returned to community pharmacies and £50 million of unused medicines disposed by care homes [6]. • The National Audit Office estimated in 2007 for England that the value of medicines returned unused is £100 million and that the cost of destroying them was £1.5 million [42]. • Non-adherence to diabetic medication has been associated with statistically significant increased risks for all-cause hospitalization (odds ratio=1.58) and for all-cause mortality (odds ratio=1.81) [29].
Monitoring	• 5% (n=3,253) of the medication incidents reported to the National Patient Safety Agency in 2007 were caused by lack of or inappropriate monitoring. Of these, three lead to death and three lead to severe harm [42]. • The PINCER trial: 15% of patients were at risk of at least one monitoring problem. Specific monitoring problems were: 11% on long term ACE inhibitors or loop diuretics without urea and electrolyte monitoring; 39% on methotrexate for >= 3 months without full blood count in the past 3 months; 37% of patients on methotrexate for >=3 months without a liver function test in the past 3 months; 7% on warfarin for >= 3 months without an international normalised ratio (INR) in the past 3 months; 47% of patients on lithium for >= 3 months without a lithium concentration measurement in the past 3 months; 49% of patients on amiodarone for >= 6 months did not have a thyroid function test in the past 6 months [24]. • The PRACtICe study identified 55 monitoring errors in 770 prescription items reviewed that required blood monitoring (7%). The 55 monitoring errors had a median harm score of 3.8 (scale 0-10, where errors with a score of less than 3 are considered to be minor, errors with a score from 3 to 7 inclusive are classified as moderate, and errors with a score greater than 7 are severe) {Avery, 2012 #188}.	

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3. SCOPING REVIEW ON EFFECTIVENESS AND COST-EFFECTIVENESS OF INTERVENTIONS

3.1. METHODS

Data sources and searches

In order to scope the literature on the effectiveness and cost effectiveness of interventions to address sub-optimal use of medicines, bibliographic search strategies were designed to provide an overview of the literature and identify any evidence gaps. Given that the studies of interest were systematic reviews or economics evaluations, the databases searched were the NHS Economic Evaluation Database (NHS EED), the Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE). The base search strategy was constructed using The Cochrane Library and then adapted to the other resources searched. Searches were conducted in February 2013, and were limited to material published since 2000 and written in English. Appendix 1 details the search strategies.

NHS EED contains economic evaluations of health care interventions and is updated weekly. Included studies are published in the database and prioritised for abstract writing. Structured abstracts are written and independently checked by health economists. DARE contains systematic reviews of the effects of health care interventions and the delivery and organization of health services and is updated weekly; citations identified as potential systematic reviews are assessed for inclusion by two researchers. Reviews need to meet at least four of five criteria (criteria 1-3 are mandatory) to be included: (1) inclusion/exclusion criteria reported; (2) adequate search; (3) included studies were synthesized; (4) quality of the studies was assessed; (5) there are sufficient details about the included studies. Reviews are then published in the database and prioritised for abstract writing. Structured abstracts are written by researchers and checked by a technical editor. DARE includes records of all Cochrane reviews and protocols, as well as published papers associated with Cochrane reviews.

Selection criteria

The effectiveness review included systematic reviews of interventions to address one or more aspects of suboptimal use of medicines. Given that a small number of systematic reviews of economic evaluations was anticipated, this review included both primary research and systematic reviews. Studies in English set in any country were included. Only full economic evaluations were included in the economic review, i.e. studies comparing two or more interventions in terms of costs and effects. Interventions to improve clinical management in the whole disease pathway were excluded. One reviewer screened the titles for inclusion and the other confirmed inclusion with the abstracts.

