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[Intervention Review]

Pharmaceutical policies: effects of restrictions on reimbursement

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ABSTRACT

Background

Public policy makers and benefit plan managers need to restrain rising pharmaceutical drug costs while preserving access and optimizing health benefits.

Objectives

To determine the effects of a pharmaceutical policy restricting the reimbursement of selected medications on drug use, health care utilization, health outcomes and costs (expenditures).

Search methods

We searched the 14 major bibliographic databases and websites (to January 2009).

Selection criteria

Included were studies of pharmaceutical policies that restrict coverage and reimbursement of selected drugs or drug classes, often using additional patient specific information related to health status or need. We included randomised controlled trials, non-randomised controlled trials, interrupted time series (ITS) analyses, repeated measures studies and controlled before-after studies set in large care systems or jurisdictions.

Data collection and analysis

Two authors independently extracted data and assessed study limitations. Quantitative re-analysis of time series data was undertaken for studies with sufficient data.

Main results

We included 29 ITS analyses (12 were controlled) investigating policies targeting 11 drug classes for restriction. Participants were most often senior citizens or low income adult populations, or both, in publically subsidized or administered pharmaceutical benefit plans. Impact of policies varied by drug class and whether restrictions were implemented or relaxed. When policies targeted gastric-acid suppressant and non-steroidal anti-inflammatory drug classes, decreased drug use and substantial savings on drugs occurred immediately and for up to two years afterwards, with no increase in the use of other health services (6 studies). Targeting second generation antipsychotic drugs increased treatment discontinuity and the use of other health services without reducing overall drug expenditures (2 studies). Relaxing restrictions for reimbursement of antihypertensives and statins increased appropriate use and decreased overall drug expenditures. Two studies which measured health outcomes directly were inconclusive.

Authors' conclusions

Implementing restrictions to coverage and reimbursement of selected medications can decrease third-party drug spending without increasing the use of other health services (6 studies). Relaxing reimbursement rules for drugs used for secondary prevention can also remove barriers to access. Policy design, however, needs to be based on research quantifying the harm and benefit profiles of target and alternative drugs to avoid unwanted health system and health effects. Health impact evaluation should be conducted where drugs are not interchangeable. Impacts on health equity, relating to the fair and just distribution of health benefits in society (sustainable access to publically financed drug benefits for seniors and low income populations, for example), also require explicit measurement.

PLAIN LANGUAGE SUMMARY

Policies that restrict reimbursement on some drugs to ensure better use in health care

Large amounts of healthcare money is spent on medications, and these amounts are increasing. Spending more on medications could mean less money for hospitals, doctors and even other public services such as education or infrastructure. Misuse, overuse or underuse of medications may also result in poor health outcomes and a waste of money. Publically funded drug benefit plans look for ways to ensure better use of medications and to control costs without limiting health benefits. Policies that restrict reimbursement of specific prescription drugs -- often called 'prior' or 'special authorization' policies -- are one type of policy that may be used. Physicians generally apply on behalf of the patient and supply information verifying the patient's need before authorization is granted. These policies provide a safety valve when restrictions are applied by allowing for reimbursement when there is a need for the specific drug. If authorization is not obtained, an alternative and often cheaper drug with the same or similar benefit is reimbursed, or a patient may have the means to pay out-of-pocket expenses. Medications targeted for reduction in use are often newer, expensive drugs with cheaper, effective alternatives.

This review found 29 studies that evaluated policies that restrict reimbursement of specific prescriptions drugs. Where drugs have cheaper, effective alternatives and they target symptoms, this review found that reimbursement restriction polices can ensure better use of the medications with reduced costs and without an increase in the use of other health services, as would be expected if there were negative health effects of the restriction policies. Evaluation is required if alternative drugs are not effective substitutes. Removing restrictions for drugs that prevent complications of disease can result in an intended increase in their use as well as cost savings. When restrictions to reimbursement policies are designed using the best available evidence on the health impact of the medications, they support equitable access to the drugs that best support health by supporting the sustainability of publically subsidized drug plans.

A summary of this review for policy-makers is available here

Summary of findings for the main comparison. Outcome: drug use - CITS and ITS studies

Study ID* (CITS)	Outcome / drug or drug class	Immediate after transition period (95% CI)	Immediate after transition period (95% CI)	Short Term (6 mo, 1 yr) (95% CI)	Long Term (12mo, 24 mo) (95% CI)
		Absolute change in level	Relative change in level	Relative change in level	Relative change in level
Delate 2005	Per patient per month **PPI** and **H2RA** drug claims	-0.02 PPI 0.01 H2RA	- 92% PPI 98% H2RA		
Fischer 2007 / CITS	Proportion of renin- angiotensln -aldosterone system (RAAS)-blocking defined daily doses (DDDs) accounted for by **ARBs**		Any PA policy - 0.4% (NS) Slope effect 0.0% (NS) States requiring ace inhibitor trial first -1.6% (p=0.026) * one time decrease		States requiring ace inhibitor trial first -1.3 % per quarter to 18 months (p<0.001)
Fischer 2004 / CITS	Proportion of nonsteroidal anti inflammatory drugs (NSAID) DDDs accounted for by COX-**2 Inhibitors**			- 11.1% (-5.7%, -16.5%) 6 mo post relative to 6 mo pre	-1.6% (0.0%,3.1%) per quarter to 18 months (p=0.03)
Hartung 2004 /CITS	Days' supply per person-year **celecoxib**	- 0.54 (from 1.07 to 0.53)	- 58.9% (-50.0%, -67.9%)	decrease slope (P < 0.001).	
Hartung 2006	Market share in aggregate of prefered drugs in the **PPIs, NSAIDS, long-acting opioids and statin drug classes**			"Dispense as Written" period 8-9 months +28 "Soft PA period " - education 5 months	

				+42.9 Voluntary 9 months -17.4	
Keith 1994	Mean number of dosage units **H2RA**s dispensed per month			11 months - 35% (from 69,212 to 44,751 units /mo) 0.7% slope	
	Percentage of patients taking **other drugs** known to produce significant drug interactions			- 7.5 % (from 14 to 6.5%)	
Kephart 2005 /CITS	Monthly use of **wet nebulization therapy**		decrease p<0.001	slower decline p<0.001	24 months Dec 99 to 01 Decline from 100% to 36% in heavy users Decline from 67% to 20% in all users
Law 2008 / CITS	Market share level of nonpreferred **2nd generation antipsychotics**		West Virginia: - 3.5% (-5.7%, -1.3% p=0.003) Texas: -2.6% (0% , -5.2% p=0.55)	West Virginia: -1.3% (–1.8%, –.8%, p<.001) per quarter Texas: decrease in trend NS	24 months -13.8% (-9.4%, -18.2% p<0.001)
MacCara 2001	**Fluoroquinolone** claims			- 80.2%	
Marshall 2002	Mean no. defined daily doses (DDD) of all **PPI**s per 100,000 seniors per month	-22,959 (from 84,531 to 62,708)	-15.6% (during 6 mo transition following announcement)	-26% first year	13 to 41 months 9% over baseline
Marshall 2006	**Fluoroquinolone** prescriptions per week				To 15 months post policy absolute decrease of 1905 (p<0.0001)

Schneeweiss 2004	Use of **respiratory drug**s during two months follow up			At 6 months nebulised drugs - 7% p < 0.001 nebulised in combination with inhaled drugs - 25% (p < 0.001)	
Schneeweiss 2006	Monthly dispensed daily doses per 10,000 residents restricted and reimbursed **PPIs**			8 months post implementation Total PPI utilization No level change (p=0.82) - 383 slope (p-0.08) Restricted PPI - 14,850 (±1100) Reimbursed PPI rabeprazole 19,300 (± 2200) (p < .0001) with 45% switching rate	
Smalley 1995 /CITS REPORTED			- 26% (-21, -31%)		2 year period compared with baseline -19% (-13, -25)
Smalley 1995 /CITS REANALYSIS**	Days of **NSAID** use per Person-Year	-4.35	- 23%	6 months - 21% (-23%, -19%)**	At 23 months - 21% (-22, 19%)**
Soumerai 2008 /CITS	**Atypical antipsychotic** use			10 month No significant difference	
	Relaxation of restrictions to reimbursement				
Bjerrum 2001	Incidence prevalence rates of **lipid lowering drug** per 100,000 per month	14		1st year 0.4% increase prevalence	
Fretheim 2007	Proportion of **thiazide** prescriptions among all prescriptions for patients started on treatment for uncomplicated hypertension			16.5% (9.9%, 24.8%)	

			- 0.05% slope change (NS) per month (0.65% to 0.35%).		
Jackevicious 2008	Monthly rate of **clopidogrel** use within 30 days of hospital discharge following MI recieving stents	53%			
Sakshaug 2007	1 yr prevalence of **statin** use		At 1 yr 6.8% increase women 8.1% increase men		
van Driel 2008	Monthly reimbursed DDD for total **H2A**s and **PPI**s			from 1997 to 2005 222%	

* Analyses from included studies that provided comparable data on immediate, short term and long term impact are provided in this table. Some analyses, such as studies combining and comparing data over many jurisdictions, are reported narratively to aid appropriate interpretation; ** Reanalyses conducted by reviewers based on time series data provided by original study

Summary of findings 2. Outcome: drug expenditures - CITS and ITS studies

Study ID* (CITS)	Outcome / drug or drug class	Immediate after transition period (95% CI)	Immediate after transition period (95% CI)	Short Term (6 mo, 1 yr) (95% CI)	Long Term (12mo, 24 mo) (95% CI)	Long Term (>24 Months)
		Absolute change in level	**Relative change in level**	**Relative change in level**	**Relative change in level**	**Relative change in level**
Bursey 2000	PPI restriction Expenditures to treat upper gastrointestinal disorders in 6 mo intervals	$153	-19.6%	At 6 months - 85% (-92.6%, -77.9%) At 12-months - 84% (-89.7%, -79.3%)	At 24 mo - 79% (-82.8%, -75.2%)	

Delate 2005 / ITS	PPIs Per member per month		PPIs decreased 90.9% H2RAs Increased 223.2%	PPI decreased from $44.1 million to $13.5 million H2A drug expenditures increased from $6.0 million to $13.5 million	Absolute decrease from $3.44/PMPM to $1.74/PMPM Net expenditure decrease of $23.4 million	
Fischer 2007 / CITS	Angiotensin receptor blockers (ARBS)	For PDL: 0.4% p=0.049 For ACE trial: -1.0% p=0.003	ACE trial: -0.7 p<0.001 Slope Effect PDL: 0.3% p<0.001			
Fischer 2004 / CITS	COX-2 Inhibitors	- $10.28 ($7.56, $13.00) p<0.001	18%			
Grootendorst 2005 /ITS	NSAIDS, analgesic drugs				Cummulative effect per year: Type 1 RP: -$1,035,340 (95% CI -$1,505,318, -565,362 p<0.001) Type 2 RP: -$4,007,322 (-$4,378,332, -$3,36, 312 p<0.001)	Over all months: Type 1 RP: -$7,506,21 (95% CI -10,900,00, -$4,098,872) Type 2 RP (95% CI -$22,700,000 (95% CI -$24,800,000, -$20,600,000 p<0.001)
Hartung 2004 /CITS	COX-2 Inhibitors				Savings attributable to the PA policy were projected to be approximately $10,402 (linear model) and $4999 (logarithmic model) per month.	Mean projected savings attributed to the PA policy was $2.87/Person Year (PY) (linear) $1.40/PY (logarithmic) .
Hartung 2006/ ITS	PPIs, long acting opioids, NSAIDS, statins	Aggregate: DAW Exception: -$0.18 (-$0.08, -$0.02 p<0.05) Soft PA: $0.28 ($0.11, $0.44 p<0.05)	Aggregate: DAW Exception: -9.1% (95 % CI -13.8%, -4.3% p<0.05) Soft PA: -17.7% (95% CI -25.4%, -10.0% p<0.05)			Estimated savings during entire period: DAW policy: $1,727,392 (95% CI $976,102, $2,478,682) Soft PA policy: $2,223,300 (95% CI $1,816,027, $2,854,353)

		Voluntary -$0.10 (-$0.26, $0.06)	Voluntary 5.5% (95% CI--1.1%, 12.1%)			
Keith 1994 / ITS	H2RAs				Adjusted net savings of: $275,920.	
Law 2008/ CITS	2nd generation antipsychotics	No significant change				Costs rose 7.95 to $9.84 over study period, Texas: $9.19 to $10.49
MacCara 2001 /ITS	Fluoroquinolone				$605,890. (23.7%) decrease	
Marshall 2006 /ITS	Fluoroquinolones		Fluoroquinolones: $105,707 less per week, p<0.001)			
Motheral 2004	NSAIDS, PPIs, SSRIs	In all 3 therapy classes, an immediate decrease of $0.93 PMPM costs p<0.01. Savings of 19% of net costs relative to mean monthly preperiod expenditures	In month following step therapy: NSAIDS: decrease of $0.29/PMPM p<0.001 SSRI: no significant change PPIs: decrease of $0.48 net drug cost p<0.05			
Roughead 2006 /CITS	COX-2 Inhibitors					Average cost per NSAID prescription: Unrestricted access: $59.00 Late policy adopting: $46.00 Early policy: $40.00
Schneeweiss 2004 / CITS	Nebulized respiratory drugs	- $24 PMPM (-$19, $29)				
Schneeweiss 2006 /ITS	PPIs			Reduction of $3.2 per senior Estimated savings of $2.9 million		

Smalley 1995 /CITS REPORTED	Non-generic NSAIDS per person per year	- $14.63	- 65% (- 60%, -71%)	Slight upward trend of $0.17 per month ($0.02, $0.32)		- 53% (-48%, -57%)
Smalley 1995 /CITS REANALYSIS		-$13.45**	- 58.5%**	-57.2%** (-59.7%, 54.7%)	- 56.1%** (58.0%, -54.1%)	
Relaxation or exemption from restriction						
Fretheim 2007 /ITS	Antihypertensives				Savings of U.S. $0.72 million, or U.S. $0.16/inhabitant	
van Driel 2008 /ITS	H2As and PPIs					Public expenditure for acid suppressants increased from a total of € 7.5 million in 1997 to €12. million in 2005

*Analyses from included studies that provided comparable data on immediate, short term and long term impact are provided in this table. Some analyses, such as studies combining and comparing data over many jurisdictions, are reported narratively to aid appropriate interpretation; ** Reanalyses conducted by reviewers based on time series data provided by original study

Summary of findings 3. Health services utilization - CITS and ITS studies

Study ID* (CITS)	Outcome / drug or drug class	Immediate after transition period (95% CI)	Immediate after transition period (95% CI)	Short Term (6 mo, 1 yr) (95% CI)	Long Term (12mo, 24 mo) (95% CI)
		Absolute change in level	Relative change in level	Relative change in level	Relative change in level
Delate 2005/ ITS	PPI restriction Expenditure and use of ambulatory services and inpatient care (including long-term care) events and expenditures for the management of GI-related and all health conditions			At 6 mo PA request granted PPI users were more likely to have had at least 1 diagnosis for a GI condition and GI-related screening during baseline (thus were not comparable to groups	

				denied PPI reimbursement --H2RA users and nonusers)	
Farley 2008/ CITS	Atypicial antipsychotic restriction Expenditures (Medicaid payments) for outpatient, inpatient and long term care services				To 14 months post policy implementation Oupatient services: + 18% increase (1.1%, 1.2%) p<0.001 Inpatient services: + 0.96 (0.78 to 1.20) NS Long term care services: + 1.243 (0.95 to 1.62) NS
Hartung 2004/ CITS	Celecoxib restriction Medical services claims: office visits, emergency department (ED) encounters, hospitalizations Medical services claims (as above) for musculoskeletal conditions and GI ulceration	All enrollees Absolute number of GI-related events per month was 'small and sporadic' Secondary analysis 'mean of only 4.3 GI-related events' -too few for analysis	Immediate to 5 months Primary analysis (All claims) Medical claims: +18.0 (2.2, 33.9) NS at predetermined level of 0.01 + slope change, p<0.001 Musculoskeletal-related encounters: NS change in utilization + slope change, p<0.001 GI related encounters: Decline (unspecified) p = 0.003 No other notable changes Secondary analysis		

		(previous NSAID, COX-2 use) ED use: - 7.3% (-20.8%, 6.3%) - slope change (NS) Other medical services use: No significant change	
Hazlet 2002/ CITS	PPI Restriction (Relative ratio of extrapolated trend period 1 versus monthly period 2 observation) Office visits and transactions	Month 0 0.95 (0.91, 0.99) Month 1 0.93 (0.89, 0.97)	Month 5 0.86 (0.81, 0.92) Month 11 0.71 (0.65, 0.79)
	ER visits	Month 0 1.06 (0.87, 1.28) Month 1 1.08 (0.89, 1.30)	Month 5 1.17 (0.88,1.55) Month 11 1.49 (0.97, 2.28)
	Hospital admissions	Month 0 0.85 (0.67, 1.07) Month 1 0.88 (0.70, 1.10)	Month 5 1.03 (0.73, 1.46) Month 11 1.07 (0.6, 1.79)
	Length of stay	Month 0 0.75 (0.50, 1.14) Month 1 0.76 (0.51, 1.13)	Month 5 0.79 (0.44, 1.42) Month 11 0.81 (0.3,1.92)
Keith 1994	H2RA restriction Number of GI studies (n/month)		7 months post implementation

				- 5.7%	
Kephart 2005/ CITS	Wet Nebulization therapy restriction Visits to a fee-for-service general practitioner by month				To 23 months post policy announcement No change overall Wet nebulization group: decrease in general practitioner visits (p< 0.001) relative to controls Heavy wet nebulization cohort: no change
	Rates of hospital admission for a respiratory condition by month				Wet nebulization cohort: decrease in hospital admissions for respiratory conditions relative to controls (p=0.02) Heavy wet nebulization cohort: no change
Schneeweiss 2004	Restriction nebulized respiratory therapy Contacts with doctors per 100 patients per month			Followed to 6 months 2.6 (−5.0 to 10) p = 0.10	
	Admissions to emergency departments per 100 patients per month			0.4 (−0.1 to 0.9) p = 0.10	
	All admissions to hospital per 100 patients per month			0.7 (0.0 to 1.3) p = 0.08	
Schneeweiss 2006/ITS	PPIs restriction Hospitalization for GI hemorrhage per 10,000 residents per month	Immediate Level + 0.15, (-0.17 to 0.47) p=0.35 NS Slope -0.02 (-0.08 to 0.04)			

	Hospitalization for complicated peptic ulcer disease (PUD) per 10,000 residents per month	Immediate Level - 0.64, (-1.54, 0.26), p= 0.16 NS Slope 0.05, (-0.10 to 0.21), (p= 0.48)			
	Physician visits for gastroesophageal reflux (GERD), PUD, or gastritis (per 10,000 residents per month (rate) and spending)	Immediate +2.61, p= 0.59, NS Slope - 0.20 (-1.94 to 1.54) (p= 0.81) NS 3 to 5 months post policy implementation Level + 11, p= 0.01)			
	Spending on physician visits for gastroesophageal reflux (GERD), PUD, or gastritis (per 10,000 residents per month	3 to 5 months post policy implementation Spending +Can $21,000, p= 0.20, NS			
Smalley 1995/ CITS REANALYSIS	NSAIDs PA Expenditures for Outpatient Services per Person-Year ($)	Reanalysis** $9.02	Reanalysis** - 10.6% (SE 5.6)	Reanalysis at 6 months** 12.3% (6.0%, 18.7%) Reanalysis at 12 months 11.7 (6.7%, 16.8%)	From study report at 24 months 3% (-13%, 18%) (NS)

Smalley 1995/ CITS REPORTED	Expenditures for Inpatient Admissions per Person-Year ($)		From study report over 24 months -14% (-8%, 36%)
Smalley 1995/ CITS REPORTED	High dose NSAID users: Expenditures for Outpatient services per Person-Year ($)		From study report over 24 months -2% (-15%, 19%)

* Analyses from included studies that provided comparable data on immediate, short term and long term impact are provided in this table. Some analyses, such as studies combining and comparing data over many jurisdictions, are reported narratively to aid appropriate interpretation; ** Reanalyses conducted by reviewers based on time series data provided by original study

BACKGROUND

Publically subsidized pharmaceutical benefit plans in many countries are challenged to optimize the benefits of prescription drugs in relation to their costs while managing the risks and complexities associated with this rapidly evolving sector. Pharmaceutical expenditures are a large component of health expenditures, accounting for an average of 17% of total health spending in Organization of Economic Cooperation and Development (OECD) countries in 2007 and exceeding 20% of health spending in eight countries (OECD 2009). Policy makers and insurers are under pressure to control drug expenditures, and to do this without causing adverse effects on health or shifting costs to other healthcare services. In many jurisdictions, drug coverage is a prominent political issue that involves complex conflicts between advocates of new and expensive pharmaceuticals, advocates of more expenditure on non-pharmaceutical health services and advocates of healthcare cost containment.

Restriction to reimbursement policies

Pharmaceuticals are patented for particular diagnoses. Likewise, insurance coverage for a drug may be conditional upon the drug plan granting approval based on patient-specific clinical information obtained from the prescriber. Restriction to reimbursement policies are, at most, one component of the interrelated policy framework used to govern and manage public and private drug benefit plans. Where there are restriction to reimbursement policies there are also policies that determine, for example, which drugs are reimbursed, how they are priced, and how patients and physicians are informed. This review is one of 13 reviews that are anticipated as part of the Cochrane pharmaceutical policy review series (Aaserud 2003). This series was initiated to comprehensively review pharmaceutical policy interventions to identify practices that support rational prescribing; that is, prescribing practices that have been rigorously evaluated and found to have benefits that outweigh harms and costs.

Restrictions on reimbursement are defined as the sets of insurance policies that restrict reimbursement for selected drugs or drug classes, often using additional patient specific information related to health status or need. Approval may be automatic (but subject to audit) if a reason is supplied. Included in this category are policies that are labelled as special authorization, special authority, special consideration, prior authorization (PA), prior approval, pre-authorisation, restricted access, exemptions and for limited use.

There is wide variability in policy design. Drugs may be targeted because of differences or interchanged due to their similarities with alternative drugs that are also available to be prescribed. Prescribers are often required to apply for an exemption (obtain authorization prior to reimbursement) at the time of prescribing, including clinical information on disease severity and treatment history. Sometimes existing data in a database can be used, which facilitates computerized automation of PA processes and decreases physician workload. Clinical criteria may require a level of disease severity to be met or failure of treatment on a cheaper, safer alternative drug (step therapy or protocol) as a requirement for reimbursement. Policies may be applied to all new prescriptions or new patients. Sometimes PA is required to relax the rules of the insurance plan around limits to the number of pills dispensed, combinations of drugs or early refills (Thomas 2002).

How the intervention might work

Implementation of restriction to reimbursement policies

Policies that restrict reimbursement reduce pharmaceutical expenditures for third party insurers by providing a disincentive for physicians and their patients to use less effective, more harmful or more costly medications. Applying for exemption (authorization prior to reimbursement) poses a disincentive for the physician by requiring additional time to complete the paperwork. The disincentive for the patient is the requirement to pay out-of-pocket expenses for the targeted medication if coverage is not approved.

Covering restricted drugs in some circumstances provides an alternative to total restriction and acts as a type of 'safety valve'. Targeted medications remain accessible for patients when specified criteria are met, which makes the policy more acceptable to physicians and patients. Further, these policies may be used to restrict access only to patients in whom evidence on a prescription drug's efficacy, safety, and cost effectiveness are proven.

Restriction to reimbursement policies may work where drugs within a class or with the same indication are considered interchangeable. Restriction to reimbursement policies may also stimulate rational drug use in cases where there are differences in efficacy, adverse event rates or cost effectiveness.

There may also be unintended consequences of policies that restrict reimbursement. Appropriate use may decrease for a number of reasons, 1) some physicians charge for applying for exemptions and patients may be unwilling or unable to pay these charges; 2) patients may be unwilling to switch medications and may not renew the new drug prescriptions, or 3) physicians may be unwilling to take the time to apply for an exemption, leaving some patients unable to pay for additional coverage and forgoing the needed therapy. Processing PA requests is associated with administration costs for third party insurers, prescribers and pharmacies. These costs may or may not be offset by the program savings.

Relaxation or exemption from restrictions

A strategy of relaxing or exempting some drugs from PA policies is the reverse of implementation policies. With unrestricted acess to drugs that are clinically effective and cost effective for secondary prevention in the treatment of chronic diseases (such as high blood pressure) it is anticipated that their use will increase. Increased treatment is expected to decrease complications of disease as well as decrease the cost of treating complications (such as renal failure).

Why it is important to do this review

As part of the Cochrane pharmaceutical policy series of 13 reviews, the overall aim of this systematic review is to support informed decisions about pharmaceutical policies and to guide future evaluations by preparing an up-to-date, comprehensive summary of what is known from well-designed research about the effects of policies. There is not an up-to-date and rigorous review of restriction to reimbursement policies though the evidence base has grown rapidly in recent years. A 2007 non-Cochrane systematic review of PA policies documented the limitations of existing studies from an economic perspective (Puig-Junoy 2007). However this review included studies which did not meet the selection criteria of the Cochrane Effective Practice and Organisation of Care (EPOC) Review Group or

apply the same rigorous methods. In an interview study, Carlson et al found that key informants in organizations with PA policies believe that that they have achieved the intended aims of reducing utilization and expenditures, though the programs had not been formally evaluated (Carlson 2003).

This is a subreview of a comprehensive review "Pharmaceutical policies: Effects on rational drug use" with one overarching protocol (Aaserud 2003). Due to the diversity of and heterogenity between pharmaceutical policies, the total review was divided using a 12-category taxonomy that classified all pharmaceutical policies into one of the following areas: 1) registration and classification; 2) patent and profit; 3) marketing; 4) sales and dispensing; 5a) prescribing (financial incentives); 5b) prescribing (educational or regulatory policies targeting prescribers); 6) policies that regulate the provision of drug insurance; 7) policies that determine which drugs are reimbursed; 8) restrictions on reimbursed drugs; 9) price and purchasing;10) co-payment and caps; 11) patient information; and 12) multi-component policies. This taxonomy provides the organizing structure for these reviews.

OBJECTIVES

To determine the effects of a pharmaceutical policy that restrict the reimbursement of selected medicines on drug use, healthcare utilization, health outcomes and costs (expenditures).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), non-randomised controlled trials (CCTs), interrupted time series analyses (ITS) including repeated measures (RM) studies, and controlled before-after (CBA) studies.

Types of participants

Healthcare consumers and providers within a large jurisdiction or system of care were the participants. Jurisdictions could be regional, national or international. Studies within organisations, such as health maintenance organisations, were included if the organisation was multisited and served a wider population.

Types of interventions

Prescribing policies (restrictions on reimbursed drugs): Pharmaceutical policies that intend to restrict reimbursement for drugs that are covered by drug benefit insurance plans. Included in this category are pre-authorisation for individual patients and general restrictions, for example based on medical specialty, diagnostic requirements and prior use of alternative treatments. Studies were included that examined both: 1) the introduction of restriction to reimbursement policies; and 2) the relaxation of previously instituted restrictions to reimbursement or exemption from restrictive policies of targetted cost effective drugs.

Policies in this review were defined as laws, rules, financial and administrative orders made by governments, non-government organisations or private insurers. Interventions at the level of a single facility were excluded.

Types of outcome measures

Primary outcomes

To be included, a study had to include an objective measure from at least one of the following outcome categories.

- Drug use (prescribed, dispensed or actually used).
- Healthcare utilisation.
- Health outcomes.
- Costs (expenditures), including drug costs and prices, other healthcare costs and policy administration costs.

Secondary outcomes

Changes in equity of access to drugs: changes in the access to medically necessary drugs by disadvantaged groups or changes in the distribution of financial burden.

Pharmaceutical policies have an important potential impact of these. To evaluate changes in equity would require a baseline analysis and categorisation of the population of interest by socio-economic status. Any methodology for such classification was acceptable provided it was adequately described and explained.

Search methods for identification of studies

An updated search was conducted in MEDLINE (2005 to January 2009) and other databases (2005 to October 2008).

Electronic searches

The following databases were searched.

- Cochrane Central Register of Controlled Trials (CENTRAL) on Ovid (14 October, 2008).
- MEDLINE (Ovid) (27 January, 2009).
- PubMed (Oct 20, 2008) for relevant journals not indexed in MEDLINE.
- EMBASE (Ovid) (21 October, 2008).
- Web of Science, ISI (20 October, 2008).
- Worldwide Political Science Abstracts (CSA) (17 October, 2008).
- EconLit (EBSCO) (17 October, 2008).
- International Political Science Abstracts (EBSCO) (17 October, 2008).
- NHS Economic Evaluation Database (17 October, 2008).
- PAIS International (CSA) (17 October, 2008).
- IPA, International Pharmaceutical Abstracts (Ovid) (23 October, 2008).
- Organisation for Economic Co-operation and Development (OECD) (23 October, 2008).
- World Bank e-Library/ World Bank Documents & Reports (23 October, 2008).

The protocol for reviewing pharmaceutical policies, including the search strategy to identify studies for this review, was initially done as a part of a strategy for reviewing effects of pharmaceutical policies across 13 review areas (see also Aaserud 2003; Aaserud 2006; Austvoll-Dahlgren 2008; Sturm 2007). An initial search was conducted in 2006. The original strategy included terms across the 13 categories, embracing the complete pharmaceutical policy continuum. The updated search was limited only to terms such as 'prior authorization', 'pre-authorization', 'restrict', 'regulate with drug pre-

scribing' and reimbursement related terms, as appropriate to the database however used the same databases where they were still available. All search strategies used are provided in full in Additional tables section in Table 1 through Table 2.

The MEDLINE search strategies are shown here as an example.

1. (rebate or reimbursement contract? or reimburse$ or insur$ or (third party adj1 pay$) or benefit plan?).mp. or *insurance, health, reimbursement/ or *reimbursement mechanisms/ or *reimbursement, disproportionate share/ or *reimbursement, incentive/ [mp=title, original title, abstract, name of substance word, subject heading word]

2. ((prescribe$ or prescription? or substitute$) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw. or exp Pharmaceutical preparations/ or prescriptions, drug/

3. ((generic$ adj3 prescrib$) or (generic? adj3 prescription) or (generic$ adj3 substitut$)).tw.

4. 2 or 3

5. (regulat$ or requirement? or restrict$ or monitor$ or control$ or reduc$ or fix$).tw. or (Pre-authori#ation? or preauthori#ation? or prior authori#ation?).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

We used a modified version of the EPOC search strategy methodology filter to limit the MEDLINE strategy to randomised trials, controlled trials, time series analyses and controlled before-after studies. Search strategies for most of the other databases were developed on the basis of the MEDLINE strategy. Additional search strategies are presented in additional tables (Table 1, Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, Table 12, Table 13, Table 14 and Table 2).

We screened the reference lists of all of the relevant reports that we retrieved. Authors of relevant papers, relevant organizations and discussion lists were contacted to identify additional studies, including unpublished and ongoing studies.

Data collection and analysis

Selection of studies

Three authors (CJG, MM and PF) independently reviewed all of the updated search results, abstracts and reference lists of relevant reports. The full text of potentially relevant reports was retrieved (if one or both authors thought it was potentially relevant) and two (of the above) authors independently assessed the relevance of those studies and the limitations of included studies. The lead author (CJG) extracted data from the included studies in collaboration with one other author (PF or MM). For all the steps in the above process disagreements were resolved by discussion, if necessary including another author (SB).

Data extraction and management

We extracted the following information from included studies using a standardised data extraction form.

- Type of study (RCT, CCT, ITS including RM studies, CBA).
- Study setting (country, key features of the healthcare system and concurrent pharmaceutical policies).
- The sponsors of the study.
- Characteristics of the participants (consumers, physicians, practices, hospitals etc.).
- Characteristics of the policies.
- Main outcome measures and study duration.
- The results for the main outcome measures.

Assessment of risk of bias in included studies

Studies that appeared to meet inclusion criteria were assessed for risk of bias using The Cochrane Collaboration's EPOC checklists (EPOC 2008).Two of three review authors (CJG, MM, PF) independently assessed each study and reached consensus on the assessment.

Studies that, on detailed assessment, did not meet inclusion criteria were excluded (Excluded studies). Studies rated as 'fatally flawed' (untrustworthy based on an overall judgment of the risk of bias in the study and serious flaws in statistical analyses and control group composition) were also excluded from the review and the reason for exclusion was listed in the excluded studies table (see table Characteristics of excluded studies).

We used the EPOC Group risk of bias checklist for studies with a separate control group (RCTs, CCTs, CBAs) as well as the separate checklist for ITS studies (Section 6, EPOC 2008). The criteria for RCTs, CCTs and CBAs are available in full through EPOC. As the studies using these designs were not found for this review, this set of criteria is not reproduced in full here. Appraisals of studies that were originally evaluated using older criteria were updated.

ITS studies had the following requirement: "The study must have a clearly defined time of intervention AND must have at least three data points before and three data points after the intervention." We also considered designs where there was a control ITS group. Control ITS (CITS) designs are conceptually similar to a CBA design but the addition of multiple time points pre- and post-intervention decreases the likelihood of secular change bias.

The criteria for ITS studies pertained to the following.
1. Intervention independence (protection against secular changes): the intervention occurred independently of other changes over time and the outcome was not influenced by other confounding variables or historic events during study period.
2. Pre-specified intervention effect: the point of analysis was the point of intervention or a rational explanation for the shape of the intervention effect was provided.
3. Intervention unlikely to affect data collection (protection against detection bias): the intervention itself was unlikely to affect data collection (e.g. sources and methods of data collection were the same before and after the intervention).
4. Knowledge of allocated interventions prevented: the primary outcome variables corresponding to the primary hypothesis or question were explicitly reported to have been assessed blindly, or the outcomes were objective (e.g. length of hospital stay).
5. Incomplete outcome data: acceptable if missing outcome measures were unlikely to bias the results (e.g. the proportion of missing data was similar in the pre- and post-intervention periods or the proportion of missing data was less than the effect size; i.e. unlikely to overturn the study result).
6. Selective outcome reporting: no evidence that outcomes were selectively reported (e.g. all relevant outcomes in the methods section were reported in the results section).

7. Other risk of bias: no evidence of other risk of biases (e.g. should consider if seasonality is an issue; i.e. if January to June comprised the pre-intervention period and July to December the post-intervention period, could the 'seasons' have caused a spurious effect).

For CITS (controlled ITS) and CRM (controlled repeated measures (RM)) studies, the time series parts of the studies were assessed independently from the control parts, using the above described criteria for ITS and RM studies. The control series part of the study was assessed using CBA criteria. If the control part had serious limitations it was not included and the study was classified as ITS or RM, otherwise the control data were used as a control in the review. RM designs measure individual patient outcomes twice or more (repeatedly) at different time points in relation to policy change and calculate the difference in individual measures before combining data from all individuals in the sample. ITS aggregates outcome measures for the entire sample at each time point and analyses differences over the series of time periods without measuring the difference in an individual patient's measure.

ITS studies that ignored secular (trend) changes and performed a simple t-test of the pre- versus post-intervention periods without further justification were not included in the review unless reanalysis was possible. Re-analysis was done if there were at least 12 monthly data points pre- and post-intervention to meet the criterion for ITS inclusion and allow seasonal effects to be investigated using an approach developed by Ramsey et al (Ramsey 2003).

Measures of treatment effect

The preferred analysis method for ITS and RM studies was either a regression analysis with time trends before and after the intervention, which adjusted for autocorrelation and any periodic changes, or ARIMA analysis. The results for the outcomes should be presented as changes along two dimensions: change in level and change in slope. Change in level is the immediate effect of the policy and is measured as the difference between the fitted value for the first post-intervention data point (one month after the intervention) minus the predicted outcome one month after the intervention, based on the pre-intervention slope only. The relative change in level was calculated by dividing the change in level by the predicted outcome one month after the intervention, based on the pre-intervention slope only, and multiplying by 100%.

Change in slope is the change in the trend from pre- to post-intervention that reflects the 'long-term' effect of the intervention. Since the interpretation of change in slope could be difficult, we chose to present the long-term effects similarly to the way we calculated and presented the relative immediate effects. We presented the effects after half a year as the difference between the fitted value for the sixth month post-intervention data point (half a year after the intervention) minus the predicted outcome six months after the intervention based on the pre-intervention slope only and dividing by the predicted outcome six months after the intervention, based on the pre-intervention slope only, and multiplying by 100%. The effects after one year and two years were measured similarly. For drug expenditures we also calculated the savings after a half year, one and two years as the area between the predicted expenditure curves and the actual expenditure.

Given that policy changes can be announced some months prior to official implementation, a transition phase is often defined as the six months from official announcement. If applied, all results excluded the transition phase data. However, if studies provided only few data points, the data itself did not suggest a transition phase and, most importantly, the authors did not state a transition phase, it was not applied. A transition phase was explicitly incorporated into the analysis of four studies in this review (Fretheim 2007; Marshall 2002; Schneeweiss 2004; Schneeweiss 2006).

Dealing with missing data

If papers with ITS design did not provide an appropriate analysis or reporting of results but presented the data points in a scannable graph or in a table, we (CR) re-analysed the data using methods described in Ramsay 2003. The following segmented time series regression model was specified: Y(t) = B0 + B1*Preslope + B2*Postslope + B3*intervention + e(t), where Y(t) is the outcome in month t. Pre-slope is a continuous variable that indicates the time from the start of the study up to the last point in the pre-intervention phase and coded constant thereafter. Post-slope is coded 0 up to and including the first point post-intervention and coded sequentially from 1 thereafter. The intervention is coded 0 for pre-intervention time points and 1 for post-intervention time points. In this model, B1 estimates the slope of the pre-intervention data, B2 estimates the slope of the post-intervention data; B3 estimates the change in level of outcome as the difference between the estimated first point post-intervention and the extrapolated first point post-intervention if the pre-intervention line was continued into the post-intervention phase. The difference in slope is calculated by B2 - B1. The error term (t) was assumed to be first order autoregressive. For CITS studies, the difference between the relative changes of the intervention and the control groups were presented. Confidence intervals (95%) were calculated for all effect measures. For studies that were analysed as CBA by the authors and re-analysed as CITS by the review authors, results were presented for both methods; however for grading the quality of evidence, only the ITS analyses were used.

Data synthesis

Pooling ITS data from individual studies using using the DerSimonian and Laird random effects model was considered (Ramsey 2001). Estimating the effect size of difference in the slope of the trend line over time as well as a change in level were of interest. Also of interest was analyses estimating immediate, short term (6 months, 1 year) and long term (18, 24 months and longer). Pooling data was considered to be possible when data could be standardised using the standard deviation of the pre intervention data. Studies using a repeat measures approach were not suitable for pooling. We planned to tabulate and summarise the findings in a narrative form if it was inappropriate to combine the data.

As ITS may provide data on policy impact at different points in time. Of interest are the immediate impact as well as persistance over short term (6 months) and long term (24 months or longer). Tables 1 – 3 present were structured to make the results formats as common as possible across studies. Data from each study which best corresponded to each of these time points of interest were selectively included in tables. Not all studies provided analysis over the 3 time periods of interest. Some provided additional analysis and where these were contributory, they are summarized narratively in the main text sometimes along side data from the same study provided in the Tables for completeness.

Studies synthesizing individual state level data across many states were also reported narratively. Where reanalysis was possible and

more informative than that provided by the original study, this data is presented in the Tables and the narrative along with the authors reported results in narrative format only.

Subgroup analysis and investigation of heterogeneity

Statistical or clinical **heterogeneity** was explored when more than one trial was considered for inclusion in an **analysis** before pooling the data. The large numbers of studies and variability in design and settings and target drug or drug class were unanticipated and posed challenges to summarization. Clinical heterogeneity precluded meta-analysis.

RESULTS

Description of studies

See:Characteristics of included studies; Characteristics of excluded studies.

Twenty-nine studies were identified that met the selection criteria. These included 24 studies evaluating restrictions to reimbursement policies and five studies evaluating policies of releasing or relaxing past restrictions to reimbursement rules. The majority of the interventions were of newly implemented policies requiring additional information to be submited to the pharmaceutical benefit plan by the physician before all or part of the costs of the drug were reimbursed by the plan. This type of policy is most commonly known as a prior authorization (PA) policy. How PA policies were implemented and routinely managed varied between settings. Study reports generally lacked descriptive details of administrative processes and procedures. Programs from four countries were represented: USA, Canada, Norway and Denmark.

Participants

The data sources for all studies in this review were the administrative data sets of the respective pharmaceutical benefit plans. The primary purpose of the administrative data sets was to track transactions that were undertaken within the plan, rather than to support research. Researchers accessed routinely collected data through the institutionally regulated processes of the plan or government data stewards, as well as under the governance structures of the research facilities they were associated with. Individual patient data were anonymized; that is, researchers did not receive identifiable or sensitive health data about individuals.

Participants were predominantly the beneficiaries of publically subsidized or administered pharmaceutical insurance plans -- most often senior citizens aged 65 years or over and low income adult populations. Fourteen studies were from settings in the USA, 11 studies were from Canada and four studies were from countries outside of North America. Fretheim 2007 invited general practices around Oslo, Norway to participate in their study.

State administered Medicaid or Medicare pharmaceutical benefit plans in the USA provided the data resources for 12 studies (Carroll 2006; Delate 2005; Farley 2008; Fischer 2004; Fischer 2007; Hartung 2004; Hartung 2006; Law 2008; Morden 2008; Roughead 2006; Smalley 1995; Soumerai 2008). One employer group benefit plan (Motheral 2004) and one state correctional (prison) health system (Keith 1994) were the settings of the other studies from the USA.