Data Extraction and synthesis

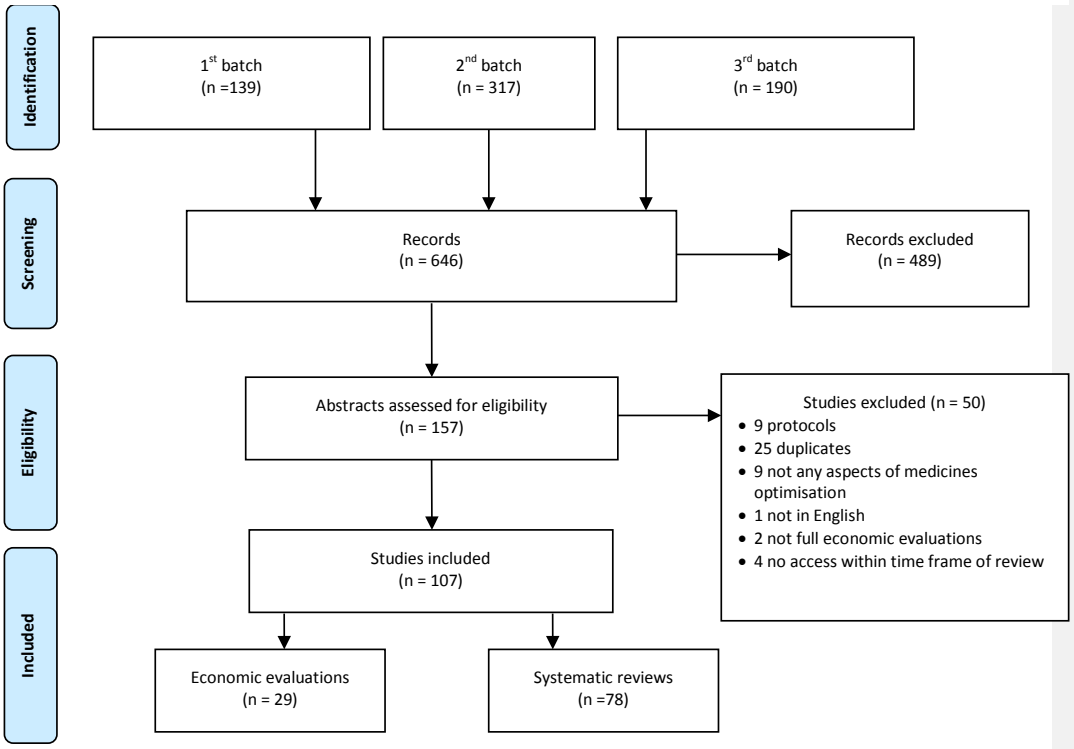
Data were typically extracted from the NHS EED or DARE structured abstracts using a standardised form. Full-text papers were consulted where the structured abstract was not available or if the abstract did not contain the information required. Data extraction included: objective, aspect(s) of suboptimal use of medicines that interventions addressed, type of intervention, target of the intervention, and outcomes. For cost-effectiveness

studies, the type of analysis (within trial or model based), the setting and the source of effectiveness data were extracted. For systematic reviews, the search period, the inclusion/exclusion criteria, type of studies included, quality assessment and data synthesis were also extracted. Data are presented in tables and figures. A narrative synthesis was undertaken.

3.2. RESULTS

Figure 2 presents the flowchart of the study selection process. A full list of publications that did not meet all of the inclusion criteria, along with the reasons for their exclusion, is available on request. Briefly, 646 records were found, of which 157 abstracts were assessed for eligibility. In total, 107 studies were included in the review (29 economic evaluations and 78 systematic reviews).

Figure 2 Flow diagram for the review of systematic reviews and economic evaluations on interventions to improve the suboptimal use of medicines (adapted from Moher et al, 2009)



Systematic reviews

All systematic reviews meeting our inclusion criteria reviewed studies on the effectiveness of interventions; none included economic evaluations. Table 2 summarises the disease areas and the type of studies included by aspect of suboptimal medicines use. With the exception of insufficient generic prescribing, every one of the aspects of suboptimal medicines use was addressed by the systematic reviews. The majority of the studies (51, 65%) focussed on interventions to improve adherence, either in any disease area (21; 27%) [43-63] or in specific conditions (30, 38%) [46, 64-92].

Nine reviews addressed more than one aspect of suboptimal use of medicines:

- poor compliance with prescribing guidance and suboptimal medicines use in care homes [93-94]
- inappropriate prescribing and adherence [44]
- poor compliance with guidelines and inappropriate prescribing [95-96]
- prescription and dispensing errors [97]
- inappropriate prescribing and medicines reconciliation and discharge [98]
- prescription, dispensing and administration errors, and medicines reconciliation [99]
- ~~and~~ inappropriate prescribing and dispensing errors [100].

Randomised controlled trials (RCTs) were available for all aspects. The number of RCTs varied from one to 81 (median=10). Approximately half of the systematic reviews included non-randomised and observational study designs (43, 55%) [9, 43-46, 48-49, 51, 56, 58, 60-62, 69, 74, 79-80, 82, 85-87, 92, 95-99, 101-116].

Table 3 indicates the country where the studies included in the systematic reviews were based. Although 33 (42%) reviews did not specify the country of origin for every study, there appears to be considerable evidence on the different aspects of suboptimal medicines use specific to the UK setting.

Table 2 Disease area and type of studies included by aspect of suboptimal medicines use (references in superscript numbers)

Aspect of suboptimal medicines use	N (%)	Disease area		Types of studies included							
		All	Specific conditions	RCT	Controlled non-randomised	Before & After	Time series	Cohort	Quasi-experimental	Observational	Other non-RCT or various study designs
Lack of compliance with guidelines	6 8%	93-96, 117	URTI [104]	93-96, 104	104, 117	104, 117				117	95-96
Insufficient generic prescribing	0										
Inappropriate prescribing (inc. antibiotics)	9 (12%)	44, 95-96, 98, 100, 111, 116, 118	Antibiotics [102]	44, 95-96, 98, 100, 102, 111, 116, 118	98	98, 102, 111, 116	102	44, 98, 116	98, 102		44, 95-96
Prescription errors	10 (13%)	96-97, 99, 101, 107, 109-110, 112, 114-115		96-97, 99, 101, 109-110	97, 109-110, 115	101, 115	101, 110, 115	101, 112, 114	99	109, 112	96, 99, 101, 107, 110, 114
Medicines reconciliation and discharge	3 (4%)	98-99, 103		98-99, 103	98	98	103	98	98-99		99
Dispensing errors	3 (4%)	97, 99-100		97, 100	97, 99				99		99
Administration errors	3 (4%)	97, 99, 113		97	97, 99, 113	113			99	113	99
Medicines management in care homes	4 (5%)	93-94, 106, 119		93-94, 106, 119					106	106	
Adherence	51 (65%)	43-63	Epilepsy [64] Depression [65-67] HIV [68-71] Cardiovascular [46, 72-79] Transplantation [80] Schizophrenia	4, 43-61, 64-85, 87-92, 120	49, 61, 68, 74, 82, 85, 87, 92	92		44, 46, 58	45, 48, 80	43, 49, 60	46, 48, 51, 56, 58, 62, 69, 74, 79, 82, 86, 121

			81-86 Osteoporosis [87] Diabetes [88] Tuberculosis [89] Asthma [90-91] Bipolar disease [92]									
Monitoring	3 (4%)	98, 100, 108		98, 100, 108	98	98, 108		98	98			
Other (any pharmacist intervention to improve patient care [105], any intervention to reduce medication adverse events [9]	2 (3%)			9, 105		9	9				105	

Table 3 Setting of primary studies included in the systematic reviews by aspect of suboptimal use of medicines (references in superscript numbers)

Aspect of suboptimal medicines use	N (%)	Countries					
		UK	Europe non-UK	US & Canada	Australia and New Zealand	Others	Not reported
Poor compliance with guidelines	6 8%	94	94, 96, 113	93-94, 96	94		95, 104
Insufficient generic prescribing	0						
Inappropriate prescribing (inc. antibiotics)	9 (12%)	44, 121	44, 96, 111	44, 96, 111, 116, 118	111	116	95, 98, 100, 102
Prescription errors	10 (13%)	99, 101	96, 99, 101	96, 99, 101, 109-110, 112	99, 101, 109	101, 112	97, 107, 114-115
Medicines reconciliation and discharge	3 (4%)	99	99	99	99		98, 103
Dispensing errors	3 (4%)	99	99	99	99		97, 100
Administration errors	3 (4%)	99	99, 113	99	99		97
Medicines management in care homes	4 (5%)	94, 119	94, 106, 119	93-94, 106, 119	94, 106, 119		
Adherence	51 (65%)	44, 46, 49, 64, 72-73, 78, 83, 85, 87-88, 90-91, 118	44, 46, 49, 55, 65, 72-73, 77-78, 85, 87, 89-91	44, 46, 49, 55, 60, 63-65, 72, 73 , 77-78, 85, 87-91, 118	49, 63, 65, 78	46, 65, 70, 72-73, 77-78, 85, 87-88, 90	43, 45-48, 50-54, 56-59, 61-62, 66-69, 71, 74-76, 79-82, 84, 86, 92, 95, 107
Monitoring	3 (4%)						95, 98, 108
Other	2 (3%)	9	9	9, 105	9		

Figure 3 shows the type of interventions included in the systematic reviews. Most (44, 56%) interventions are educational or involve software support (22, 28%). The term 'other' includes activity programmes [94], changes in work schedules [99], health coaching [60] and telemonitoring [61].