The following Canadian provincially administered drug benefit plans were represented: British Columbia (Grootendorst 2005; Hazlet 2002; Marshall 2002; Marshall 2007; Schneeweiss 2004; Schneeweiss 2006), Ontario (Jackevicious 2008; Marshall 2006; Marshall 2007); Nova Scotia (Kephart 2005; MacCara 2001) and Newfoundland and Labrador (Bursey 2000).

Four studies from outside North America investigated policies that released restrictions to reimbursement to encourage the use of a drug for secondary prevention. Bjerrum 2001 investigated a Danish policy of reimbursing all lipid lowering drugs used for secondary prevention (Bjerrum 2001). Van Driel investigated a policy of removing restrictions to reimbursement for histamine2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs) (van Driel 2008). Norway made available one statin (simvastatin) for cholesterol lowering without PA (Sakshaug 2007) as well as thiazides for newly treated, uncomplicated hypertension (Fretheim 2007). A fifth study from Ontario, Canada was of a policy of releasing a restriction on clopidogrel reimbursement for patients undergoing percutaneous coronary intervention with stenting after acute myocardial infarction The reimbursement policy was changed from access only with PA to the requirement that a "limited-use code" be written on the prescription (Jackevicious 2008).

Drug classes

Eleven drug classes were represented among the included studies with anti-inflammatory and gastrointestinal drug classes being targeted most frequently. Policies targeting anti-inflammatory drugs including nonsteroidal anti-inflammatory drugs (NSAIDS) were the most frequent (10 studies) (Bursey 2000; Carroll 2006; Fischer 2004; Grootendorst 2005; Hartung 2004; Hartung 2006; Marshall 2007; Motheral 2004; Roughead 2006; Smalley 1995). Cyclo-oxygenase-2 (COX-2) selective inhibitors were a frequently targeted drug in this class. Policies targeting gastrointestinal drugs including PPIs and H2RAs were the second largest set (nine studies) (Bursey 2000; Delate 2005; Hartung 2006; Hazlet 2002; Keith 1994; Marshall 2002; Marshall 2007; Motheral 2004; Schneeweiss 2006). Two studies examined the impacts of policies on multiple drug classes: Hartung 2006 (PPIs, NSAIDS, long-acting opioids, statins); Motheral 2004 (PPIs, NSAIDs, selective serotonin reuptake inhibitors (SSRIs)).

There were fewer studies of policies targeting drugs that affect more challenging clinical conditions: statins, lipid lowering drugs (three studies) (Hartung 2006; Sakshaug 2007; Bjerrum 2001); antipsychotics (three studies) (Farley 2008; Law 2008; Soumerai 2008); wet nebulizer asthma medications (two studies) (Kephart 2005; Schneeweiss 2004); fluoroquinolone antibiotics (two studies) (MacCara 2001; Marshall 2006); long-acting opioid analgesics (two studies) (Hartung 2006; Morden 2008); antihypertensive angiotensin-receptor blockers (ARBs) (one study) (Fischer 2007) and thiazides (one study) (Fretheim 2007); clopidogrel, antiplatelet drug (one study) (Jackevicious 2008); and SSRIs (one study) (Motheral 2004).

Outcomes

Drug use and drug expenditures were outcome measures in 24 studies each. Although these were largely the same studies there were some differences in the sets. Health outcome data (measures of health or loss of health directly experienced by patients, including pain, illness or death) was measured directly in only two studies and healthcare utilization was measured in nine studies. Healthcare utilization, for example emergency room visits, could be viewed as a surrogate measure of adverse events and therefore health outcomes.

The characteristics of each of the included studies are described in the table 'Characteristics of included studies' with a general description of methods, participants, intervention and outcomes. Our appraisal of each study, according to EPOC criteria, is presented in the 'Risk of bias' table. The summaries of evidence by outcome are provided in tables 1 to 4 (Summary of findings for the main comparison, Summary of findings 2, Summary of findings 3, and Table 15).

Results of the search

Seventeen of the 29 studies that met the inclusion criteria for this review were identified through the main literature search that covered all 13 pharmaceutical policy areas outlined in the "Pharmaceutical policies: effects on rational drug use, an overview of 13 reviews" protocol (Aaserud 2003); not only restricted to reimbursement policies. The original search generated over 17,000 references which were sifted by several members of the pharmaceutical policy review group (updated to 2007). The updated search for restriction on reimbursement in MEDLINE, EMBASE, Science Citation Index and websites resulted in 1873 new references. We retrieved full text copies of 33 papers that were potentially relevant and excluded all but 13 papers.

Included studies

Study designs

Twenty-nine studies that were conducted using administrative databases met the inclusion criteria, all used ITS study designs. Of these, 14 were controlled interrupted time series (CITS) studies (Carroll 2006; Farley 2008; Fischer 2004; Fischer 2007; Fretheim 2007; Hartung 2004; Hazlet 2002; Kephart 2005; Law 2008; Marshall 2007; Motheral 2004; Roughead 2006; Schneeweiss 2004; Smalley 1995) and 11 had no control group (Bursey 2000; Delate 2005; Grootendorst 2005; Hartung 2006; Jackevicious 2008; Keith 1994; MacCara 2001; Marshall 2002; Marshall 2006; Schneeweiss 2006; van Driel 2008). Four studies used epidemiological and health services research approaches to study design that approximated standard ITS designs, therefore they were evaluated using ITS criteria and re-analysed when possible. These included a controlled cohort analysis (Soumerai 2008) and two prevalence studies with before-after analyses (Bjerrum 2001; Sakshaug 2007). Morden 2008 analysed state level Medicaid ITS data in a regression analysis and random-effects model meta-analyses (Morden 2008).

For studies which used combined study designs, only that part which met the selection criteria of this review was used. A mailed questionaire that was part of the Motheral 2004 study and the controlled before-after component of Carroll 2006 were not included (Carroll 2006; Motheral 2004). The randomised controlled trial analysis of a PA policy on wet nebulizer therapy did not meet inclusion criteria because the randomisation process was disrupted, however a CITS component of the same study provided valid analysis (Schneeweiss 2004).

Excluded studies

Thirteen studies were excluded. Inappropriate study design was the most common reason for exclusion. The most frequent of these were before-after studies without control groups (five studies). Other studies had fatal design flaws in assumptions or group composition. These are described in the table 'Characteristics of excluded studies'.

Risk of bias in included studies

A 'Risk of bias' table is presented for each individual study as part of the 'Characteristics of included studies' tables (see Characteristics of included studies). Figure 1 provides a review of authors' judgements about each methodological quality item, presented as percentages across all included studies (see Figure 1). Figure 2 provides a summary of review authors' judgements about each methodological quality item for each included study (see Figure 2).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

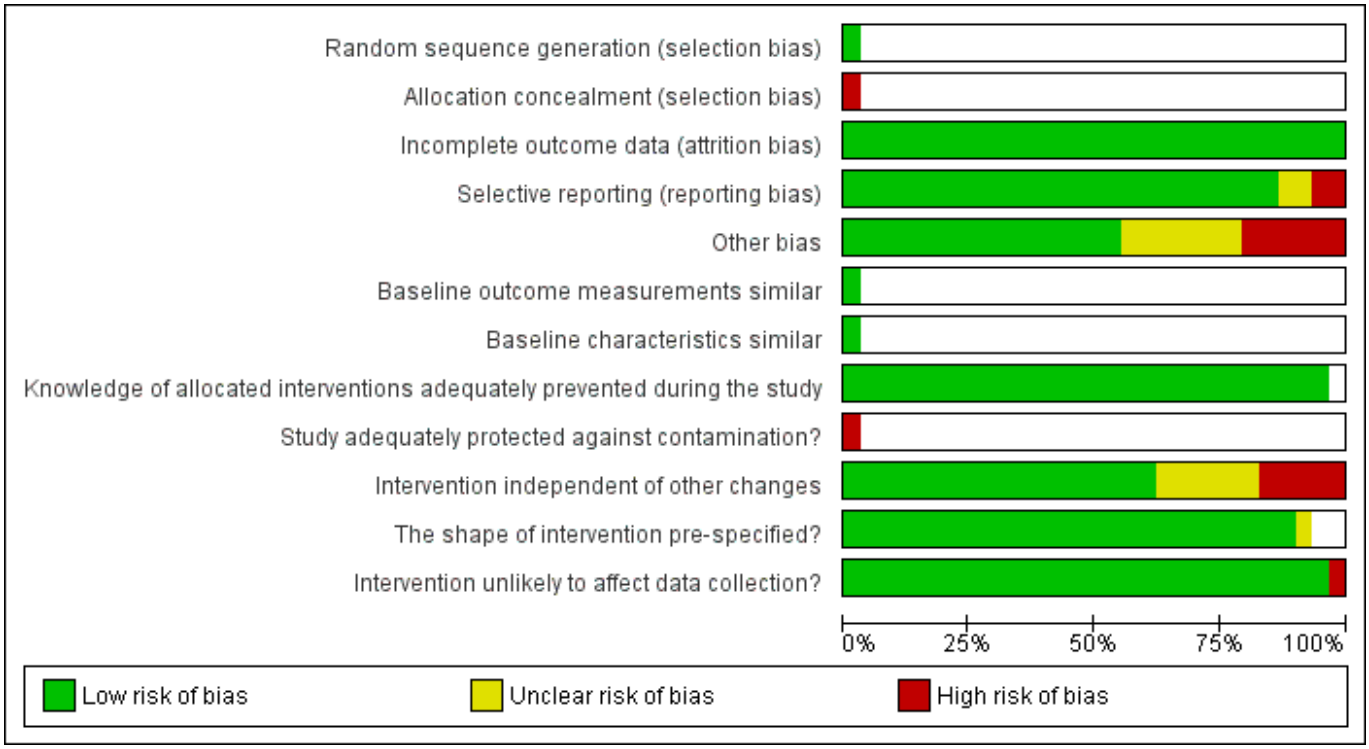


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

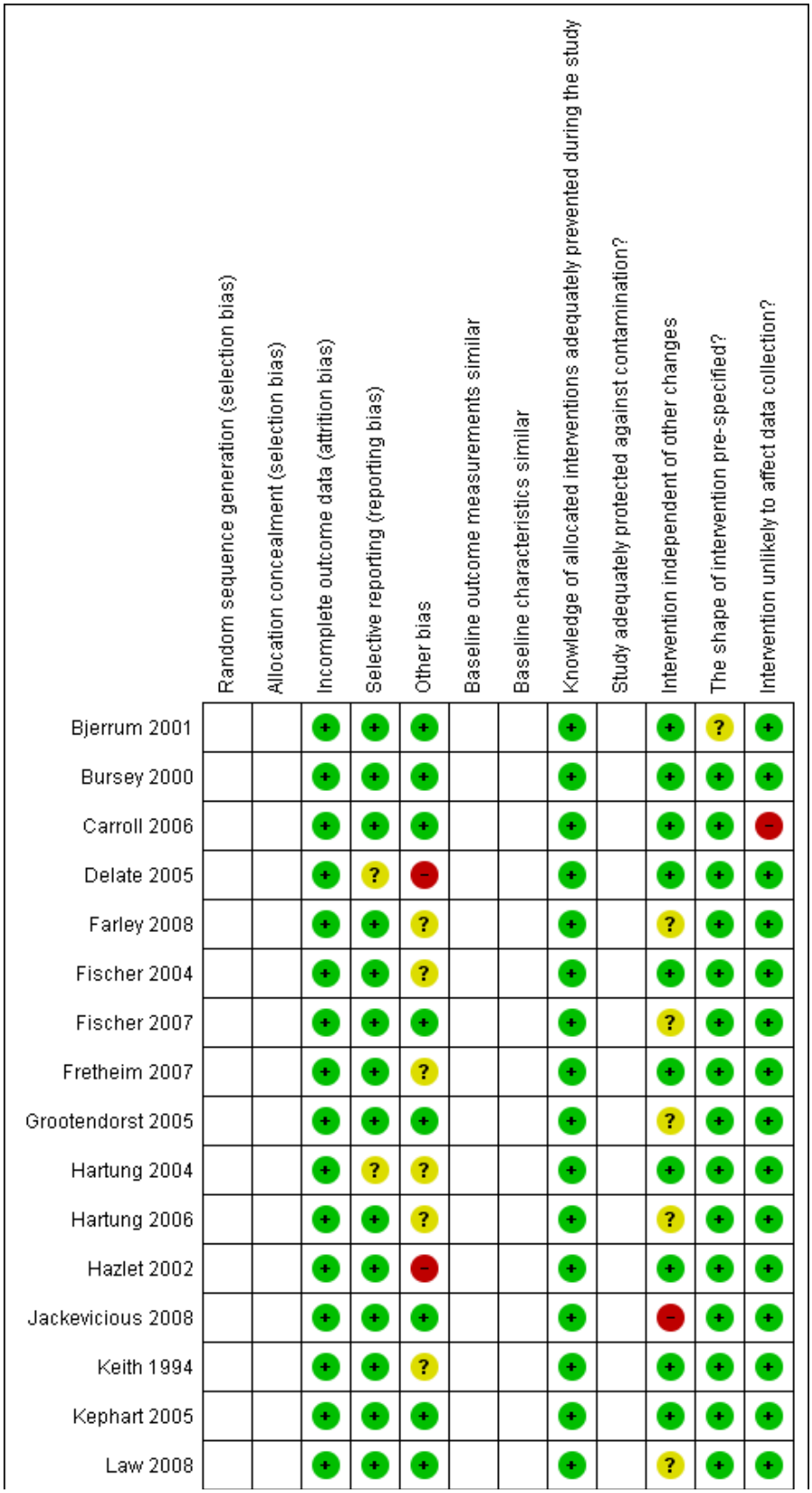
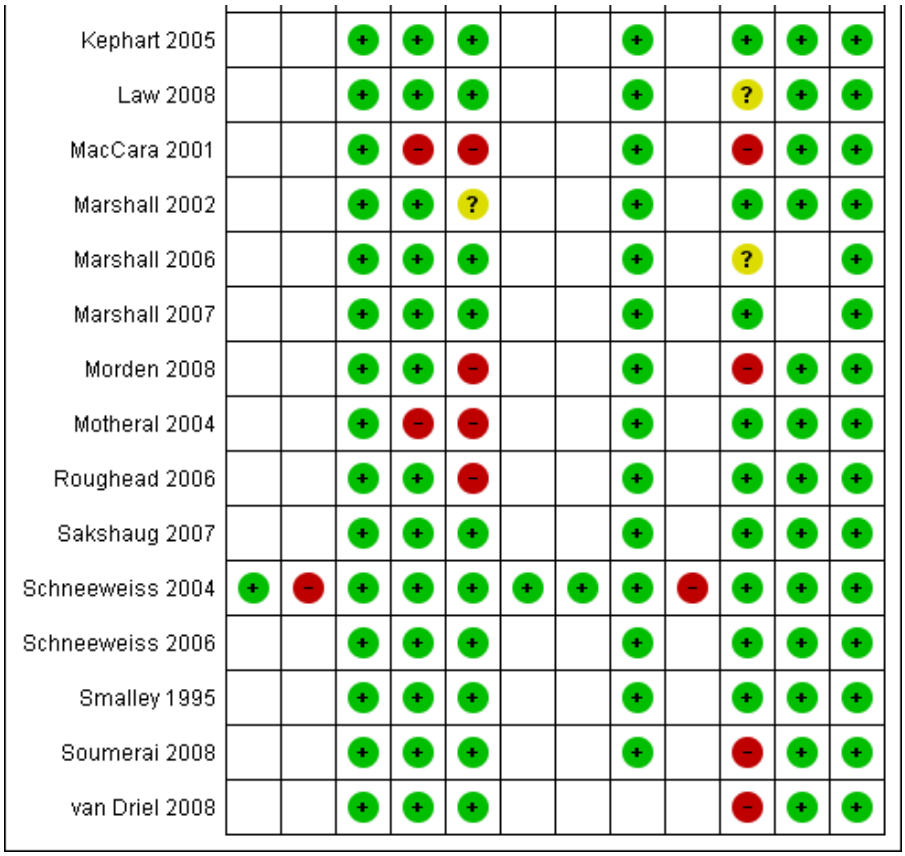


Figure 2. (Continued)



The 29 included studies were appraised using the seven EPOC criteria for ITS.

1. Intervention independent of other changes: factors that could contribute to bias related to other changes occurring over time can be categorized as relating to the population, setting, policy environment or the implementation intensity. Population factors, for example, include the Jackevicious report on "differences in baseline characteristics between patients in the prior-authorization period and those in the limited-use period. In particular, during the limited-use period, patients had lower rates of aspirin use and higher rates of statin use" (Jackevicious 2008). This difference could explain the difference in health outcomes found. In contrast, Keith 1994 reported an increase in the prison population and duration of stay, however these changes would tend to increase rather than decrease drug use, resulting in an underestimate of the policy effect (Keith 1994). MacCara 2001 reported on a policy to decrease antibiotic use that was implemented on December 1st when infectious diseases are on the rise, going into the winter months (MacCara 2001). Marshall 2007 suggested that the lack of cost savings they found following implementation of a PA policy could be explained by higher utilization of more costly drugs, more repeat prescriptions, or the use of drugs requiring longer durations of therapy (Marshall 2007).

Some of the changes that occurred over time were related to implementation intensity and may have enhanced or diminished the effect of the restriction to reimbursement policies pertaining to education about rational prescribing of the targeted drug classes. For example, Bursey 2000 report that implementation intensity was increased through the distribution of algorithms for the management of dyspepsia and gastroesophogeal reflux to all physicians and pharmacists (Bursey 2000). Bjerrum 2001 noted that local medical journals had an increased focus on the subject at the time of the intervention (Bjerrum 2001). MacCara 2001 reported a media campaign on antibiotic resistance that was started soon after policy implementation (MacCara 2001). A coalition of medical organizations started a national campaign to combat the misuse of antibiotics and heighten the awareness of the Canadian public to the dangers of antibiotic resistance within weeks of the introduction of the policy. Sakshaug 2007 reported changes in prescribing with the announcement of the policy and price changes that could be considered part of the policy intervention (Sakshaug 2007).

Other widespread changes were noted. Farley 2008 reported that one of the target drugs (the atypical antipsychotic olanzapine) gained US Food and Drug Administration approval shortly before the policy was enacted (Farley 2008). Fischer 2007 reported that total prescribing for hypertension in Medicaid more than doubled between 1996 and 2005, from about eight million prescriptions per quarter to more than 17 million prescriptions (Fischer 2007). Hartung 2006 reported that the list of reimbursed drugs they were investigating was dynamic during the time period of the study and was evaluated dynamically (Hartung 2006). Morden 2008 reported that drug manufacturers' marketing and other tactics in response to PA implementation may have contributed to the limited success of restriction efforts (Morden 2008).

2. The shape of the intervention pre-specified: for this analysis the point of analysis was required to be the point of intervention; that is, the date the policy intervention was implemented. This date needed to be used to delineate pre- and post-policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time. The expected shape of the intervention effect, though implicit, was an immediate decrease in use of the drugs targeted for decrease and increased use of drugs targeted for increase.

3. Intervention unlikely to affect data collection: the data were objective as they was obtained from administrative databases with standard collection rules for ITS and CITS studies. The Carroll 2006 study aimed to improve implementation by electronic processing of PA rules at the point of sale.

4. Knowledge of allocated interventions adequately prevented during the study: knowledge of the intervention (the policy) is an essential part of policy implementation. Data in ITS studies come from administrative datasets, primarily claims transactions, and therefore are not easily altered by data processors (including researchers and data analysts). However, data analyses for most policy studies are not blinded; the analysts usually know what results are expected after the policy compared with before implementation.

5. Incomplete outcome data: incompleteness of outcome data was usually not well documented in these studies. However, losses to follow up of physicians and patients by the claims databases over the short periods of follow up were likely to be small. Likewise, differences in the proportion of missing data in the administrative datasets pre- and post-intervention were unlikely to be great. Therefore, missing data cannot account for the large associations observed in these studies. Law 2008 is an example of a paper in which the authors addressed concerns about data completeness in one jurisdiction as the data were otherwise consistent (Law 2008). This alerts readers that the finding for this jurisdiction may not have been trustworthy. We noted the widespread lack of health outcome data in administrative databases. Most authors dealt with this by narrowing their hypotheses to the readily measurable variables.

6. Free of selective reporting: we found no studies that cited outcomes measures in the methods section that were not reported in the results section.