Figure 3 Types of interventions included in the systematic reviews

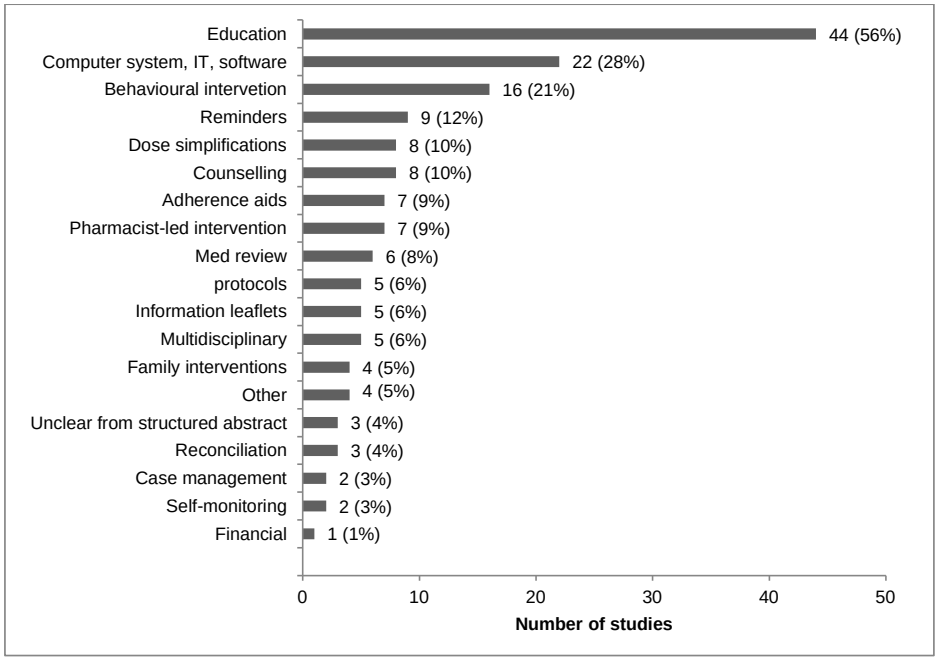


Table 4 summarises the type of measures reported in the systematic reviews. Most studies report measures of adherence (53, 68%) [43-46, 48-54, 56-92, 95, 98, 103, 105], followed by clinical outcomes (24, 31%) [9, 43, 45, 47, 52-53, 55, 59-60, 63, 65, 70, 74, 77-78, 88, 91-92, 94, 96, 102, 105-107] and adverse drug events (16, 21%) [9, 95-96, 98-99, 101-102, 105-107, 109-112, 114-115]. No study reports quality-adjusted life years but four (5%) report measures of quality of life [59-60, 63, 105]. Clinical outcomes are reported in 17 (22%) systematic reviews of interventions to improve adherence [43, 45, 47, 52-53, 55, 59-60, 63, 65, 70, 74, 77-78, 88, 91-92].

Table 4 Types of outcome measures (references in superscript numbers)

Types of outcome measures	Number (%)	References
Mortality	9 (12%)	9, 94, 98, 100, 105-106, 112, 114, 118#
Healthcare resource use or costs	14(18%)	9, 46, 60, 62-63, 82, 91, 94, 98, 105, #47, 109-110, 118
Quality of life	4 (5%)	59-60, 63, 105
Adverse drug events	16 (21%)	9, 95-96, 98-99, 101-102, 105-107, 109-112, 114-115
Medication errors	15 (19%)	62, 96-97, 99-101, 105-106, 109-112, 114, 116, 119
Measure of adherence	53 (68%)	43-46, 48-54, 56-92, 95, 98, 103, 105
Clinical outcome	24 (31%)	9, 43, 45, 47, 52-53, 55, 59-60, 63, 65, 70, 74, 77-78, 88, 91-92, 94, 96, 102, 105-107
Patient satisfaction	4 (5%)	62, 65, 98, 105
Patient's knowledge	3 (5%)	47, 65, 105
Discrepancies in medication records	3 (4%)	103, 106, 113

Measure of appropriate medication	9 (12%)	93-94, 100, 104-106, 111, 113, 118
Days lost from work	1 (1%)	91
Laboratory monitoring	1 (1%)	108

Economic evaluations

Table 6 (next page) presents the aspects of suboptimal medicine use addressed in the included economic evaluation studies. The majority of the studies (16, 55%) examined interventions to improve adherence [1, 122-135], followed by prescription errors (8, 28%) [5, 24, 126, 136-140] and inappropriate prescribing (4, 14%) [120-121, 130, 138].

Six studies (21%) addressed more than one aspect of suboptimal use of medicines:

- Compliance with guidelines and adherence [125]
- Prescription errors and adherence [126]
- Prescription and dispensing errors [137]
- Prescription, dispensing and administration errors [136]
- Inappropriate prescribing and adherence [130]
- Inappropriate prescribing and prescription errors [138].