7. Free of other bias: we identified the following other potential sources of bias from study reports. Farley 2008 included dementia as a condition of interest even though it is not a recommended indication for antipsychotics (Farley 2008). Fisher 2004 reported lower prescribing of COX-2 inhibitors and NSAIDS in states which implemented Medicaid PA programs prior to implementation compared to control states which did not implement PA policies (Fischer 2004). Fretheim 2007 noted that 40% of invited general practices declined to participate in the study (Fretheim 2007). Hartung 2004 noted that the participants in the control population were older and sicker therefore likely to use more medications (Hartung 2004). Modeling assumptions may have introduced bias in Farley 2008 and Hazlet 2006 (Farley 2008, Hazlet 2002). There was a change in the number of upper-gastrointestinal assessments (a 5.7% decrease post-implementation) in Keith 1994 (Keith 1994). Senior citizens who opted to pay out-of-pocket expenses for a fluoroquinolone were not included in the MacCara 2001 study (MacCara 2001). Marshall 2002 reported that "The reasons for the observed growth in PPI use are unclear and are beyond the scope of this analysis" however overall trends in the drug market could have been examined with data from another province as a control (Marshall 2002). Reimbursement figures did not reflect manufactur-

ers' rebates to states in Morden 2008 (Morden 2008). No baseline characteristics of the patient population were provided in Motheral 2004 (Motheral 2004). There were also small sample sizes at the level of drug class. Roughead 2006 reported that "data on age, gender, and racial differences within the Medicaid markets for each quarter were not available for all states so these characteristics were uncontrolled in the models" (Roughead 2006). Also, there were individual patient, physician prescribing and policy differences between early and late adopting states (Roughead 2006). A relevant trend that may have contributed bias in Grootendorst 2005 was a moderate upward trend in use of opiates that was almost a mirror image of the decline in NSAID use from 1998 to 2001 (Grootendorst 2005).

Summary of appraisal

Overall, the 29 studies represent a body of evidence with a measure of protection against bias. Seven studies met all quality criteria (Bursey 2000; Fischer 2004; Kephart 2005; Marshall 2007; Sakshaug 2007; Schneeweiss 2006; Smalley 1995). Two or more criteria were not met by four studies (Hartung 2006; MacCara 2001; Morden 2008) and Motheral 2004. One of the ITS appraisal criteria was not met by the remainder of studies (18 studies).

Effects of interventions

See: **Summary of findings for the main comparison** Outcome: drug use - CITS and ITS studies; **Summary of findings 2** Outcome: drug expenditures - CITS and ITS studies; **Summary of findings 3** Health services utilization - CITS and ITS studies

Effects of interventions

Detailed results for the included studies are provided in three summary of findings tables: Summary of findings for the main comparison presents drug use; Summary of findings 2 presents drug expenditure outcomes and Summary of findings 3 presents health services utilization data.

Drug use

Drug use was an outcome measure in 24 studies (Summary of findings for the main comparison). Results are presented first for introduction of policies and then for removal of restrictions to reimbursement. Both immediate, short- and long-term change in level and change in slope results are presented sequentially. Limitations of individual studies with regards to drug use as an outcome measure are briefly explained. Finally, results by drug class are summarized.

Introduction of a restriction to reimbursement policy: absolute changes in level immediately after the transition period following restriction to reimbursement policy implementation were reported by three studies: Hartung 2004 reported that the days' supply of per person-year celecoxib decreased (-0.54, 1.07 to 0.53); Smalley reported a decrease of 4.35 days of NSAID use per person-year; Marshall 2002 reported a drop of 22,050 in the mean number of defined daily doses (DDDs) of all PPIs per 100,000 senior citizens per month (which equaled about 2.5 days per person-year) (Hartung 2004; Marshall 2002; Smalley 1995). Relative changes in levels immediately after the transition period were reported by seven studies: Delate 2005 reported a decrease of 92% in PPIs with a 98% increase in H2RA claims (Delate 2005); Fischer 2007 reported no statistically significant change in ARB DDDs as a proportion of the renin-angiotensin-aldosterone system (RAAS) blocking drugs in states with PA policies unless an angiotensin converting enzyme (ACE) inhibitor trial was required (Fischer 2007); Hartung 2004 reported an immediate drop of -58.9% (95% confidence interval (CI) 50.0% to 67.9%) in days' supply per person-year of celecoxib (Hartung 2004); Kephart reported a significant decrease in monthly use of wet nebulization therapy (Kephart 2005); Law 2008 a -3.5% (-5.7%, -1.3%, P = 0.003) decrease of market share of second-generation antipsychotics in West Virginia and a 2.6% (0%, -5.2%, P = 0.55) decrease in Texas (Law 2008); Marshall 2002 reported a 15.6% drop during a six month transition following policy announcement in mean number of DDDs for all PPIs per 100,000 senior citizens per month (Marshall 2002); Smalley reported a 26% (95% CI 21% to 31%) decrease in days of NSAID use per person-year (Smalley 1995).

Six months post-policy implementation: two studies reported on policy effects, Fischer 2004 reported a decrease of 11.1% (5.7% to 16.5%) six months post-implementation relative to six months pre-policy implementation; Schneeweiss 2004 reported a decrease in use of nebulised drugs of 7% (P < 0.001) and a 25% decrease of nebulized drugs in combination with inhaled drugs (P < 0.001) (Fischer 2004; Schneeweiss 2004).

At eight months post-implementation: Schneeweiss 2006 found no change in total PPI utilization (P = 0.82) with a - 383 slope change (P = 0.08); however within PPI utilization there was an absolute decrease of 14,850 (± 1100) DDD per 10,000 residents per month of the restricted PPI, and an increase of the reimbursed PPI rabeprazole (plus 19,300 ± 2200, P < 0.0001) with a 45% switching rate (Schneeweiss 2006). Hartung 2006 reported on 3 intensities of PA (dispense as written (DAW), soft education and voluntary) for multiple drug classes implemented for varying time periods of 5 to 9 months with varying impact on market share (increase of 28% with DAW, increase of 42.9% with soft education and a decrease of -17.4% when compliance became voluntary) (Hartung 2006).

First year post-implementation: results were reported by eight studies. Hartung 2004 reported a decrease in slope (rate of increase) that was not further specified (P < 0.001) (Hartung 2004); Keith 1994 reported a decrease at 11 months of 35% (from 69,212 to 44,751 dosage units H2RAs/month) with an increase of 0.7% in the slope (Keith 1994); Kephart reported a slower decline in wet nebulization therapy (P < 0.001) (Kephart 2005); Law 2008 found a continuing decrease in second generation antipsychotic use per quarter of -1.3% (-1.8%, -0.8%, P < 0.001) in West Virginia and a non-significant trend in Texas (Law 2008); MacCara found a decrease in fluoroquinolone claims of 80% (MacCara 2001); Marshall 2002 found a decrease of 26% in mean number of DDD of all PPIs per 100,000 senior citizens per month (Marshall 2002); Smalley 1995 found a decrease of -23% (-22.9%, -18.9%) in days of NSAID use per person-year at one year post implementation (re-analysis) (Smalley 1995); Soumerai 2008 found no statistically significant difference in atypical antipsychotic use at 10 months (Soumerai 2008).

Keith 1994 also measured the effect of restrictions of gastrointestinal drugs on the percentage of patients taking other drugs known to produce significant drug interactions. A relative decrease of 7.5% (from 14% to 6.5%) was found (Keith 1994).

Longer-term results: were reported in seven studies. Marshall 2002 reporteed a decrease in absolute numbers of fluoroquinolone prescriptions of 1905 per week (P < 0.001) (Marshall 2006). To 18 months, Fischer 2007 found that states requiring an ACE inhibitor trial before being granted prior approval for an ARB had a decrease

of 1.3% per quarter (P < 0.001); and Fischer 2004 reported a decrease of 1.6% (0.0%, 3.1%) per quarter to 18 months (P = 0.03) for COX-2 inhibitors; over 24 months, Kephart 2005 found a decline from 100% to 36% in heavy users of wet nebulization therapy and a decline from 67% to 20% in all users; Law 2008 found a decrease in second-generation antipsychotic use per quarter of 13.8% (9.4%, 18.2%, P < 0.001); Smalley 1995 found a decrease of 21% (-19.3%, -22.4%) in days of NSAID use per person-year at two years post-implementation (re-analysed data from figure) (Fischer 2007; Fischer 2004; Kephart 2005; Law 2008; Smalley 1995). At 41 months, Marshall 2002 reported a 9% increase over baseline in use of all PPIs (Marshall 2002).

A number of studies used the national US Medicaid or Medicare program, or both, datasets to compare states with and without PA policies. Notwithstanding the many known demographic, management and policy differences between states, highly aggregated data provides a macro level overview. For example, Fischer 2004 found an overall 15% reduction in use of COX-2 inhibitors as a proportion of all NSAIDs in states that had implemented PA programs as part of Medicaid drug benefit programs (Fischer 2004). However, the proportion of COX-2 inhibitor use of all NSAID use was highly variable between states, ranging from 11% to 70%.

Roughead 2006 compared states that initiated a PA policy restricting COX-2 inhibitors within a year of market entry (early) with those who initiated PA policies at least two years post-market entry (late) or had unrestricted access policies (never) (Roughead 2006). COX-2 inhibitor use, as measured in DDD per 1000 population per day, varied from 11 (± 2.9) in early policy state Medicaid plans to 29 (± 7.2) in never PA policy states. In states with late policy implementation, use varied from 23 (± 9.9) pre- to 14 (± 7.2) post-PA policy implementation. Fischer 2007 found no reduction in ARB use as a proportion of all RAAS blocking drugs unless a trial with an ACE inhibitor was a criterion for authorizing reimbursement (Fischer 2007).

A number of studies contributed findings that were consistent with those above, however they had the following limitations. Bursey 2000 did not report on PPI drug use in the pre-policy time period (Bursey 2000). Carroll 2002 reported the annual drug mean per number of paid prescription claims per patient per year (PPPY) for COX-2 inhibitors without providing immediate, monthly or quarterly data (Carroll 2006).

Grootendorst 2005 included an ITS of delisted drugs requiring authorization before reimbursement in an analysis of the impact of reference pricing on NSAIDS use from 1993 to June 2001 in British Columbia, Canada (Grootendorst 2005). Use of delisted drugs requiring special authorization for reimbursement, as measured by average monthly number of days of therapy dispensed per 1000 senior citizens, fell continuously from 189,100 in the period February 1993 to March 1994; to 137,720 in April 1994 to October 1995; to 103,540 in November 1995 to October 1996; to 47,250 in the delisting, special authorization period November 1996 to June 2001 (Grootendorst 2005).

Marshall 2007 compared the use of COX-2 inhibitors in British Columbia, Canada (which introduced a restriction to reimbursement policy) with two other provinces for the first and second year after provincial formulary listing (Marshall 2007). In British Columbia Pharmacare, use increased from 2 to 16 DDD per 1000 senior beneficiaries, whereas the increase was from was 56 to 270 with the Ontario Drug Benefit Plan and 122 to 228 in the Quebec drug plan R´egie de l'assurance maladie du Qu´ebec (RAMQ). Differences between the provinces extended beyond the restriction to reimbursement policies and diminished the causal inferences and estimates of effect size that could be attributed to the restriction to reimbursement policy.

Relaxation or exemption from restriction to prescribing policy: Fretheim reported an increase of thiazide prescriptions of 16.5% (95% CI 9.9 to 24.8) during the policy transition phase for patients with new diagnoses when thiazide was made the only reimbursed drug class for uncomplicated hypertension(Fretheim 2007). Four studies evaluated the relaxation of a restriction to reimbursement policy, Bjerrum reported an absolute level increase in the use of lipid lowering drugs of 14 per 100,000 population and an increased prevalence rate in the first year of 0.4% (Bjerrum 2001); Jackevicious reported a 53% increase in the monthly rate of clopidogrel use within 30 days of hospital discharge following myocardial infarction (MI) and receiving stents (Jackevicious 2008); Sakshaug found that at one year the prevalence of statin use increased by 6.8% in women and 8.1% in men (Sakshaug 2007). Van Driel measured the monthly reimbursed DDD for total H2RAs and PPIs from 1997 to 2005 and found a 222% increase with relaxation of a restriction to reimbursement policy (van Driel 2008).

Drug use effects by drug class

Introduction of a restriction to reimbursement policy: Nine studies investigated anti-inflammatory and gastroprotective drugs. The studies that investigated restriction to reimbursement of anti-inflammatory drugs measured a decrease in use of targeted drugs: immediately, over the short term to one year, and over the long term to 24 months and longer (Carroll 2006; Fischer 2004; Grootendorst 2005; Hartung 2004; Hartung 2006; Marshall 2007; Motheral 2004; Roughead 2006; Smalley 1995). Primarily targeted by these policies were the NSAIDs and included COX-2 inhibitors such as rofecoxib and others which had been withdrawn from the market due to previously unrecognized side effects. An unintended consequence of the PA policies, therefore, was less exposure to harm from new drugs. Best estimates of the overall policy effect on drug use for this class of drugs was provided through a re-analysis of the Smalley 1995 ITS trend data: an immediate decrease of 26% (95% CI -21% to -31%), a six month decrease of 23% (95% CI -22.9% to -18.9%) and a decrease at 24 months of 21% (95% CI -22.4% to -19.3%) (Smalley 1995). Over a shorter time span, Hartung 2004 found a -58.9% immediate decrease with a statistically significant decrease in slope, representing a slowing of rising use (Hartung 2004). Other studies confirmed decreasing use on a national scale in the US (Fischer 2004; Roughead 2006) and Canada (Marshall 2007). Roughead 2006 found that states that initiated policies of restriction to reimbursement within the first year had lower use of targeted drugs as well as demonstrating the variability of baseline usage between jurisdictions (Roughead 2006).

Gastrointestinal drugs, including PPIs and H2RAs, were the target drugs of policies investigated in nine studies (Bursey 2000; Delate 2005; Hartung 2006; Hazlet 2002; Keith 1994; Marshall 2002; Marshall 2007; Motheral 2004; Schneeweiss 2006). Schneeweiss 2006 found no change in level of total PPI use but a decrease in rise of use (slope P = 0.08) with a 45% switching rate between the PPI targeted for reduction and the PPI targeted for increase (Schneeweiss 2006). Delate found an immediate 92% decrease in targeted PPIs while preferred H2RAs increased by 98% (Delate 2005). Marshall 2002 found a long (to 41 months) term 9% increase over baseline

after a decrease of -26% over the first year following policy implementation (Marshall 2002).

The two studies that examined the impact of policies on multiple drug classes found the policies achieved their desired effects on usage: Motheral 2004 (PPIs, NSAIDs, SSRIs) found decreased use of the targeted drugs in the short term; and Hartung 2006 (PPIs, NSAIDS, long-acting opioids, statins) found an increase in targeted drugs with the greatest effect evident with an educational PA policy (Hartung 2006; Motheral 2004).

Desired decreases of target drugs were also documented for asthma medication (wet nebulizers) (Kephart 2005; Schneeweiss 2004); antibiotics (fluoroquinolones) (MacCara 2001; Marshall 2006); long-acting opioid analgesics (two studies) (Hartung 2006; Morden 2008) and SSRIs (Motheral 2004).

In two studies of policies targeting second-generation antipsychotics, one found decreased use (Law 2008) and another no difference over the short term (Soumerai 2008). Both study authors expressed concern over inappropriately setting barriers to medication use in a vulnerable population of mentally ill patients.

Release or exemption from restriction to reimbursement policy: where policies released or exempted drugs from restrictions to reimbursement to increase use of preferred drugs, the desired increase was observed for antihypertensives (Fischer 2007 (ARBS); Fretheim 2007 (thiazides)); and cardiac medications (clopidogrel) (Jackevicious 2008). Of the studies that investigated the effect of relaxation of restriction to reimbursement policies on statin use, all found increased use (desired policy outcome) (Bjerrum 2001; Hartung 2006; Sakshaug 2007).

Drug expenditure

Changes in drug expenditures were measured in 24 studies. Analyses or reanalyses are presented in the Summary of findings 2 for the 17 studies presenting findings in the immediate, short term and long term timeframes of interest to the review. The remaining studies either did not report expenditure outcomes in format compatible with categorization as immediate, short term or long term or the study design contained complexity that required narrative presentation to inform interpretation. Decreased expenditures were reported by the majority of studies though outcomes, currencies and measurement approaches varied considerably. Results are presented first for studies investigating the introduction of policies and then for studies investigating the removal of restrictions to reimbursement. Both immediate relative and absolute changes in level are reported by length of follow up: short- (six months to one year) and long-term (one year plus) change in level and change in slope results, where available. Studies or analyses which provided limited expenditure data are reported narratively. Finally results by drug class are summarized.

Three studies investigating restrictive policy introduction for which ITS data were analysed in a standardized way are presented first to provide an overview of how policies can have different impacts on expenditures over time. The immediate change in level for absolute and relative drug expenditures was obtained through a reanalysis of ITS data for three studies: Bursey 2000 data on a PA policy for PPIs revealed a relative decrease of 19.6% that corresponded to a $153 immediate change in level of expenditures for PPI, a 85% relative decrease at six months (95% CI -92.6% to -77.9%), a 12 month decrease of 84% (95% CI -89.7% to 79.3%) and a 24 month decrease of 79% (95% CI -82.8% to -75.2%) (Bursey 2000). Marshall 2002 measured mean monthly expenditures ($ CDN) per 100,000 senior citizens for PPIs in the context of reference pricing for the H2RA drug class. The absolute immediate change in level was -$79005.50 which corresponded to a 38.4% relative decrease. At six months the relative change in level was - 36.0% (95% CI -40.8% to -31.1%); at 12 months - 31.0% (95% CI -34.4% to -27.0%); and at 24 months - 18.0% (Marshall 2002).

Smalley 1995 measured NSAID expenditures per person-year ($) reporting a $14.63 per person per year immediate absolute decrease for a relative decrease of -65% (95% CI -60%, -71%). At 6 months a slight upward trend of $0.17 per month (95% CI $ 0.02, $0.32) was reported. A 53% decrease (95% CI -48, -57) was reported over the 2 year period (Smalley 1995). Reanalysis that examined the time series more precisely at different time points revealed an immediate absolute decrease of $13.45 for a relative decrease of 58.5%; a 57.2% (95% CI -59.7% to -54.7%) decrease at six months; and a 56.1% (95% CI -58.0% to -54.1%) decrease at 12 months

The Immediate period and beyond: six studies provided data on absolute change in expenditures however these numbers corresponded with data extending beyond the immediate period. Delate 2005 reported a relative level change of 90.9% decrease in per member per month (PMPM) for PPI and + 223.2% PMPM increase in expenditure for H2RAs in the month immediately following introduction and an overall mean decrease in PMPM expenditures from $3.44 to $1.74 over a 12 month period (Delate 2005). Hartung 2004 reported an absolute decrease of $1.40 per year and $0.12 PMPM for celecoxib (Hartung 2004). This corresponds to an immediate relative decrease in level of 15% although this was not quantified for the immediate period and therefore this approximation is not included in Table 2.

Hartung 2006 reported the following absolute changes in PMPM aggregate pharmacy costs that corresponded to PA policy time periods of various intensity implemented sequentially and legislatively for PPIs, long-acting opioids, NSAIDs and statins: DAW exception, -$0.18 (-$0.08, -$0.02, P < 0.05); soft PA (education), $0.28 ($0.11 to $0.44, P < 0.05); voluntary, -$0.10 (-$0.26 to $0.06). These absolute changes corresponded to the following relative changes in levels: DAW exception from 8 to 9 months, -9.1% (-13.8% to -4.3%, P < 0.05); soft PA (DAW +5 months), -17.7% (-25.4% to -10.0%, P < 0.05); voluntary (DAW + soft PA periods +1 year) - 5.5% (-1.1%, -12.1%) (Hartung 2006).

MacCara 2001 reported an absolute average cost decrease per antimicrobial user per year of $7.73 with fluoroquinolone PA (a decrease of $35.24 to $27.51) for a relative decrease of 23.7% over one year (MacCara 2001). Motheral 2004 reported absolute decreases in PMPM drug costs for: NSAIDs (- $0.29, P < 0.001); PPIs (- $0.48, P < 0.05); and all three therapy classes (- $0.93, P < 0.01); however there was no significant change for SSRIs, an overall relative decrease of 19% and net administrative costs of $0.10 PMPM (Motheral 2004).

Schneeweiss 2004 reported absolute decreased expenditure on respiratory drugs with of $C24 per patient month (-$19 to -$29) countered by an increase in inhaler expenditure of $3 ($1.4 to $4.5) (Schneeweiss 2004). Schneeweiss 2006 reported an absolute decrease of $3.2 per senior citizen over the first six months of policy implementation, which corresponded to total decreased expenditures for PPIs of C$ 2.9 million (Schneeweiss 2006).

A reference pricing analysis by Grootendorst 2005 provided an example of how policies of different types are combined and complement each other to reduce drug expenditures (Grootendorst 2005). They reported that: "Some of the savings attributed to Type 2 RP are actually because of the delistings of the second line restricted NSAIDs (subsequently only available with PA policy). This latter policy was responsible for about $0.04 or 10% of the $0.40 reduction in Pharmacare reimbursement prices that eventually accrued after the introduction of Type 2 (reference pricing policy). Hence, the delistings policy produced savings of about $400,000 annually (10% of $4,000,000)" (Grootendorst 2005).