More than half of the studies (17, 59%) examined interventions targeted at a specific disease area, such as cardiovascular disease (7, 24%) [125, 141], HIV (3,10 %) [131, 133, 142], antibiotics (2, 7%) [120-121], cancer [138], paediatric use of injectable medication [136], anaesthesia [4], psychoactive medication [143], eradication of Helicobacter pylori [122] and anticoagulant monitoring [144]. Various types of interventions were evaluated: pharmacist-led interventions (17, 59%) [1, 122-130 53-54, 57 24 60 143 144], support tools or devices (5, 17%)[122 136-138 62], software support (4, 14%) [136-137, 139 141], nurse-led support (4, 14%) [131-132, 142 136], multidisciplinary medicines management (2, 7%)[135 120], financial incentives (2, 7%) [133-134], dose simplifications [135] and quality improvement initiatives[5]. Three studies (10%) compared different types of interventions [135-137] and in another the intervention consisted of pharmacist-led counselling in association with leaflets and compliance diary charts [122].

Table 7 summarises the type of analysis and the sources of effectiveness data. Most studies (19, 66%) conducted a within-trial economic evaluation using data from a single randomised controlled trial (RCT) [122, 124-125, 129, 132-133, 141, 143] or a non-randomised study, such as before and after studies [4-5, 121, 123, 127, 144] or cohort [1, 120, 130, 138, 140]. Eleven studies (38%) used a model, either based on a single study [24, 128], a review of the literature [126 134, 135 , 142 139, 142 131] or from expert elicitation [137]. De Giorgi *et al.* estimated cost-effectiveness using effectiveness estimates derived by a consensus panel [136].

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Table 5 Methods used in the economic evaluation studies included in the review (references in superscript numbers)

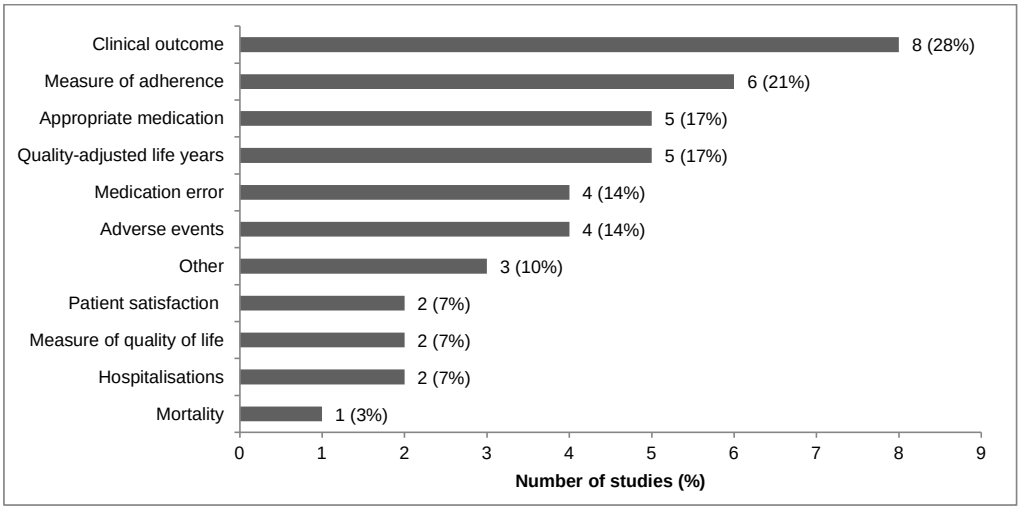
Source of effectiveness data	N (%)	Single RCT	Single study (non-RCT)	Review of the literature	Other
Type of analysis					
Simple extrapolation	1 (3%)				136
Within-trial	19 (62%)	122, 124-125, 129, 132-133, 141, 143	1, 4-5, 120-121, 123, 127, 130, 138, 140, 144		
Model based – Decision tree	4 (14%)	24, 128		126	137
Model based – Markov cohort	2 (7%)			134, 135	
Model based- other	3 (14%)			139, 142 131	
Total (%)	29 (100%)	10 (34%)	11 (38%)	6 (21%)	2 (7%)

Table 6 Aspect of suboptimal use of medicines and interventions in cost-effectiveness studies (references in superscript numbers)

Aspect of suboptimal medicines use	N (%)	Disease area		Software	Pharmacist-led intervention	Nurse-led support	Multidisciplinary medicines management	Financial incentives	Tools or devices	Dose simplifications	Quality improvement initiative
		All	Specific conditions								
Lack of compliance with guidelines	2 (7%)		Cardiovascular [125, 141]	[141]	[125]						
Insufficient generic prescribing	0										
Inappropriate prescribing (inc. antibiotics)	4 (14%)	[130]	Antibiotic prescribing [120-121] Cancer [138]		[121,-130]		[120]		[138]		
Prescription errors	8 (28%)	[5, 24, 126, 137, 139-140]	Injectables in paediatrics [136] Cancer [138]	[136-137,-139]	[24,-126,-136-137,-140]	[136]			[136-138]		[5]
Medicines reconciliation and discharge	0										
Dispensing errors	2 (7%)	[137]	Injectables in paediatrics [136]	[136-137]	[136-137]	[136]			[136-137]		
Administration errors	2 (7%)		Injectables in paediatrics [136] Analgesia [4]	[136]	[136]	[136]			[4, 136]		
Medicines management in care homes	1 (3%)		Psychoactive medication [143]		[143]						
Adherence	16 (55%)	[123-124, 126-128, 130]	Erradication of H.pilory [122] HIV [131,-133,-142] Cardiovascular [1, 125,-129,-132,-134-135]		[1,-122-130]	[131-132,-142]	[135]	[133-134]	[122]	[135]	
Monitoring	1 (3%)		Anticoagulant monitoring [144]		[144]						
Total (%)	-	12 (41%)	17 (59%)	4 (14%)	17 (59%)	4 (14%)	2 (7%)	2 (7%)	5 (17%)	1 (3%	1 (3%)

Figure 3 presents the effectiveness measures used in the economic evaluation studies. Clinical outcome measures were the most frequently used (8, 28%), namely blood pressure [1, 125, 132], cholesterol levels [141], proportion of treatment success [120, 122], and rate of thrombotic or haemorrhagic events [130, 144]. Measures of adherence were used in six studies (21%) [127-130, 132-133]. Measures of appropriateness of the medication were used in five studies (17%), such as proportion of patients on first line anti-hypertensive [125], point reduction in the critically index [136], proportion of patients on inappropriate psychoactive medication [143], and proportion of patients on the appropriate drug [120-121]. ~~Quality-adjusted life years (~~QALYs~~)~~ are used in five studies (17%) [131, 134-135, 137, 142].

Figure 4 Types of effectiveness measures used in the economic evaluation studies



Other types of outcome refer to patient's willingness to pay for the service [1], drug preparation time, safety and usability scores [4] and proportion of patients with allergy status documented [5].

4. DISCUSSION

There is a large body of evidence on the effectiveness of interventions to improve adherence to medication; however, most are specific to a particular disease area. Interventions to improve the different aspects of suboptimal prescribing form the second largest body of literature, particularly those aimed at reducing prescription errors and inappropriate prescribing. Interventions to address other aspects of suboptimal use of medicines have been evaluated to a lesser extent. The literature on cost-effectiveness is much smaller than on effectiveness. Nonetheless, a similar picture emerges: interventions to improve adherence are the focus of the majority of cost-effectiveness studies, particularly in specific clinical areas such as cardiovascular disease, followed by interventions to improve prescribing. Only one study evaluated interventions to address suboptimal use of medicines across the full medicines pathway.

In general, research has focused on the areas where the issues are more prevalent or the burden most evident. Non-adherence appears to be a key aspect of suboptimal use of medicines and largely dominates the topics examined by systematic reviews and cost-effectiveness studies. No evidence was found on interventions to improve generic prescribing, but this topic may have limited relevance to the UK as generic prescribing rates are generally high compared with other countries.

The results indicate that interventions to improve suboptimal use of medicines tend to be specific to a particular aspect of the pathway and/or to a particular disease area. This fragmentation has two main consequences. Firstly, interventions may not be generalisable to other disease areas or in patients with co-morbidities and using multiple medications. Secondly, it is difficult to draw conclusions on which aspect of suboptimal use of medicines should be prioritised for investment. However, examining an intervention across the full medicines pathway may be unfeasible in controlled studies. Another issue is related to the outcome measures used in the literature. Since most of the studies used intermediate outcome measures, such as adherence or error rates, it remains unclear whether interventions have an impact on final health outcomes. However, using outcomes such as mortality or QALYs in primary research may require large sample sizes to detect any effect.

This review has provided an indication of the scale, costs and health lost as a result of suboptimal use of medicines in the NHS. It has also scoped the evidence on effectiveness and cost-effectiveness of interventions to address this problem. The scoping review was systematic, in terms of the searches, data extraction and presentation of results. Only systematic reviews were included in the review of effectiveness for pragmatic reasons; a review of the primary literature would have been impractical within the time available. The same motive guided the decision to use NHS EED and DARE abstracts as the main source of data.