State level analysis: five studies used data from national US Medicaid datasets. Fischer 2004 reported an immediate 18% decrease in spending per NSAID prescription, corresponding to a decrease of - $10.28 ($7.56 to $13.00, P < 0.001) (Fischer 2004). Fischer 2007 reported on spending for ARBS as a proportion of all antihypertensives under a preferred drug listing (PDL) PA approach (+ 0.4%, P = 0.049; slope 0.3% per quarter, P < 0.001) versus PA policies which required a trial with an ACE inhibitor before reimbursement was authorized (-1.0%, P = 0.003; slope -0.7 per quarter, P < 0.001) (Fischer 2007). Law 2008 reported on costs level or trends in total Medicaid reimbursement of all antipsychotic medications per 1000 medicaid enrollees (see below) (Law 2008). Morden 2008 reported on average expenditure per DDD for long-acting opiates and all opiates over a 10 year period in all US states with a PA policy on long-acting opiates. The study found a decrease of $0.31 (-$0.06 to -$0.56) for long-acting opiates and a decrease of $0.18 ($0.05 to $0.31, P = 0.006) for all opiates (Morden 2008). Roughead 2006 found that the absolute average cost per NSAID prescription varied depending on the time of PA introduction: from a high with unrestricted access states of $59.00 through to $46.00 for late policy adopting states to a low of $40.00 for early PA policy adopters (Roughead 2006).

Three studies provided limited expenditure data or analyses. Carroll 2006 described and graphed the immediate decrease and subsequent decreases in PPPY use of COX-2 inhibitor expenditures (Carroll 2006) but did not quantify these. Farley 2008 reported absolute decreases of $19.62 PMPM for atypical antipsychotic drugs and increases of $2.20 PMPM for typical antipsychotic drugs over an 11 month time period in Georgia with a PA policy compared to Mississippi with no PA policy This corresponded to a total reduction in expenditure for the state of $7 million (Farley 2008). Keith 1994 reported a total adjusted net savings on H2RAs at one year of $275,920 for a state correctional health system (Keith 1994).

Three studies reported no decrease in expenditures following the implementation of a PA policy. Law 2008 reported no significant change in costs level or trends in total Medicaid reimbursement of all antipsychotic medications per 1000 Medicaid enrollees in each quarter, as well as reimbursement per DDD to Medicaid in each quarter (Law 2008). Though Law 2008 noted that their drug use measure showed a shift towards preferred agents they explained the lack of change in expenditure by noting that individuals who were already receiving antipsychotics did not need to switch; newly treated patients were a smaller proportion of all patients and clinicians may have been more likely to apply for and receive authorization for mentally ill patients (Law 2008). Marshall 2006 measured weekly antibiotic expenditures following implementation of a fluoroquinolones PA policy and found the absolute decrease for fluoroquinolones was $105,707 $C (P < 0.001) to 19 months, and for ciprofloxin - $129,421, which was counterbalanced by increases in other antibiotics such as nitrofurantoin ($2082 increase) and trimethoprim-sulphamethoxazol ($1473 increase) (Marshall 2006). When adjusted for overall trends there was no statistically significant change in expenditures -- the relative 13% decrease in fluroquinolones expenditures was completely offset. Van Driel 2008 showed an increase in expenditures with a relaxation of gastroprotective PA policies (see below) (van Driel 2008).

Relaxation or exemption from restriction to reimbursement policies

Three studies examined the impact of relaxations of restrictions to reimbursement on drug expenditures. Fretheim 2007 found an absolute decrease in costs of antihypertensives of $0.16 per inhabitant in Norway, corresponding to a relative USD 0.72 million decrease over one year (Fretheim 2007). Saskshaug 2007 reported a 20.5% decrease in total annual expenditure on statins in Norway following an absolute decrease from 959 to 762 million NOK (Sakshaug 2007). Van Driel 2008 found an increase in expenditures for acid suppressants per 1000 inhabitants covered by the Belgian National Institute for Sickness and Invalidity Insurance (RIZIV-INAMI) with relaxation of restrictions to reimbursement of two H2RAs and two PPIs, of 60% over a 10 year period (€7.5 million in 1997 to €12 million in 2005) (van Driel 2008).

Drug expenditure effects by drug class

The effects of restrictions to reimbursement on drug expenditure are consistent for gastroprotective (PPI, H2RAs) and NSAID drug classes. The re-analysed studies had no obvious risks of bias on appraisal. The re-analysed studies of policies that restricted gastroprotective (Bursey 2000; Marshall 2002) and NSAID (Smalley 1995) drug classes demonstrated immediate and sustained decreases in absolute and relative expenditures. The findings were consistent with the other studies of these classes of drugs that had less extensive analysis and greater risk of bias. Seven studies of gastroprotective drugs also found a decrease (Delate 2005; Hartung 2006; Hazlet 2002; Keith 1994; Marshall 2007; Motheral 2004; Schneeweiss 2006). Consistent with these, van Driel 2008 demonstrated an increase in expenditure over a 10 year period with the relaxation of PA policies of gastroprotective drugs (van Driel 2008).

Decreased expenditures with NSAID use were also demonstrated in seven studies (Carroll 2006; Fischer 2004; Grootendorst 2005; Hartung 2004; Hartung 2006; Motheral 2004; Roughead 2006). Roughead 2006 demonstrated that US states that adopted PA policies on NSAIDs early on had lower expenditures than states that adopted restrictions later or never (Roughead 2006). Hartung 2006 demonstrated a difference in drug expenditure with different intensities of the PA policy for NSAIDs, gastroprotective and other drug classes (Hartung 2006).

Studies of long-acting Opioids were few but consistently found a decrease in drug expenditures with restrictions to reimbursement (Hartung 2006; Morden 2008). Wet nebuliser PA policies were found to decrease short-term drug costs (Schneeweiss 2004).

Studies were inconsistent on PA policies restricting fluoroquinolone antimicrobial and second-generation antipsychotic medications. MacCara 2001 reported absolute and relative decreases in drug expenditures with fluroquinonlone restriction (MacCara 2001) whereas Marshall 2006 adjusted for a decreasing trend over time with no statistically significant difference (Marshall 2006). Law 2008 found no decrease in drug expenditure for antipsy-

chotics medications (Law 2008) whereas Farley 2008 found a decrease (Farley 2008). PA policies for ARBS were found to only reduce drug expenditures when PA authorization was granted following a trial with ACE inhibitors (Fischer 2007).

Relaxing or exempting restrictions to reimbursement for selected antihypertensives and statins decreased overall drug expenditures whereas relaxing gastroprotective drug restrictions increased overall drug expenditures.

Health outcomes

Health outcomes were only measured in two studies. A study of the Norwegian policy of reimbursing only thiazides for newly diagnosed, uncomplicated hypertension found no significant difference in the proportion of patients who reached recommended blood-pressure goals within four months (absolute decrease 0.5%, 95% CI -21.4% to -10.1%) (Fretheim 2007).

A one year composite cardiovascular outcome (re-admission for MI, death, repeat percutaneous coronary interventions (PCI) and coronary artery bypass graft surgery (CABG) within one year of discharge, rates of death from any cause and major bleeding, drug use) was used to measure the change from a PA policy to a limited use policy for clopidogrel prescriptions for patients receiving coronary stents. The measured change from 15% in the PA group to 11% in the limited use group (P = 0.02) was not well supported because patients also had lower rates of aspirin use and higher rates of statin use during the limited use period (increased from 63% to 80%, P < 0.001) (Jackevicious 2008).

Health services utilization and expenditures

Nine studies investigated changes in health services utilization and expenditure, including outpatient physician, non-physician and emergency department (ER) visits; diagnostic and screening test use; as well as inpatient acute care hospital and long-term care (Summary of findings 3). Studies reported effects at different time points after the intervention, over one to 24 months, resulting in 47 analyses. Populations used for analysis ranged from all members within a benefit plan or populations formed by drug use history or the condition of interest. Overall the quality of measurement was not as robust as for drug use and cost.

Immediate to five months

Three studies using US data estimated the immediate absolute impact of a restriction to reimbursement policy on health services utilization. A re-analysis using CIT data on outpatient services expenditures (Smalley 1995) found an absolute decrease of $9.02 in expenditures for outpatient services per person-year immediately following implementation of a PA program restricting NSAIDs. In an investigation of a celecoxib restriction policy, Hartung 2004/CITS found that the absolute number of gastrointestinal-related events per month that resulted in medical service claims was 'small and sporadic'. A secondary analysis of medical service claims for musculoskeletal conditions and gastrointestinal ulceration found that the numbers were too few for analysis with an average (mean) of only 4.3 gastrointestinal-related events per month (Hartung 2004). Schneeweiss 2006 found no statistically significant immediate level changes following a restriction of PPI reimbursement in rates of hospitalizations for gastrointestinal hemorrhage; hospitalizations for complicated peptic ulcer disease (PUD); or physician visits for gastroesophageal reflux disease (GERD), PUD or gastritis (per 10,000 residents per month); or corresponding slope changes. However, visits for GERD, PUD or gastritis increased in the period from three to five months post-implementation (95% CI 11.0, P = 0.01). The authors attributed this change to 9% of new rabeprazole users being switched back to a restricted PPI (Schneeweiss 2006).

Three studies provided analyses on the relative change in level of health services utilization from immediately after policy implementation to up to six months post-implementation. Re-analysis of the Smalley1995 data revealed a relative increase of 10.6% immediately following the one month transition period after the implementation of a PA program restricting NSAIDs (Smalley 1995). Hazlet, 2002 and Hartung 2004 calculated changes in health services utilization from restriction implementation to five months without the use of a restriction.

A CIT study of PPI restriction by Hazlet, 2002 found no statistically significant difference in number of office visits and transactions, hospital admissions, ER visits or length of hospital stay (Hazlet 2002). The Hartung 2004 CIT analysis of a celecoxib restriction found that the rate of increase (slope rise) in medical claims increased significantly (P < 0.001) however the change in level was not significant at the pre-determined leval of 0.01. Similarily, for a subgroup analysis of musculoskeletal-related encounters, there was a positive slope change (P < 0.001) with no significant change in level of utilization. Gastrointestinal-related encounters declined (P = 0.003). A secondary analysis of previous NSAID or COX-2 use found a decrease in ER use (-7.3%, 95% CI -20.8% to 6.3%) with no significant change in slope. There were no other significant changes in health services use including hospitalizations (Hartung 2004).

Six months to one year

Four studies provided analyses with follow-up durations from six months to one year following restriction to reimbursment. The Smalley 1995 re-analysis identified a relative increase in expenditures for outpatient services per person-year that persisted at six months (12.3%, 95% CI 6.0% to 18.7%) and 12 months (11.7%, 95% CI 6.7%,16.8%) following introduction of an NSAID restriction policy (Smalley 1995). At six month post-policy implementation of a restriction to reimbursement of nebulized respiratory therapy, Schneeweiss, 2004 found no significant increase in health services utilization: contacts with doctors per 100 patients/month (2.6, 95% CI 5.0 to 10, P = 0.10), admissions to ER per 100 patients/month (0.4, 95% CI 0.1 to 0.9, P = 0.10), and all admissions to hospital per 100 patients per month (0.7, 0.0 to 1.3, P = 0.08) (Schneeweiss 2004). At seven months post-implementation of an H2RA restriction, Keith 1994 found a 5.7% decrease in the number of gastrointestinal studies per month (Keith 1994). Delate 2005 compiled and compared groups based on whether their applications for exemption from PPI reimbursement restriction led to PPI use, H2RA use or non-use. Within group before-after comparisons did not meet the inclusion criteria for this Cochrane review (Delate 2005).

One year to 24 months

Three studies provided data on the impact of a restriction to reimbursement policy on health services utilization from one year to 24 months post-policy implementation. Farley 2008 investigated a restriction of atypical antipsychotic medications and found an 18% increase in outpatient services (95% CI 1.1% to 1.2%, P < 0.001) but no change in inpatient and long-term care services in an analysis to 14 months post-implementation (Farley 2008). Kephart 2005 found no change following implementation of a wet nebulization therapy

restriction overall or in a heavy wet nebulizer cohort relative to controls, but a decrease in visits to fee-for-service general practitioners (P < 0.001) and hospital admissions for respiratory conditions (P = 0.02) for all wet nebulizer users relative to controls (Kephart 2005). Smalley 1995 report an overall analysis to 24 months reporting that expenditure for outpatient services per person year was not significantly different overall but decreased 2% (-15% to 19%) for a subgroup of high dose NSAID users. Expenditures for inpatient services per person-year decreased 14% (-8% to 36%) (Smalley 1995).

By drug class

Anti-inflammatory drugs: two studies investigated the impact of restricted reimbursement of NSAID medications on health services utilization (Hartung 2004; Smalley 1995). A re-analysis of Smalley 1995 time series data found an initial relative decrease in expenditures for outpatient services of 10% that then reversed to increase by 12.3% (6.0%, 18.7%) at 6 months and 11.7 (6.7%, 16.8%) at 12 months he first year post-implementation of an NSAID restriction (Smalley 1995). This differs from the non significant 3% (-13%, 18%) increase reported by the authors for the first 24 months following policy start date. Differences in the analysis include the elimination of 3 months of data before and after policy start date when useage was changing. Also the authors analysis was calculated with all data over 2 years which obscures fluctuation of use during the time period. The wide confidence intervals highlight the lack of precision of these estimates. Hartung 2004 measured the absolute number of gastrointestinal-related events per month that resulted in medical services claims as well as claims for musculoskeletal conditions and gastrointestinal ulceration but found that events were too few for analysis (Hartung 2004).

Gastrointestinal drugs: four studies investigated restricted reimbursement of gastrointestinal drugs on health services utilization. Hazlet 2002 found no change in hospital admissions, length of stay, ER or office visits and transactions following implementation of a PPI restriction monitored month to month for one year post-implementation (Hazlet 2002). Keith 1994 found a decrease in the number of gastrointestinal studies (5.7%) over seven months post-implementation of an H2RA restriction (Keith 1994). Schneeweiss 2006 found no statistically significant immediate level changes in rates of hospitalizations for gastrointestinal hemorrhage; hospitalizations for complicated PUD; or physician visits for GERD, PUD or gastritis (per 10,000 residents per month); or corresponding slope changes following restriction of PPI reimbursement. However, rates of office visits for GERD, PUD or gastritis per 10,000 increased from three to five months post-implementation (11.0, P = 0.01). The authors attributed this change to 9% of new rabeprazole users being switched back to a restricted PPI (Schneeweiss 2006). The Delate 2005 analysis of health service utilization data were flawed because groups were based on the results of applications for exemption from PPI restricted reimbursement (Delate 2005).

Wet nebulizer respiratory therapy: two studies investigated restrictions to reimbursement of wet nebulization respiratory therapy (Kephart 2005; Schneeweiss 2004). Kephart found a decrease (P < 0.001) in general practitioner visits in the wet nebulizer group relative to controls over 23 months of follow up after the PA policy announcement (Kephart 2005). Schneeweiss found no changes in contacts with doctors, admissions to ER or all hospital admissions at six month follow up (Schneeweiss 2004).

Atypical antipsychotic medications: Farley 2008 found an 18% increase in outpatient services in the 14 months following introduction of a restriction to atypical antipsychotic medication and no increase in inpatient or long-term care services (Farley 2008).

DISCUSSION

Summary of main results

We systematically reviewed 29 interrupted time series (12 controlled) of pharmaceutical policies restricting reimbursement for prescribed medications by drug benefit plans. Studies that tracked the impact for up to two years or longer permitted an investigation of the duration of the impact. The impact of reimbursement restriction policies varied among the 11 targeted drug classes investigated and are summarized below by drug class. The settings and populations were predominately publically subsidized drug plans benefiting senior citizens and low income populations. Most policies were 'prior authorization' (PA) policies meaning that the drug benefit plan required physicians to apply for exemption from restriction before permission was granted to have all or part of the cost of the targeted drug paid for by the insurance plan. PA policies serve a 'safety valve' function by providing exceptions which permit reimbursement to the restricted drug when criteria indicating rational use are met. If exemption from the policy is denied (or not sought), an alternative drug with a comparable health benefit is paid for. Patients with sufficient discretionary income may opt to pay for restricted drugs out-of-pocket. Five studies investigated the impact of lifting restrictions to reimbursement policies.

Frequently targeted drug classes

Seventeen of the 29 studies investigated newly implemented restrictions of relatively expensive, high volume new drugs in the NSAID and gastric-acid suppression drug classes in North American settings. Studies consistently demonstrated decreased use of target drugs and related expenditures without changes in the use of other health services that could indicate cost shifting or negative health outcome effects. On the other hand, use of 'other health services' outcome measures might not be sensitive enough to be significantly effected by restrictions to reimbursement policies. None of the studies of policies targeting NSAIDS or gastric-acid suppressants measured health outcomes directly.

Two studies that met all quality criteria and were suitable for reanalysis demonstrated a sustained impact of policies over time, from implementation to two years. The two studies that examined the impact of policies of multiple drug classes including the frequently targeted NSAID and gastric-acid suppression drug classes found that the policies achieved their desired effect of increasing rational use. These were Motheral 2004 (PPIs, NSAIDs, SSRIs) and Hartung 2006 (PPIs, NSAIDS, long-acting opioids, statins). The costs of policy implementation may include the administrative costs of managing change with physicians as well as reconfiguring administrative and information systems. These nontrivial costs were not measured.

Gastric-acid suppressants

For those policies that targeted gastric-acid suppressant drugs, studies consistently supported reduced use of target drugs and substantial savings without changes in utilization of other health services. Marshall 2002 found absolute reductions in DDD of PPIs per 100,000 senior citizens per month of 16% at six months, 26% at

one year and 9% from baseline at 13 to 41 months in the context of reference pricing for the H2RA drug class. Bursey 2000 found a decrease in drug expenditures for third party payers of -85% (95% CI -93% to -78%) at six months, -84% (95% CI -90% to -79%) at 12 months and -79% (95% CI -83% to -75%) at 24 months. Lifting restrictions to gastric-acid suppressants in Denmark resulted in a 62% increase in public expenditure on medications (€7.5 million in 1997 to €12 million in 2005) (van Driel 2008). Six studies that investigated the impact of gastric acid suppressant restriction on other health services (a proxy measure of health outcomes) found no significant change.

Non-steroidal anti-inflammatory drugs (NSAIDs)

For policies targeting NSAIDs, reanalysis of the controlled ITS by Smalley 1995 found an immediate decrease in relative drug use of -23% followed by a 12 month decrease of -21% (95% CI -23% to -19%) and a 24 month decrease of -21% (95% CI -22% to -19%). Other health services use was also examined. The authors report a non significant increase of 3% (-13%, 18%) in outpatient services at 24 months and non significant increases in inpatient expenditures. Reanalysis was able to demonstrate variation of impact on outpatient services within the first year from a 10% decrease immediately after to 11 and 12% increases at 6 and 12 months. The wide 95% confidence intervals around these estimates indicated that they may not be stable estimates if measured repeatedly. Fischer 2004 found that the proportion of NSAIDs accounted for by COX-2 Inhibitors decreased at six months by 11.1% (95% CI -5.7% to -16.5%), with a decrease of -1.6% (95% CI 0.0% to -3.1%) per quarter to 18 months (P = 0.03).

The CITS study by Hartung 2004 of celecoxib restriction found an increase of 18% over six months that was not statistically significant at the pre-determined level of P = 0.01. The COX-2 inhibitor rofecoxib (Vioxx), which was later withdrawn from the market due to its high serious adverse event rate, was included in a number of studies that investigated policies targeting NSAIDs. That raises the possibility that restricting COX-2 inhibitors may have protected patients from adverse events including death. An association between restricted access to COX-2 inhibitors and fewer hospital admissions for gastrointestinal hemorhage was identified by Mamdani 2006 which examined province level data in Canada, however the observational study design precluded causal interpretations and therefore the findings can only be considered as hypothesis generating.

Four studies reported substantial savings with NSAID policy restrictions. Using data from individual US states, Smalley 1995 found a reduction of $11.78/person-year or a relative decrease of 53% (95% CI 48% to 57%) and Hartung 2004 estimated $2.87/person-year (PY) (linear) and $1.40/PY (logarithmic) savings. Using state level data Fischer 2004 found a reduction of $10.28 (95% CI $7.56 to $13.00, P < 0.001) per patient and Roughead 2006 found that the average cost per NSAID prescription was $19 dollars less in states with early policy adoption.

Drug targets with insufficient evidence

Careful selection of the target drug for restriction is important to get the policy results that we have demonstrated for gastric-acid suppressant and NSAID drug classes. Cochrane reviews of NSAIDs (Roelofs 2008) and gastrointestinal drugs (van Pinxteren 2006) for common uses found limited symptomatic (PPIs) or no (NSAID) therapeutic advantage within these targeted drug classes. The available evidence does not adequately document that policy objectives were met for policies targeting antiplatelet drugs, second-generation anti-psychotics and ARBs.