Despite the limitations of this review, there are some implications for research given the gaps identified in the evidence. First, more research is needed on the effects of interventions to improve suboptimal use of medicines in terms of final outcomes such as costs and quality adjusted survival. Second, interventions should be investigated for their generalisability across different patient populations and contexts. Third, research should consider the full medicines pathway and establish which aspect of suboptimal medicines use fits in the wider optimisation context. Decision analytic modelling has the potential to address implications 1 and 3. A decision analytic model could link the different intermediate outcomes to the end outcomes of interest. Most importantly, a decision model has the potential to map the full medicines pathway and indicate which aspects are driving the costs and health lost and which aspects offer 'easy-win' opportunities for optimisation. Such a model would not be a small undertaking but could offer important benefits. Not only can modelling inform decisions with direct positive effects on health and costs, but also indicate where primary research should focus.

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6. APPENDICES

6.1. APPENDIX 1 FULL SEARCH STRATEGIES:

Cochrane Database of Systematic Reviews (The Cochrane Library – http://www.thecochranelibrary.com/)
Issue 1 of 12 Jan 2013
Searched on 22/02/2013
Retrieved 63 hits

Key:
MeSH descriptor = indexing term (MeSH heading)
* = truncation
" " = phrase search
:ti,ab = terms in either title or abstract fields
near/1 = terms within one word of each other (any order)
near/2 = terms within two words of each other (any order)
next = terms are next to each other

Search Strategy:
ID Search
#1 MeSH descriptor: [Medication Reconciliation] this term only
#2 (Medication* near/3 (concordance or compliance or comply or adherence or adhere or optimal or optimisation)):ti,ab
#3 (Medicine* near/3 (concordance or compliance or comply or adherence or adhere or optimal or optimisation)):ti,ab
#4 (drug* near/3 (concordance or compliance or comply or adherence or adhere or optimal or optimisation)):ti,ab
#5 (Prescription* near/3 (concordance or compliance or comply or adherence or adhere or optimal or optimisation)):ti,ab
#6 (prescrib* near/3 (concordance or compliance or comply or adherence or adhere or optimal or optimisation)):ti,ab
#7 MeSH descriptor: [Medication Errors] this term only
#8 MeSH descriptor: [Inappropriate Prescribing] this term only
#9 (Medication* near/3 (nonconcordance or noncompliance or nonadherence or non-concordance or non-compliance or non-adherence or suboptimal or error* or mistake* or mismanage* or misuse or over-use or overuse or inappropriate or irrational or waste or wastage)):ti,ab
#10 (Medicine* near/3 (nonconcordance or noncompliance or nonadherence or non-concordance or non-compliance or non-adherence or suboptimal or error* or mistake* or mismanage* or misuse or over-use or overuse or inappropriate or irrational or waste or wastage)):ti,ab

#11 (drug* near/3 (nonconcordance or noncompliance or nonadherence or non-concordance or non-compliance or non-adherence or suboptimal or error* or mistake* or mismanage* or over-use or overuse or inappropriate or waste or wastage)):ti,ab
#12 (Prescription* near/3 (nonconcordance or noncompliance or nonadherence or non-concordance or non-compliance or non-adherence or suboptimal or error* or mistake* or mismanage* or misuse or over-use or overuse or inappropriate or waste or wastage)):ti,ab
#13 (prescrib* near/3 (nonconcordance or noncompliance or nonadherence or non-concordance or non-compliance or non-adherence or suboptimal or error* or mistake* or mismanage* or misuse or over-use or overuse or inappropriate or waste or wastage)):ti,ab
#14 (underprescrib* or overprescrib* or misprescrib* or under-prescrib* or over-prescrib* or mis-prescrib*):ti,ab
#15 (or #1-#14) from 2000 to 2013, in Cochrane Reviews (Reviews and Protocols)

DARE – Database of Abstracts of Reviews of Effects, and NHS EED - NHS Economic Evaluation Database
(The Cochrane Library – http://www.thecochranelibrary.com/)
Issue 1 of 4 Jan 2013
Searched on 22/02/2013
Retrieved 393 hits

Key:
MeSH descriptor = indexing term (MeSH heading)
* = truncation
" " = phrase search
:ti,ab = terms in either title or abstract fields
near/1 = terms within one word of each other (any order)
near/2 = terms within two words of each other (any order)
next = terms are next to each other