Antiplatelet drugs

Jackevicious 2008 attempted to measure health outcomes, with inconclusive results, following a change from PA to limited-use policy in patients receiving intracoronary stents following myocardial infarction. A Cochrane review by Bosch 2001, updated to 2007, found that the use of antiplatelet drugs following stent implantation significantly reduced death and cardiovascular events. Two other studies of similar limited-use policies did not meet the inclusion criteria for this review (Ackman 2006; Sheely 2008) nevertheless the Canadian provinces that were the settings of this research (Alberta, Ontario and Quebec) have subsequently lifted PA policies for clopidogrel. Ontario, for example, now provides access with a prescription code for indications such as acute coronary syndromes and percutaneous coronary intervention.

Second-generation antipsychotics

The three studies that investigated second-generation anti-psychotic drug restrictions in US Medicaid and Medicare plans did not establish clear savings and raised concerns about possible harm and cost shifting. Each study met six of seven quality criteria. Soumerai 2008 found a trend towards increased treatment discontinuity (evidence of a gap in therapy, switching to or augmentation with another antipsychotic) however the analysis was underpowered because the policy was cancelled before sufficient data had been accumulated to provide statistically significant results. Farley 2008 found an 18% increase in outpatient services (95% CI 1.1 to 1.2%, P < 0.001) but no change in inpatient and long-term care services at 14 months post-implementation. Farley 2008 also noted a relative decrease in expenditures for the second-generation antipsychotic drugs themselves while Law 2008 demonstrated that the policy did not reduce overall drug dispersements because the alternative drugs used were also expensive. A primary concern is that PA policies may pose a barrier to treatment that a severely mentally ill patient may have difficulty negotiating. The evidence from Cochrane reviews does not endorse a clear therapeutic advantage to all second-generation antipsychotics. Hunter 2003, for example, cautions that any ‘marginal benefit’ the second-generation anti-psychotic drug risperidone may have over first-generation antipsychotic drugs for schizophrenia must be weighed against adverse events such as weight gain. Also, the manufacturer's evidence of long-term favorable effects on relapse needs replication by independent researchers (Hunter 2003).

Angiotensin-receptor blockers (ARBs)

Only one US state level study on restriction of ARBs used for hypertension met the inclusion criteria. Fischer 2007 reported no statistically significant change in ARB use as a proportion of RAAS blocking drugs in states with PA policies unless an ACE inhibitor trial was required first (Fischer 2007). Given the importance of hypertension control over the lifespan and the need to use multiple medications to control hypertension as well as gaps in evidence and evolving guidelines, this review has not found sufficient evidence to support policies restricting reimbursement of this drug class. The strategy of lifting restrictions for first-line therapy is an alternative strategy (see discussion of Fretheim 2007 below).

Relaxing restrictions or exempting drugs from restrictions for secondary prevention

Two scandinavian countries with national drug plans covering all citizens were the settings of studies investigating the impact of lifting restrictions to reimbursement for drugs to increase their use for secondary prevention. A Cochrane systematic review has verified that thiazides are the most effective first-line drug for uncomplicated high blood pressure and are also relatively inexpensive (Wright 2009). Norway effectively lifted all reimbursement restrictions for thiazides by making it the only reimbursable drug for first-line treatment. Fretheim 2007 found that this policy increased thiazide use, as a proportion of newly prescribed antihypertensive drugs, by 16.5%. This resulted in savings in the first year of US$ 0.72 million, with no statistically significant change at four months in the proportion of patients who met blood pressure reduction treatment goals or who started a second antihypertensive drug. Norway also introduced regulations making only one statin (generic simvastatin) available without PA for blood cholesterol lowering (Sakshaug 2007). This resulted in increased statin use of 8.1% in men and 6.8% in women, with approximately 20% reduction in costs for this drug class. Denmark lifted a PA policy for lipid lowering drugs prescribed for secondary prevention and also reported increased use of these agents (Bjerrum 2001). The strategy of lifting restrictions would appear to be promising for channeling drug use in alignment with rational prescribing objectives.

Less frequent targets

Fluroquinolone antimicrobials

Concerns about overuse of fluroquinolones and resistance to these broad spectrum antibiotics have lead Canadian provincial drug plans to restrict their use as first-line treatment (Drug Quality and Therapeutic Committee 2001). In Nova Scotia, MacCara 2001 found a desired decrease in fluoroquinolone claims of 80% and a relative cost decrease of 24% over one year, with a concurrent media campaign. In Ontario, Marshall 2006 also found decreased use but after adjustment for overall trends the relative 13% decrease in fluroquinolone expenditures was completely offset. More rational prescribing objectives were achieved but without savings.

Wet nebulizer respiratory drugs

Drug benefit plans following clinical practice guidelines have restricted wet nebulizers for adults with chronic asthma or chronic obstructive pulmonary disease because they are relatively more expensive, less portable and are associated with more bacterial contamination than inhalers (Dolovich 2005). Two studies found restriction to reimbursement policies decreased their use and increased savings with no increase in other health service utilization, as might occur with cost shifting or a negative health impact.

Modifying effects

The restriction to reimbursement policies investigated in the set of studies included in this review are most commonly known as prior authorization or PA policies. How PA policies were implemented and routinely managed varied between settings and study reports were generally lacking in descriptive details of administrative processes and procedures. In general, administrative and implementation policies were not described in sufficient detail however there was evidence from accompanying subgroup analyses (not necessarily meeting inclusion criteria or risk of bias criteria as the main measures did) that the following features were effect modifiers.

Roughead 2006 found that early implementation (at the time of market entry) had a greater impact than late implementation, after a new drug had been on the market for two years or more. Fischer 2007 and Motheral 2004 found stepped approaches that required a trial of a non-restricted drug before reimbursement were more effective. Carroll 2006 found that automating PA systems at the point of sale enhanced the effect.

Bjerrum 2001, Bursey 2000, Keith 1994 and Kephart 2005 partially credited concurrent physician education for the impact obtained. Morden 2008 reported that stricter policies lead to a greater effect and Hartung 2006 found educational strategies worked better than voluntary compliance or no enforcement. Conversely, Fischer 2004 found that programs that incorporated evidence-based prescribing recommendations had no modifying effect.

The use of PA policies with other pharmaceutical policies may also modify their effect. For example, the study by Marshall 2002 provides findings on the impact of PA for PPIs in the context of reference pricing policies for H2RAs showing increasing impact as PA policies were added (Marshall 2002). Multi-component policies are to be examined in another Cochrane review in the pharmaceutical policy series.

Overall completeness and applicability of evidence

This body of evidence does not directly investigate the health effects of treatment changes. Only two of the studies included in this review reported health outcome data, precluding any conclusions about the impact of PA policies on patient outcomes. This suggests a significant gap in knowledge in the data emanating from studies of policies that restrict reimbursement.

The administrative health datasets which provided the data for these ITS analyses generally do not track health outcome data. Routinely linking measures of health outcome to administrative datasets would increase their usefulness for this type of research. Changes in other health services utilization were used as a convenient proxy for health outcomes as a type of sentinel pharmacosurveillance method. An increase in 'other related health services' would indicate cost shifting or unexpected adverse health outcomes. On the other hand, use of other health services might not be sensitive enough to be significantly effected due to the changed reimbursement policy. When the underlying primary clinical trial data and post-market safety data support the relative efficacy of drugs that are used interchangeably, not directly measuring health outcomes may be justified. When drugs are less interchangeable the impact on health outcomes should be evaluated before widespread adoption of restriction to reimbursement policies. 'Coverage with evidence development' research may be appropriate if there is insufficient post-market experience to establish the harm profile of new drugs and the impact of restriction to reimbursement policies in real world settings.This gap could also be filled by conducting primary health outcomes research and linking it to administrative data on utilization and cost.

It is perhaps not surprising that policies that restrict reimbursement reduce drug usage and drug expenditures in targeted classes, however it is not known whether these policies impact on the health of the patient or the frequency with which they access the

healthcare system. One of the major arguments against policies that restrict reimbursement is that they may limit or delay treatment and adversely impact on the health of the patient, leading to increased utilization of the healthcare system and completely offsetting any cost savings that might have been achieved by the policy. As policymakers consider increasing their use of restrictions to reimbursement policies to mitigate the impact of rising drug prices, studies that report on the overall budget impact of such policies will become increasingly important.

The influence of the pricing strategies of the pharmaceutical industry within the drug classes requiring restriction to reimbursement is an important consideration related to the importance and relevance of PA to the decision maker. PA policies were established due to the higher cost of these drug classes compared to the first-line therapies. In addition, pricing differences within the classes led to the establishment of reference pricing policies. Subsequently, the pricing policies of manufacturers within new drug classes have minimized any differences, therefore minimizing the cost saving value of these policies other than to restrict, control or discourage the use of the entire class of drugs. In this new environment, policy makers have updated their cost management strategies from reference drug pricing and PA to negotiated or competitive pricing strategies that reduce the net price to payers. The manufacturer with the lowest price in a competitive environment may get preferential, if not exclusive, listing in the formulary. The preferred drug, available through general availability rather than PA, is now determined by the best negotiated price rather than the list price.

Equity outcomes have not been explicitly measured. The evidence is however predominantly from publicly funded drug benefit plans. These plans are instituted to relieve senior citizens and low income groups of the costs of medications that they would not otherwise be able to afford, therefore, the policies of restriction to reimbursement have the potential to have consequential equity impacts. They may preserve access to necessary medications by reducing the excessive costs associated with medications that do not provide any benefit over less costly alternatives. Where medications do not have an equivalent, cheaper substitute, restrictions may have negative health impacts.

It is also likely that restrictions to reimbursement policies could disadvantage patients deferentially depending on their abilities to access or understand information about the implication of restrictions on their medical care as well as to and effectively interact through physicians to ensure that they have access to optimal treatment.

There are other detailed measures of drug use that were not measured, such as the impact on medication adherance, persistence, switching and discontinuation. To the extent that these may be important to achieve optimal health outcomes they could also be measured. Finally, the majority of studies came from North America, therefore the findings may not be generalizable to healthcare systems that are differently configured.

Quality of the evidence

Overall, the included studies represent a body of evidence with good protection against bias, provided by the study design employed, for the outcomes of drug use and drug cost (expenditures). Seven studies met all quality criteria (Bursey 2000; Fischer 2004; Kephart 2005; Marshall 2007; Sakshaug 2007; Schneeweiss 2006; Smalley 1995). Four studies did not meet two or more criteria. The remainder did not meet one criteria. Only two studies attempted to measure health outcomes and both analyses had major limitations.

The one RCT that was identified was not included as the randomization process had been disrupted. Although RCTs are rarely used to evaluate pharmaceutical policy impacts, they are the gold standard design for determining causal associations. Well done trials could reduce the risk of bias, and could perhaps be done more quickly and efficiently than observational studies (Schneeweiss 2004a), especially to evaluate health and health care utilisation outcomes.

Many studies did not report baseline characteristics, highlighting that clearer reporting is important for future research. Studies that measured health services utilization outcomes were fewer in number and most did not track service utilization serially over many time intervals. Instead, the data were summarized at various intervals following policy implementation. An exception is provided by a small set of re-analysed studies that followed changes in level from the immediate post-implementation period to two years for drug use, cost and health services outcomes.

A limitation of the evidence base for restriction to reimbursement policies is the diversity of drugs and related conditions that have been targeted by restrictions to reimbursement policies as compared to the number that have been subject to rigorous evaluation.

Potential biases in the review process

Changes over time are of interest as restrictions to reimbursement could produce savings in drug expenditures but increase the use of and costs to the healthcare system overall through changes in health services utilization immediately and over longer periods of time. Health services utilization outcomes included expenditures and utilization of outpatient physicians, non-physician healthcare providers, ER visits, diagnostic and screening tests as well as inpatient acute care hospital and long-term care use. The two studies that measured health outcomes provide inconclusive results. Longer-term studies, studies measuring health outcomes directly and studies that explicitly use equity outcomes as well as better standardized pharmaceutical policy intervention designs would support more robust conclusions.

Agreements and disagreements with other studies or reviews

The number of studies on restriction to reimbursement policies has increased rapidly in recent years. A systematic review by Puig-Junoy, published in 2007, included only 30% of the studies included in this Cochrane review. That review included studies that did not meet the selection criteria of our review (six before-after studies without control groups) and excluded studies published before 2006 that our search picked up (Puig-Junoy 2007). Our reviews are in agreement that drug use and expenditure significantly decrease without change in utilization of other healthcare services and that health outcomes have not been directly evaluated. We limit the generalizability of these conclusions to circumstances where drugs are interchangeable. We would also agree that outcome measures require improvement, in particular through standardization. Puig-Junoy noted the small number of drug classes that had been reviewed. While the number has increased to 11 in this review, many drug classes that have not been evaluated as targets, and therefore application of restrictions, do not have evidence of effectiveness.

There were a number of studies included in this review that looked at medium (24 months) if not longer-term policy effects, as Puig-Junoy recommended.

AUTHORS' CONCLUSIONS

Implications for practice

•	Prior authorization policies are an acceptable component of pharmaceutical plans that seek to influence prescribing behaviour so that the right drug is used for the right problem. Designed appropriately, it would appear that PA policies can support sustainability of drug benefit plans and thereby preserve access to necessary drugs for low income populations
•	When drugs are interchangeable, restrictions to reimbursement policies decrease prescription drug utilization and costs for the targeted drugs often without increases in the utilization of other health services however this proxy for health outcomes may not be sensitive enough to detect all important impacts
•	Results may not be generalizable beyond the drugs that are most easily interchangeable, like NSAIDs and PPIs. Selection of drugs for restriction or removal should be based on the clinical attributes of the drug class and properly designed interrupted time series evaluation is important to measure impact
•	Application for exemption from restrictions to reimbursement provides a 'safety valve' allowing access to restricted drugs under some circumstances thereby maintaining a range of therapeutic options and facilitating acceptance by physicians and patients
•	Relaxation of or exemption from reimbursement restriction policies for drugs that are useful for secondary prevention and under-used drugs increase appropriate use and produce more modest savings
•	High quality studies with measures of health outcomes are few and, where available, are inconclusive highlighting the requirement that restrictions be solidly based on clinical trial and and pharmacosurveillance studies

Implications for research

•	The adoption of restriction to reimbursement policies for less interchangeable drugs and drugs for non-symptomatic conditions should be accompanied by impact evaluations
•	More rigorous study designs including randomization with implementation delays, health outcome evaluation, reporting of baseline characteristics, measurement over longer time periods and in a greater range of settings and drug classes as well as in combination with other pharmaceutical policies are appropriate

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bjerrum 2001

Methods	Equivalent to ITS with monthly incidence rates calculated using an epidemiology approach
Participants	County of Funen, Denmark, n=470,000 inhabitants
Interventions	Release of restriction to prescribing lipid lowering drugs (LLD) to encourage use for secondary prevention. After policy date there was no need for special authorization to recieve reimbursement for LLD with known coronary heart disease (CHD), inherited hyperlipidimia, high cholesterol and concurrent important risk factors for developing CHD.
Outcomes	Incidence and annual prevalence rate of LLD use
Notes	Included as tracks lipid lowering drugs usage 5 years prior to implementation and 12 months after policy implementation

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Odense University Pharmacoepidemiological Database covers whole population of the county with an age sex distribution corresponding to the Danish population.
Selective reporting (reporting bias)	Low risk	Incidence and prevalence rates for all years calculated
Other bias	Low risk	No other bias detected
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	Low risk	Reviewers note that published educational guidelines on the prevention of CHD were part of intervention. The authors describe this as a mixed intervention combining guidelines with changes in reimbursement however an integral part of most implementations is providing prescribers with guidelines so this could be interpreted as a difference in intensity. The authors also report that ' local medical journals had an increased focus on the subject at the time of intervention.'
The shape of intervention pre-specified?	Unclear risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time

Bjerrum 2001 *(Continued)*

Intervention unlikely to affect data collection?	Low risk	Sources and methods of data collection were the same before and after the intervention

Bursey 2000

Methods	ITS in 6 month intervals
Participants	Newfoundland and Labrador drug subsidy program for seniors ≥ 65 years: 1996 n=117,637; 1997 n=11403, 1998 109797; (population decrease of 6%)
Interventions	Special authorization policy implemented July 1, 1996 for PPIs famotidine and nizatadine
Outcomes	Drug use and drug costs
Notes	Follow up 6 months after policy implementation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any undocumented difference in the proportion of missing data in the administrative datasets pre- and post-intervention is unlikely to overturn study results
Selective reporting (reporting bias)	Low risk	All outcomes listed in the methods section are reported in the results section
Other bias	Low risk	Drop of 6% in plan enrollment noted but unlikely to overturn study results
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of health care utilization
Intervention independent of other changes	Low risk	Reviewers note that implementation intensity was increased through the distribution of algorithms for the management dyspepsia and gastroesophogeal reflux distributed to all physicians and pharmacists
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	"analysis of DHCS (Department of Health and Community Services) database" (p 820) Sources and methods of data collection were the same before and after the intervention

Carroll 2006

Methods	ITS with monthly data points and no transition period
Participants	Fee-for-service (FFS) plan members in Missouri Medicaid program n=42,262

Carroll 2006 *(Continued)*

Interventions	Automated PA program for COX-2 inhibitors
Outcomes	Drug costs - figure
Notes	Baseline period was 12 months immediately preceding intervention and post intervention period was 12 months after date of implementation. Controlled Before After (CBA) analysis did not meet selection criteria and therefore drug use data was not included.

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any undocumented difference in the proportion of missing data in the administrative datasets pre- and post-intervention is unlikely to overturn study results
Selective reporting (reporting bias)	Low risk	All use and cost outcomes from methods section reported in findings
Other bias	Low risk	No bias detected that pertained to the ITS data presented in figure
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of health care utilization
Intervention independent of other changes	Low risk	Known and unknown changes in the environment are unlikely to be responsible for sudden change and magnitude of effect size
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time (time series data provided).
Intervention unlikely to affect data collection?	High risk	Intervention aimed at better implementation through better data collection at the point of sale source.

Delate 2005

Methods	ITS calculated on a per month per member basis
Participants	Plan members in medicaid program n=1,142,866 to n=1,324,643 during 24 month study period
Interventions	PPI PA program
Outcomes	Drug use, health services utilization, drug costs
Notes	Data collected 12 months prior and 12 months post-implementation. Time series consisted of 24 PMPM (per member per month) for PPI and H2RA expenditures

Risk of bias

Bias	Authors' judgement	Support for judgement

Delate 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Any undocumented difference in the proportion of missing data in the Medicaid administrative datasets pre- and post-intervention is unlikely to overturn study results
Selective reporting (reporting bias)	Unclear risk	It is not clear whether the restriction of the analysis to charges that were at lease partially reimbursed to the extent to which they were reimbursed introduced a selective reporting bias
Other bias	High risk	New claims for PPIs were not separated from renewals so the before-after comparison is confounded by the indication. New claims would be triggered by sickness just before. The ratio of new to continuing users might differ between the 3 groups. People with Helicobacter infection were granted 1-month of PPI. PPI users were more likely to have a gastro intestinal (GI) diagnosis and GI screening that H2RA users or non-users
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of health care utilization
Intervention independent of other changes	Low risk	Known and unknown changes in the environment are unlikely to be responsible for sudden change and magnitude of effect size
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	Sources and methods of data collection were the same before and after the intervention

Farley 2008

Methods	Controlled ITS measured per member per month
Participants	Intervention: Georgia N=5178 Medicaid members n=984,843; control: Mississippi members N=2218 (no restriction) Medicaid members n= 434,782
Interventions	To document effect of step therapy PA policy for atypical antipsychotics
Outcomes	Health services utilization, drug costs
Notes	Jan 1-1996-Dec 31 1997 modeled 10 months pre-policy, 11 months policy period (long transition period), 3 months post-policy

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any undocumented difference in the proportion of missing data in the administrative datasets pre- and post-intervention is unlikely to overturn study results
Selective reporting (reporting bias)	Low risk	All outcomes listed in the methods section are reported in the results section

Farley 2008 *(Continued)*

Other bias	Unclear risk	Unclear as it is difficult to evaluate model assumptions Dementia was included as a condition of interest (along with schizophrenia, bipolar, depression and other mental health conditions) even though antipsychotics are not recommended in dementia, because they are commonly used to control symptoms.
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	Unclear risk	"Our study examined a period of adoption for atypical antipsychotic medications. The atypical antipsychotic olanzapine, for example, was approved by the US Food and Drug Administration during the prepolicy period shortly before the policy was enacted."
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	Sources and methods of data collection were the same before and after the intervention

Fischer 2004

Methods	Controlled ITS with quarterly data points
Participants	50 Medicaid programs in 22 states
Interventions	PA policy for COX-2 inhibitors
Outcomes	Drug use and drug costs
Notes	Policies classified based on 5 cinical risk factors for gastrointestinal adverse effects: More strict ≥4 gastrointestinal complicatons, and patients have a history of GI complications from NSAIDS, Strict ≥4 gastrointestinal, all others defined as less restrictive

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any undocumented difference in the proportion of missing data in the administrative datasets pre- and post-intervention is unlikely to overturn study results
Selective reporting (reporting bias)	Low risk	All outcomes listed in the methods section are reported in the results section
Other bias	Unclear risk	"States with prior-authorization programs may have differed systematically from states without such programs in ways not captured by our data, since states with these programs had slightly lower rates of coxib use before the programs were implemented. Patterns of NSAID prescribing for Medicaid beneficiaries appear to have similar variability, even independent of the effects of prior-authorization programs, and should be a target of subsequent studies."