Search Strategy:
#1 MeSH descriptor: [Medication Reconciliation] this term only
#2 (Medication* near/3 (concordance or compliance or comply or adherence or adhere or optimal or optimisation))
#3 (Medicine* near/3 (concordance or compliance or comply or adherence or adhere or optimal or optimisation))
#4 (drug* near/3 (concordance or compliance or comply or adherence or adhere or optimal or optimisation))
#5 (Prescription* near/3 (concordance or compliance or comply or adherence or adhere or optimal or optimisation))
#6 (prescrib* near/3 (concordance or compliance or comply or adherence or adhere or optimal or optimisation))
#7 MeSH descriptor: [Medication Errors] this term only
#8 MeSH descriptor: [Inappropriate Prescribing] this term only
#9 (Medication* near/3 (nonconcordance or noncompliance or nonadherence or non-concordance or non-compliance or non-adherence or suboptimal or error* or mistake* or mismanage* or misuse or over-use or overuse or inappropriate or irrational or waste or wastage))

#10 (Medicine* near/3 (nonconcordance or noncompliance or nonadherence or non-concordance or non-compliance or non-adherence or suboptimal or error* or mistake* or mismanage* or misuse or over-use or overuse or inappropriate or irrational or waste or wastage))
#11 (drug* near/3 (nonconcordance or noncompliance or nonadherence or non-concordance or non-compliance or non-adherence or suboptimal or error* or mistake* or mismanage* or over-use or overuse or inappropriate or waste or wastage)):ti,ab
#12 (Prescription* near/3 (nonconcordance or noncompliance or nonadherence or non-concordance or non-compliance or non-adherence or suboptimal or error* or mistake* or mismanage* or misuse or over-use or overuse or inappropriate or waste or wastage))
#13 (prescrib* near/3 (nonconcordance or noncompliance or nonadherence or non-concordance or non-compliance or non-adherence or suboptimal or error* or mistake* or mismanage* or misuse or over-use or overuse or inappropriate or waste or wastage)):ti,ab
#14 (underprescrib* or overprescrib* or misprescrib* or under-prescrib* or over-prescrib* or mis-prescrib*)
#15 (or #1-#14) from 2000 to 2013, in Other Reviews and Economic Evaluations

DARE – Database of Abstracts of Reviews of Effects, and NHS EED - NHS Economic Evaluation Database
(CRD website – http://www.crd.york.ac.uk/crdweb/)
Searched on 26/02/2013
Retrieved 187 hits

Key:
* = truncation
Each line was limited to “all fields”

Search strategy:
1 (Medication* OR Medicine OR drug* OR prescription OR prescrib*) IN DARE, NHSEED WHERE PD FROM 17/12/2012 TO 28/02/2013 1005
2 (concordance or compliance or comply or adherence or adhere or optimal or optimisation) IN DARE, NHSEED WHERE PD FROM 17/12/2012 TO 28/02/2013 93
3 (nonconcordance or noncompliance or nonadherence or non-concordance or non-compliance) IN DARE, NHSEED WHERE PD FROM 17/12/2012 TO 28/02/2013 2
4 (nonconcordance or noncompliance or nonadherence) IN DARE, NHSEED WHERE PD FROM 17/12/2012 TO 28/02/2013 1
5 (non-adherence) IN DARE, NHSEED WHERE PD FROM 17/12/2012 TO 28/02/2013 2
6 (suboptimal or error* or mistake* or mismanage*) IN DARE, NHSEED WHERE PD FROM 17/12/2012 TO 28/02/2013 213
7 (over-use) IN DARE, NHSEED WHERE PD FROM 17/12/2012 TO 28/02/2013 0
8 (overuse*) IN DARE, NHSEED WHERE PD FROM 17/12/2012 TO 28/02/2013 0
9 (overuse or inappropriate or irrational or waste or wastage) IN DARE, NHSEED WHERE PD FROM 17/12/2012 TO 28/02/2013 7
10 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 277
11 (underprescrib* or overprescrib* or misprescrib* or under-prescrib* or over-prescrib* or mis-prescrib*) IN DARE, NHSEED WHERE PD FROM 17/12/2012 TO 28/02/2013 0

12 (underprescrib* or overprescrib* or misprescrib*) IN DARE, NHSEED WHERE PD FROM 17/12/2012 TO 28/02/2013 0

13 (under-prescrib* or over-prescrib* or mis-prescrib*) IN DARE, NHSEED WHERE PD FROM 17/12/2012 TO 28/02/2013 0

14 MeSH DESCRIPTOR medication errors EXPLODE ALL TREES IN DARE,NHSEED 37

15 #1 AND #10 150

16 #14 OR #15 187