Fischer 2004 *(Continued)*

Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	Low risk	Known and unknown changes in the environment are unlikely to be responsible for sudden change and magnitude of effect size
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	Sources and methods of data collection were the same before and after the intervention

Fischer 2007

Methods	Controlled ITS with quarterly data points
Participants	Intervention: n=19 state Medicaid programs with PA for ARBs before 3rd quarter of 2004, Control: n=18 states without PA
Interventions	PA policies on the use of ARBS
Outcomes	Drug use, drug costs
Notes	States very as to how strictly the policy was implemented. As well some states have rebate arrangements. These differences explain some of the variability.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any undocumented difference in the proportion of missing data in the administrative datasets pre- and post-intervention is unlikely to overturn study results.
Selective reporting (reporting bias)	Low risk	All outcomes listed in the methods section are reported in the results section
Other bias	Low risk	No evidence of other risk of bias including seasonality.
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	Unclear risk	Total prescribing for hypertension in Medicaid more than doubled from 1996 to 2005, from about eight million prescriptions per quarter to more than 17 million.
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time peri-

Fischer 2007 *(Continued)*

		ods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	Sources and methods of data collection were the same before and after the intervention.

Fretheim 2007

Methods	Controlled ITS with monthly data ponts
Participants	All patients in 3 groups of general practice sites in and around Oslo Norway n=61 practices:1. practices randomized to guideline intervention, 2. practices in the control group, 3. practices that did not participate in the trials
Interventions	Thiazides made the only reimbursable drug for non-complicated hypertension. Documenting a reason for prescribing non thiazides in the medical record was the only requirement to prescribe an alternate drug.
Outcomes	Patient health outcomes, drug use, drug costs
Notes	Incorported a transition period from Dec 2003 to Feb 2004 with 11 monthly measurements before and after the intervention period

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data from 3 practices excluded due to technical difficulties
Selective reporting (reporting bias)	Low risk	Change from protocol documented and reasonable
Other bias	Unclear risk	We do not know how representative the study practices are of general practices in Norway. Almost 40% of the invited practices did not agree to participate in our study, and this may have introduced some degree of bias.
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	Low risk	Changes in policy and market environment (changes in drug prices) a consequence of the policy and not bias.
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	Sources and methods of data collection were the same before and after the intervention

Grootendorst 2005

Methods	ITS monthly data points
Participants	Senior beneficiaries in provincial drug benefit plan, British Columbia, Canada
Interventions	Type 2 reference pricing for first line restricted non-steroidal anti-inflammatory drugs (NSAIDs) (different NSAIDs considered interchangeable)
Outcomes	Drug costs, drug use
Notes	Pharmacare data aggregated from Feb 1993 to June 2001

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any undocumented difference in the proportion of missing data in the administrative datasets pre- and post-intervention is unlikely to overturn study results
Selective reporting (reporting bias)	Low risk	All outcomes listed in the methods section are reported in the results section
Other bias	Low risk	No evidence of other risk of bias including seasonality.
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	Unclear risk	A moderate upward trend in use of opiates that was almost a mirror image of the decline in NSAID use from 1998 to 2001.
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	Sources and methods of data collection were the same before and after the intervention however the introduction of PharmaNet at the same time as RP (in Sep 95) caused better capture of drug claims because it eliminated the need for seniors to mail in their drug claims.

Hartung 2004

Methods	Controlled ITS with monthly data points
Participants	Intervention group Medicaid managed care organization (MCO): 1999: n=74,866 patients, 200: n=91,816; control group (fee for service): 1999:n=110,076, 2000: n=153,784. Control group: members of the same MCO with past NSAID or COX2 use and continuous enrollment
Interventions	PA policy for celecoxib
Outcomes	Drug use, health servics utilization, drug costs

Hartung 2004 *(Continued)*

Notes	No notification to physicians and payments as to when the policy implemented.

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any undocumented difference in the proportion of missing data in the administrative datasets pre- and post-intervention is unlikely to overturn study results
Selective reporting (reporting bias)	Unclear risk	All outcomes listed in the methods section are reported in the results sections
Other bias	Unclear risk	Control population consisted of patients who were generally older and likely to be more severely ill which would tend to increase drug use
Knowledge of allocated interventions adequately prevented during the study	Low risk	Data objective: All Medicaid claims for patients in CareOregon and in a Medicaid fee-for-service program were reviewed.
Intervention independent of other changes	Low risk	Known and unknown changes in the environment are unlikely to be responsible for sudden change and magnitude of effect size
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	Sources and methods of data collection were the same before and after the intervention

Hartung 2006

Methods	ITS monthly data points
Participants	129, 021 patients enrolled in a fee for service Medicaid plan
Interventions	Reimbursement restrictions on PPI, NSAIDS, long-acting opioids and statins - compare 'dispense as written' policy, soft PA (had to listen to comparative evidence message), and voluntary period
Outcomes	Drug costs
Notes	Analyzed prescription drug claims from Jan 2001 (pre-policy) to June 2004, 1 month transition period and 3 consecutive policy periods

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any undocumented difference in the proportion of missing data in the administrative datasets pre- and post-intervention is unlikely to overturn study results

Hartung 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes listed in the methods section are reported in the results section
Other bias	Unclear risk	"In January 2003, in the midst of a major budget shortfall, the OHP reorganized its Medicaid program into two distinct benefit packages that differed in benefit structure: Oregon Health Plan (OHP) Plus and OHP Standard. To minimize the confounding effects of this policy, we excluded all OHPStandard benefit recipients from our analysis."...Co-payment introduced January 2003 may have added to impact on Statin use
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	Unclear risk	Authors report that the "The (formulary) list was dynamic and was evaluated similarly."
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	Sources and methods of data collection were the same before and after the intervention

Hazlet 2002

Methods	Controlled ITS with monthly data points
Participants	Senior beneficiaries in provincial drug benefit plan, British Columbia, Canada Random sample of 10,000 seniors exposed to reference drug pricing followed for 21 months - 9 months before reference pricing and 12 months after implementation Control was 10,000 members whose 21 months of observation preceded reference pricing
Interventions	Special authority for PPIs (reference pricing for H2RAs)
Outcomes	Health services utilization
Notes	No transition period

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any undocumented difference in the proportion of missing data in the administrative datasets pre- and post-intervention is unlikely to overturn study results
Selective reporting (reporting bias)	Low risk	All outcomes listed in the methods section are reported in the results section
Other bias	High risk	Modeling assumptions are strict and unrealistic. Raw data not shown

Hazlet 2002 *(Continued)*

Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	Low risk	Use of closest cohort in time an attempt to protect against secular change Reference based pricing for H2A implemented at same time as PA for PPIs
The shape of intervention pre-specified?	Low risk	The date the policy intervention was implemented was used to delineate pre and post policy time periods. Raw data points on outcomes were not shown, only the fitted estimates
Intervention unlikely to affect data collection?	Low risk	Data collection was mostly the same before and after except that PharmaNet introduction coincided with this policy. Some of the continuing growth of costs might have been due to more complete submission of reimbursement claims.

Jackevicious 2008

Methods	ITS with monthly data points
Participants	N=6161 who received a PCI with coronary stenting during hospitalization in Ontario
Interventions	Change in a PA policy to a limited use policy allowing for use of clopidogrel for approved indicatons according to pre-specified prescribing codes
Outcomes	Health: composite rate of readmission for myocardial infarction, death, repeat percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG) within 1 year of discharge, rates of death from any cause and major bleeding, drug use
Notes	Baseline characteristics differed: during the limited use period, patients had lower rates of aspirin use and higher rates of statin use (increase from 63% to 80% P<0.001)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any undocumented difference in the proportion of missing data in the administrative datasets pre- and post-intervention is unlikely to overturn study results
Selective reporting (reporting bias)	Low risk	All outcomes listed in the methods section are reported in the results section
Other bias	Low risk	No evidence of other risk of bias including seasonality.
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	High risk	"There were some differences in baseline characteristics between patients in the prior-authorization period and those in the limited-use period. In particu-

Jackevicious 2008 *(Continued)*

		lar, during the limited-use period, patients had lower rates of aspirin use and higher rates of statin use"
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	Sources and methods of data collection were the same before and after the intervention

Keith 1994

Methods	ITS with monthly data points
Participants	Texas Dept of Criminal Justice Institutional Division 1991: n=46,762, 1992: n=50,740
Interventions	Formulary H2RA program to limit duration of treatment dosages and promote maintenance therapy in appropriate individuals
Outcomes	Drug use, health services utilization, drug costs
Notes	Drug use evaluation (DUE) completed in May 1991, program implemented Nov 1991, follow-up DUE completed in May 1992, no transition period

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any undocumented difference in the proportion of missing data in the administrative datasets pre- and post-intervention is unlikely to overturn study results Non-prescription medication not maintained on automated system.
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Number of upper gastrointestinal studies decreased by 5.7% - appropriateness of diagnostic studies unknown.
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization Approvals done on automated system
Intervention independent of other changes	Low risk	Changes occurred in duration of inmate stays and total number of inmates (8% increase) however this would tend to produce an increase in the use of restricted drugs not a decrease as observed
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time

Keith 1994 *(Continued)*

Intervention unlikely to affect data collection?	Low risk	Sources and methods of data collection were the same before and after the intervention Pre-defined criteria and authorization communicated by computer to regional pharmacies

Kephart 2005

Methods	Controlled ITS with monthly data points
Participants	Nova Scotia Seniors' Pharmacare Program: ≥ 65 years N=21,864 received at least one prescription for inhaled repiratory drugs; n=5129 with one prescription for wet nebulization therapy, 108,160 beneficiaries from 1998–1999, 103,400 from 1999–2000, and 95,550 from 2000–2001
Interventions	PA policy requiring specific criteria to be met for utilization of wet nebulizer therapy
Outcomes	Drug use, health services utilization
Notes	Study period April 1998–February 2002, 6 month transition (policy intervention) period

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Low risk	Rates were adjusted for loss to follow up due to death, migration, and dropping out of the program.
Selective reporting (reporting bias)	Low risk	All outcomes listed in the methods section are reported in the results section
Other bias	Low risk	No evidence of other risk of bias including seasonality
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	Low risk	Known and unknown changes in the environment are unlikely to be responsible for sudden change and magnitude of effect size
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	Sources and methods of data collection were the same before and after the intervention

Law 2008

Methods	Controlled ITS with quarterly data points

Law 2008 *(Continued)*

Participants	Intervention: West Virginia and Texas Medicaid programs; control: weighted average of 38 states with no PA
Interventions	PA policies for 2nd generation antipsychotics
Outcomes	Drug Use, drug costs
Notes	Assessed national trends in prescribing and utilization by calculating expenditures and dosing from 1991-2005

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	"we have some concerns about the data for total reimbursement in West Virginia. Figure 3 shows that despite a consistent trend, reported reimbursements varied significantly between quarters."
Selective reporting (reporting bias)	Low risk	All outcomes listed in the methods section are reported in the results section
Other bias	Low risk	"Texas and West Virginia may not be representative of the experience in other states and may differ in their authorization criteria, drugs covered, and implementation. However, given the broad geographic dispersion and differing population sizes, we feel that the consistency of results is important.Moreover, the drugs typically subject to PA in other state programs are similar to those in the study states."
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	Unclear risk	Known and unknown changes in the environment are unlikely to be responsible for sudden change and magnitude of effect size
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	Sources and methods of data collection were the same before and after the intervention

MacCara 2001

Methods	ITS with monthly data points
Participants	Nova Scotia Seniors' Pharmacare Program: 1995/96: n=107,827, 1996/97: n=10,707, 1997/98: n=107,668
Interventions	Indications had to meet specific criteria for prescription to be filled for reimbursement for fluroquinolones
Outcomes	Drug use, drug costs

MacCara 2001 *(Continued)*

Notes	Included 1-12 month periods prior to policy (Dec 1994-Nov 1996), Policy implementation Dec 1-31 1996. On march 1 1998 policy changed and physicians could write specific indication and criteria on prescription slip, Transition period Dec 1, 96 to Feb 28 '97, Post policy analysis to Dec 31 1998. Analysis is confounded by simultaneous publicity campaign on antibiotic resistance.

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any undocumented difference in the proportion of missing data in the administrative datasets pre- and post-intervention is unlikely to overturn study results
Selective reporting (reporting bias)	High risk	
Other bias	High risk	Seniors who opted to pay out-of-pocket for a fluoroquinolone were not included in the study
Knowledge of allocated interventions adequately prevented during the study	Low risk	Data objective: the administrative drug claims database of the Nova Scotia Senior's Pharmacare Program (NSSPP)
Intervention independent of other changes	High risk	A coalition of medical organizations started a national campaign to combat the misuse of antibiotics and heighten the awareness of the Canadian public to the dangers of antibiotic resistance within weeks of the policy introduction. Seasonal bias may also have occurred pre and post as the policy implementation date was December 1st when infectious diseases are on the rise going into winter.
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	Sources and methods of data collection were the same before and after the intervention

Marshall 2002

Methods	ITS with monthly data points
Participants	Senior beneficiaries in provincial drug benefit plan, British Columbia, Canada
Interventions	PA policies for PPIs in the context of reference based pricing of H2RAs
Outcomes	Drug use, drug costs
Notes	Analysis from January 1993-May 1999

Risk of bias

Bias	Authors' judgement	Support for judgement

Marshall 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Any undocumented difference in the proportion of missing data in the administrative datasets pre- and post-intervention is unlikely to overturn study results notwithstanding that differences in completeness of data may have varied over time as a new administrative drug database was implemented coincident with the policy under evaluation
Selective reporting (reporting bias)	Low risk	All relevant outcomes listed in the methods section are reported in the results section
Other bias	Unclear risk	"The reasons for the observed growth in PPI use are unclear and are beyond the scope of this analysis." Overall trends in the drug market could have been examined with data from another province as a control.
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	Low risk	Known and unknown changes in the environment are unlikely to be responsible for sudden change and magnitude of effect size All prescriptions for PPIs issued by gastroenterologists were automatically exempted from the special authority policy.
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	Aggregate monthly claims data for H2RAs, PPIs, sucralfate, prokinetic agents and misoprostol were provided by British Columbia Pharmacare for the period January 1993 to May 1999, inclusive, to cover periods before and after introduction of the reference-based pricing and special authority policies

Marshall 2006

Methods	ITS with weekly data points
Participants	Ontario Drug Benefit (ODB) benficiaries
Interventions	Reimbursement of 2 fluoroquinolone antibiotics, ciprofloxacin and ofloxacin limited to beneficiaries for whom second line antibiotics were indicated
Outcomes	Drug use, drug costs
Notes	Data from Jan 1999 to Sep 2002, policy implemented Mar 4 2001

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	First, antibiotic groups were specified based on the active ingredient, irrespective of manufacturer, dosage form, or strength, and were not adjusted to account for formulation or dosing regimen using defined daily doses. Measurement of drug use in this study was measured by the number of prescription

Marshall 2006 *(Continued)*

		claims, because this is the approach used by the Ontario Ministry of Health in its annual update on the ODB programme
Selective reporting (reporting bias)	Low risk	All outcomes reported: The model results for antibiotic expenditures generally reflect the results for antibiotic use. There was a statistically significant decrease in expenditures for ciprofloxacin and the fluoroquinolone group and an increase for Trimethoprim-sulfamethoxazole (TMP/SMX) and nitrofurantoin, but no change in overall antibiotic expenditure.
Other bias	Low risk	Although antibiotic use and expenditures were expected to change during the month the policy was implemented, the data were tested for breaks at other ates. Failure to account for the presence of other breakpoints might bias the estimates of the policy implementation indicator variable.
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes objective: Our objective was to determine the impact of this policy on the volume and cost of antibiotic prescribing.
Intervention independent of other changes	Unclear risk	Second, it is possible that the changes in antibiotic use and expenditure were due to factors other than the implementation of the LU policy....The lack of cost savings could be explained by higher utilization of more costly drugs, more repeat prescriptions, or the use of drugs requiring longer duration of therapy.
Intervention unlikely to affect data collection?	Low risk	Data objective: weekly data on the prescribing volumes and expenditures (excluding dispensing fees) on individual antibiotics reimbursed by the ODB were analysed from January 1999 to September 2002.

Marshall 2007

Methods	Controlled ITS with monthly data points
Participants	Seniors ≥ 65 years (provincial drug plan beneficiaries) in Quebec (control), Ontario and British Columbia (interventions)
Interventions	Effects of different reimbursement policies on the use of COX-2 inhibitors, NSAIDS, and gastrointestinal protective agents
Outcomes	Drug use
Notes	Quebec: no restrictions, Ontario: submit indication with prescription, British Columbia: request PA

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Low risk	Our study spanned a period of 5 years. This provides a sufficient number of observations in both the pre-coxib and post-coxib time periods to capture meaningful trends and avoid spurious spikes in the data.
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No other bias detected.

Marshall 2007 *(Continued)*

Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes objective: how do these different prescribing restrictions affect the uptake and expenditures on COX-2 inhibitors? Is Ontario's Limited Use policy an effective deterrent to the prescribing of COX-2 inhibitors? To what extent are increased coxib expenditures in jurisdictions which do not restrict their use (Quebec) offset by reductions in gastro-protective agent (GPA) expenditure?
Intervention independent of other changes	Low risk	"The Therapeutics Letter was found to have shifted prescribing an average of 30% from baseline according to an aggregate analysis of 12 letters using randomised controls [24]. Four letters were published during the period between 1999 and 2004 [25–28], the first of which pointed to the lack of published clinical data on coxib effectiveness and the other three which focused on serious adverse events associated with COX-2 inhibitors (fewer gastrointestinal events, but more myocardial infarctions)." Nonetheless, the strong temporal correlation between the introduction of administrative restrictions for COX-2 inhibitors, and the lack of other trends to explain the change in NSAID utilisation, support our findings. In all three jurisdictions, the policy environment for pharmaceuticals as stable over the observation period. There were no significant changes in the insurance environment that would be expected to have had an effect on uptake of NSAIDs.
Intervention unlikely to affect data collection?	Low risk	Aggregate data on anti-inflammatory and GPA use between April 1997 and December 2002 were obtained from each of the three provincial drug plans (Regie de l'assurance maladie du Quebec (RAMQ), ODB, and BC PharmaCare). These data reported the number of prescriptions filled and the total reimbursement by the drug plan on a monthly basis.

Morden 2008

Methods	Regression and random-effects meta-analyses of state level Medicaid ITS data with quarterly data points
Participants	48 states, n=21 states implemented PA policies for controlled-release oxycodone
Interventions	Impact of no PA, strict PA and lenient PA
Outcomes	Drug use, drug costs
Notes	Novel method of analysing state level administrativ data - evaluated using ITS critieria Analysis between 1996-2005

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	For 10 states that did not respond to interview requests by phone and e-mail, only website data were included.
Selective reporting (reporting bias)	Low risk	All outcomes listed in the methods section are reported in the results section
Other bias	High risk	Reimbursement figures do not include dispensing fee or reflect manufacturers' rebates to states.

Morden 2008 *(Continued)*

Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	High risk	"It is also likely that drug manufacturers' marketing and other tactics in response to PA implementation contribute to the limited success of such access restriction efforts.
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	Sources and methods of data collection were the same before and after the intervention

Motheral 2004

Methods	Controlled ITS with monthly data points
Participants	Intervention: n=20,000 enrollees in Midwest employer plan, Control: random sample of members from commercial plans n=1.9 million member in 1021 different plans
Interventions	Effects of step therapy programs for PPI, NSAIDS, and SSRIs
Outcomes	Drug costs per member per month
Notes	Analyzed claims from Sep 1, 2001 to June 30, 003. A mailed survey component of the study did not meet the selection criteria of this review and therefore was not included or ROB for this component evaluated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Low risk	Re:Drug cost data only; Any undocumented difference in the proportion of missing data in the administrative datasets pre- and post-intervention is unlikely to overturn study results.
Selective reporting (reporting bias)	High risk	All 3 therapy class trends for control group not shown (just aggregated data)
Other bias	High risk	No baseline characteristics of patient population provided. Small sample sizes at drug class level.
Knowledge of allocated interventions adequately prevented during the study	Low risk	Drug cost data only: Outcomes are objective measures of health care utilization
Intervention independent of other changes	Low risk	Drug cost data only: Known and unknown changes in the environment are unlikely to be responsible for magnitude of effect size demonstrated.
The shape of intervention pre-specified?	Low risk	Drug cost data only: The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and

Motheral 2004 *(Continued)*

		post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time.
Intervention unlikely to affect data collection?	Low risk	Drug use data only: Automated pharmacy claims pre and post intervention

Roughead 2006

Methods	Controlled ITS with quarterly data points
Participants	35 US state Medicaid programs
Interventions	Reimbursement restrictions on COX-2 inhibitors and NSAIDs comparing states with 1. unrestricted access N=17, 2. Early policy adopters (within 1 year of market entry N=6, Late policy developers ≥2 years after market entry N=12
Outcomes	Drug use and costs
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any undocumented difference in the proportion of missing data in the administrative datasets pre- and post-intervention is unlikely to overturn study results
Selective reporting (reporting bias)	Low risk	All outcomes listed in the methods section are reported in the results section
Other bias	High risk	Individual patient, physician prescribing and policy differences between early and late adopting states "Data on age, gender, and racial differences within the Medicaid markets for each quarter were not available for all states so these characteristics were uncontrolled in the models"
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	Low risk	Known and unknown changes in the environment are unlikely to be responsible for magnitude of effect size demonstrated.
The shape of intervention pre-specified?	Low risk	The date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	"We obtained complete quarterly aggregate medication utilization data from the Centers for Medicare and Medicaid Services (CMS) for 35 state Medicaid programs from January 1996 to September 2003."

Sakshaug 2007

Methods	Prevalence study equivalent to ITS using monthly data points
Participants	Population of Norway (4.6 million)
Interventions	National restriction on statin prescribing to simvastatin generics
Outcomes	Drug use, drug costs
Notes	Data from Jan 2005 to June 2006, policy implemented June 2005

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	"...all dispensed prescriptions of statins to individuals in the total population in Norway. The NorPD contains information that makes it possible to follow each individual over time in order to study changes in pharmacological treatment"
Selective reporting (reporting bias)	Low risk	All outcomes listed in the methods section are reported in the results section
Other bias	Low risk	No other bias detected
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	Low risk	Changes in prescribing with announcement and price changes part of intervention
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	Sources and methods of data collection were the same before and after the intervention

Schneeweiss 2004

Methods	Controlled ITS with repeated measures analysis with monthly data points
Participants	Senior and low income beneficiaries in provincial drug benefit plan, British Columbia, Canada N=53 pairs of clusters of doctors in British Columbia matched by size of location and number of patients. Policy implementation group n=449 patients affected by policy, policy exempt group n=386 patients. Observational cohort N=4624 patients (excluding n=386 in control goup)
Interventions	Restricted reimbursement for nebulizers, doctors had to request exemption
Outcomes	Drug use, health services utilization, durg costs

Schneeweiss 2004 *(Continued)*

Notes	Control group contaminated by announcing policy change to all doctors (including control doctors) therefore cluster randomized controlled trial component of this study was excluded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We randomly assigned one cluster of each pair to either the policy implementation group or the policy exempted control group. Randomising isolated but matched clusters of doctors minimised the risk of contamination and reduced imbalances owing to chance."
Allocation concealment (selection bias)	High risk	"The non-compliance resulted from a change that Pharmacare made to the protocol at the last minute, which can be avoided in future policy trials. Wanting to underscore the independence of the evaluation from the government, Pharmacare cautiously sent letters announcing the policy change six weeks in advance to all doctors in the province. Control doctors were not told of their exemption until they received a separate letter from the investigators two weeks later. Many control doctors either overlooked the second letter or decided to switch patients to inhaler drugs in anticipation of the new policy."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported and adjusted
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the methods section are reported in the results section
Other bias	Low risk	Considered by authors: "in the first month after the policy was implemented doctors reduced their office hours to meet budget caps at the end of the fiscal year, possibly more than in the previous year. The randomised analysis was protected from this bias since the concurrent control patients were equally as affected as the intervention patients.
Baseline outcome measurements similar	Low risk	"The historical control groups showed some seasonal variation, with higher use of respiratory drugs in the six months preceding 1 March compared with the subsequent six months."
Baseline characteristics similar	Low risk	"The baseline distributions of age, sex, drug use, comorbidity score, and use of healthcare did not differ between the randomised groups (table 1; all P values > 0.1). The observational cohorts had slightly more women than the randomised groups (62% v 59%). Otherwise the observational cohorts were comparable to each other."
Knowledge of allocated interventions adequately prevented during the study	Low risk	"We used de-identified data from the databases of British Columbia's Ministry of Health "
Study adequately protected against contamination?	High risk	Control doctors were notified of the policy change 2 weeks before recieving a letter informing them of their exemption.
Intervention independent of other changes	Low risk	We first adjusted for seasonality separately, using each of the two historical control cohorts.A significant interaction would mean that changes in end point trends because of the policy were different from the control cohorts, independent of seasonality.
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time peri-

Schneeweiss 2004 *(Continued)*

		ods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	"We used de-identified data from the databases of British Columbia's Ministry of Health to monitor use of and expenditure..."

Schneeweiss 2006

Methods	ITS with monthly data points
Participants	Senior beneficiaries in provincial drug benefit plan, British Columbia, Canada, N=501,104
Interventions	Restricted coverage to rabeparazole and required treatment failure with a H2RAs. Omeprazole, pantoprazole, and lansoprazole had to be paid for out-of-pocket unless physician requested exemption
Outcomes	Utilization of PPIs, drug discontinuation rates, gastrointestinal hemorrhage rates, drug expenditures
Notes	Introducton of a general 30% coinsurance requirement (Fair PharmaCare) 2.5 months earlier may have diminished some of the potential savings of the PPI restriction. Time series analysis between January2002 and June 2004.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The databases comprehensively covered all British Columbia seniors with the exception of a very small number of patients who left the province.This censoring is most likely random in a province that has net in-migration of elderly persons.
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	"The design of our study implicitly controlled for many confounding factors including health status by adjusting for baseline time trends in utilization and health outcomes."
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	Low risk	Known and unknown changes in the environment are unlikely to be responsible for sudden change and magnitude of effect size
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time
Intervention unlikely to affect data collection?	Low risk	Sources and methods of data collection were the same before and after the intervention

Smalley 1995

Methods	Controlled ITS using segmented regression model with monthly data points
Participants	Tennessee Medicaid Program N=495,821 to 547,403, included regular NSAID users who received either non-generic or generic NSAIDs for at least 274 days prior to policy.
Interventions	PA policy on NSAIDs
Outcomes	Health services utilization, Drug costs
Notes	Duration from baseline year: Oct 1, 1988 -Sep 30, 1989, post policy: Oct 1, 1989 - Sept 30 1991, no transition period

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any difference in the proportion of missing data data in state Medicaid datasets pre to post intervention is unlikely to overturn study results
Selective reporting (reporting bias)	Low risk	All outcomes listed in the methods section are reported in the findings section
Other bias	Low risk	
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	Low risk	Changes in the environment are unlikely to be responsible for magnitude of effect size.Note: In the second year after the policy change Medicaid prescriptions for non-study drugs increased by 8%, an increase that corresponded to the implementation of the provisions of the Omnibus act of 1990.
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time.
Intervention unlikely to affect data collection?	Low risk	Objective data obtained from an administrative database with standard collection rules

Soumerai 2008

Methods	Controlled cohort study - ITS with monthly data points
Participants	Maine, USA, Medicaid and Medicare, newly treated patients with schizophrenia diagnosis n=4600
Interventions	PA policy on atypical antipsychotics
Outcomes	Drug use, drug costs, time to treatment discontinuation
Notes	Intervention state: Maine, control state: New Hampshire; Medicaid claims for 201-2004. Policy period too short (policy discontinued) and study lacked power to detect treatment discontinuities.

Soumerai 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any undocumented difference in the proportion of missing data in the administrative datasets pre- and post-intervention is unlikely to overturn study results "Only Maine had enough patients to analyse utilization trends by preferred and nonpreferred categories"
Selective reporting (reporting bias)	Low risk	All outcomes listed in the methods section are reported in the results section
Other bias	Low risk	Treatment discontinuities common in schizophrenia. Maine had a significantly greater percentag of patients in the 18-34 categories - could confound the treatment discontinuities however these were not a study outcome.
Knowledge of allocated interventions adequately prevented during the study	Low risk	Outcomes are objective measures of healthcare utilization
Intervention independent of other changes	High risk	"The termination of Maine's PA policy after out study began resulted in limited follow-up, reducing our statistical power to detect treatment discontinuities among newly treated patients"
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time.
Intervention unlikely to affect data collection?	Low risk	Objective data obtained from an administrative database with standard collection rules.

van Driel 2008

Methods	ITS with segmented regression analysis with monthly data points
Participants	Belgian National Health Insurance members
Interventions	Two policies issued: March 2001: H2As became available without restrictions; March 2003: two PPIs became available without resrictions
Outcomes	Utilization and costs
Notes	4 month transition period (2 months before and 2 months after) were included retrospectively

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Any undocumented difference in the proportion of missing data in the administrative datasets pre- and post-intervention is unlikely to overturn study results

van Driel 2008 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No other source of bias detected
Intervention independent of other changes	High risk	"an evidence report that was distributed to all physicians and pharmacists in September 2004. Several events and interactions interfering with the policies have been discussed, but many other events may also have played a role."
The shape of intervention pre-specified?	Low risk	The point of analysis is the point of intervention; ie, the date the policy intervention was implemented was used to delineate pre and post policy time periods with adequate data points to capture the shape of the pattern of intervention effect over time.
Intervention unlikely to affect data collection?	Low risk	Objective data obtained from an administrative database with standard collection rules.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ackman 2006	Fatally flawed study design: populations defined for comparison on the basis of prescription filling behaviour without knowledge of application for or denial of the medication targeted for restriction
Bloom 1985	Inadequate study design: uncontrolled before-after (BA) study also excluded patients that discontinued treatment after policy implementation thereby producing an inadequate compartor
Gleason 2005	Inadequate study design: described as 'Prospective, pre- and post-implementation cohort study with reference group.' Reference groups not suitable as comparators as they differed by prescription filling, use and PA authorization patterns. Quarterly drug usage and cost data with insufficient data points pre-implementation.
Kahan 2006	Insufficient observation points before PA implementation
Kotzan 1993	Inadequate study design: uncontrolled BA study
Lu 2007	Inadequate study design: national trends in the use of DMARDs before and after the introduction of the PBS access criteria for biologicals. Study limitations include the absence of data on use of biologicals (the drug targeted by the restrictive policy) and the assumption that because the drugs studies were 'mainly' used as DMARDS that the national trend for all users of DMARDS would reflect changes in use patterns for the largest RA subpopulation
McCombs 2002	Inadequate study design: BA study without adequate control group: logistic regression analysis adjusted for differences between treated and untreated groups with major depressive disorder
Meissner 2007	Inadequate study design: uncontrolled BA study of medication switchers
Momani 2002	Inadequate study design: uncontrolled BA study
Phillips 1997	Inadequate study design: uncontrolled BA study - simple comparison of baseline with after observation without consideration of time trend or bias arising from other environmental or policy changes
Sheely 2008	Inadequate study design: fatally flawed. Groups were compiled for comparison on the basis of prescription filling history without additional information on authorization process. Also patient

Study	Reason for exclusion
	deaths were attributed to failure to fill a clopidogrel prescription because of delays caused by the PA process whether or not the clopidogrel had been prescribed or authorization sought.
Siracuse 2007	Inadequate study design: denominator data not specified. The study design was labelled as cross-sectional however data collected from administrative datasets on a quarterly basis so snapshot was not taken at a consistent point in time and individuals could have contributed data multiple times.
Virabhak 2005	Inadequate study design: regression modelling using data from 2 states with PA policies that differed in criteria used to determine reimbursement
Yokoyama 2007	Insufficient denominator data on PA applications for analysis within this study of step therapy versus PA only. "The use of rejected and paid claims data in this analysis, compared with PA data only, allows for identification of cost savings associated with ARB claims avoided or delayed as a result of the step-therapy program. We identified those patients who encountered a rejected claim for an ARB and followed them for 12 months. While we do not know which patients attempted to get a PA or did not attempt to get a PA but were denied, we identified the antihypertensive therapy and associated costs in the 12-month follow-up period."

ADDITIONAL TABLES

Table 1. Search strategies: MEDLINE Ovid to Jan 2009 *(Continued)*

1. (rebate or reimbursement contract? or reimburse$ or insur$ or (third party adj1 pay$) or benefit plan?).mp. or *insurance, health, reimbursement/ or *reimbursement mechanisms/ or *reimbursement, disproportionate share/ or *reimbursement, incentive/ [mp=title, original title, abstract, name of substance word, subject heading word]

2. (prescribe$ or prescription? or substitute$ or drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$).mp. or exp Pharmaceutical preparations/ or prescriptions, drug/ [mp=title, original title, abstract, name of substance word, subject heading word]

3. ((generic$ adj3 prescrib$) or (generic? adj3 prescription) or (generic$ adj3 substitut$)).tw.

4. 2 or 3

5. (regulat$ or requirement? or restrict$ or monitor$ or control$ or reduc$ or fix$).tw. or (Pre-authori#ation? or preauthori#ation? or prior authori#ation?).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

6. 1 and 4 and 5

7. limit 6 to (humans and yr="2005 - 2008")

Table 2. Search strategies: Central to 2005 all pharmaceutical policy areas *(Continued)*

CENTRAL, The Cochrane Central Register of Controlled Trials, Ovid
Search elds: A combination of MeSH terms and text words
1. (regulat$ or requirement? or restrict$ or monitor$ or control$).tw.
2. (legislation? or law? or act? or policy or policies or politics or reform$ or system? or plan$ or program$ or strateg$).tw. or Policy Making/ or Legislation, Drug/ or Public Policy/ or Health Policy/ or Politics/ or Health Care Reform/
3. (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$).tw. or exp Pharmaceutical Preparation/ or Drug Utilization/
4. (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$).tw. or exp Pharmaceutical Preparation/ or Drug Industry/ or Drug Utilization/

Table 2. Search strategies: Central to 2005 all pharmaceutical policy areas *(Continued)*

5. (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$).tw. or exp Pharmaceutical Preparation/ or Prescriptions,
Drug/ or Drug Utilization/
6. Drug Approval/ or (approv$ adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
7. Licensure/ and 4
8. Drug Labeling/
9. ((licens$ or registrat$ or label$) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
10. (6 or 7 or 8 or 9) and (1 or 2)
11. Classication/ and 3 and 2
12. ((classify$ or classication?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw. and 2
13. 11 or 12
14. 10 or 13
15. Patents/ and 4
16. (patent? adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
17. ((prot$ adj3 (control$ or reduc$ or regulat$ or x$ or restrict$)) and (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
18. (15 or 16 or 17) and (1 or 2)
19. (Marketing/ or Marketing of Health Services/ or Advertising/) and 4
20. ((advert$ or promot$ or market$) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
21. (19 or 20) and (1 or 2)
22. (Insurance, Hospitalization/ or Insurance, health, reimbursement/ or Reimbursement Mechanisms/ or Reimbursement, disproportionate share/ or Reimbursement, incentive/) and 5
23. Insurance, pharmaceutical services/
24. ((reimburse$ or insur$ or (third party adj1 pay$) or benet plan?) adj3 (drug or drugs or pharmaceutic$ or pharmacy or pharmacies or medicines or medicament? or medicat$)).tw.
25. (22 or 23 or 24) and (1 or 2)
26. Formularies/ and 5
27. Formularies, Hospital/ and 3
28. ((formulary or formularies or positive list? or negative list?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$ or hospital?)).tw.
29. (26 or 27 or 28) and (1 or 2)
30. Drugs, Essential/
31. (essential adj3 (drug? or pharmaceutic$ or medicine? or medicament?)).tw.
32. ((drug? or pharmaceutic$ or medicine? or medicament?) adj3 list?).tw.
33. 31 and 32
34. 30 or 33
35. ((pre-authori#ation? or preauthori#ation? or prior authori#ation?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
36. Reminder Systems/ and 5 and 2
37. (reminder? adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw. and 2
38. Prescriptions, Drug/
39. (continu$ adj3 education).tw.
40. Education, Continuing/
41. Education, Pharmacy, Continuing/
42. (improv$ or incentive?).tw.
43. 39 or 40 or 41 or 42
44. 38 and 43 and (1 or 2)
45. (((prescrib$ or prescription?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)) and ((continu$ adj1 education) or (improv$ or incentive?))).tw. and (1 or 2)
46. (Guidelines/ or Practice Guidelines/ or Guideline Adherence/) and 2 and 5
47. (((guideline? or recommendation?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)) and (disseminat$ or implement$ or complian$ or adherence)).tw. and 2
48. 46 or 47
49. (((generic$ adj3 prescrib$) or (generic$ adj3 prescription?)) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
50. ((local$ or global$) adj3 budget$).tw.
51. (budget$ adj3 (general pract$ or GP? or physician? or doctor?)).tw.

52. 50 and 51
53. (fundhold$ adj3 (general pract$ or GP? or physician? or doctor?)).tw.
54. 52 or 53

Table 2. Search strategies: Central to 2005 all pharmaceutical policy areas *(Continued)*

55. 54 and 3
56. \Pharmacy and Therapeutics Committee"/ and 2 and 5
57. ((drug? or formulary or pharmac$) adj3 committee?).tw. and 2
58. 56 or 57
59. (Drug Monitoring/ or Adverse Drug Reaction Reporting Systems/ or (safe$ adj1 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.) and 2
60. Product Surveillance, Postmarketing/ and 3 and 2
61. 59 or 60
62. 36 or 37 or 44 or 45 or 48 or 49 or 55 or 58 or 61
63. (Cost Control/ or Cost Savings/) and 5 and 2
64. ((control$ or containment or curtailment or reduc$ or save or saving) adj3 cost?).tw.
65. (cost? adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
66. 64 and 65 and 2
67. ((control$ or reduc$ or cut$ or regulat$ or negotiat$ or x$) adj3 (price? or pricing)).tw.
68. ((price? or pricing) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
69. 67 and 68 and 2
70. (reference$ adj3 (price? or pricing)).tw.
71. ((price? or pricing) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
72. 70 and 71
73. (index$ adj3 (price? or pricing)).tw.
74. ((price? or pricing) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
75. 73 and 74
76. (maxim$ adj3 (price? or pricing)).tw.
77. ((price? or pricing) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
78. 76 and 77
79. (cost? effect$ adj3 (price? or pricing)).tw.
80. ((price? or pricing) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
81. 79 and 80
82. (reimbursement contract? adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
83. (Drug Cost/ or Economics, Pharmaceutical/) and (1 or 2)
84. (Purchasing, Hospital/ or Group, Purchasing/) and 3
85. (purchas$ adj3 (group? or join$ or hospital? or shared)).tw.
86. ((group? or join$ or hospital? or shared) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
87. 85 and 86 and 2
88. (procurement$ adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw. and 2
89. (rebate? adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw. and 2
90. 63 or 66 or 69 or 72 or 75 or 78 or 81 or 82 or 83 or 84 or 87 or 88 or 89
91. Marketing/ or Marketing of Health Services/ or Advertising/ or Licensure/ or Drug Labeling/
92. Pharmacies/ or Pharmacists/ or (pharmacy or pharmacies or pharmacist? or retailer? or wholesaler? or supplier? or dispens$).tw.
93. 91 and 92 and 3 and (1 or 2)
94. (advert$ or promot$ or market$).tw.
95. Pharmacies/ or Pharmacists/ or (pharmacy or pharmacies or pharmacist? or retailer? or wholesaler? or supplier? or dispens$).tw.
96. 94 and 95 and 3 and (1 or 2)
97. 93 or 96
98. ((control$ or reduc$ or regulat$ or x$ or restrict$) adj3 prot?).tw.
99. (prot? adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
100. Pharmacies/ or Pharmacists/ or (pharmacy or pharmacies or pharmacist? or retailer? or wholesaler? or supplier? or dispens$).tw.
101. 98 and 99 and 100
102. (generic$ adj3 substitut$).tw.
103. (substitut$ adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
104. 102 and 103
105. (licens$ adj3 (pharmacy or pharmacies)).tw.
106. (((supply or supplies or distribut$ or sale$) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament$ or medicat$)) and (pharmacy or pharmacies or retailer? or wholesaler? or supplier? or dispens$)).tw. and (1 or 2)
107. 97 or 101 or 104 or 105 or 106
108. Cost Sharing/ and 5
109. (cost? adj3 (sharing or share)).tw.
110. ((sharing or share) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
111. 109 and 110
112. (out of pocket? adj3 pay$).tw.

Table 2. Search strategies: Central to 2005 all pharmaceutical policy areas *(Continued)*

113. (pay$ adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
114. 112 and 113
115. ((copay$ or co pay$) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
116. ((prescrib$ or prescription? or pharmaceutic$ or pharmacy or pharmacies or dispens$) adj3 (charg$ or fee?)).tw.
117. ((charg$ or fee?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
118. 116 and 117
119. ((prescrib$ or prescription?) adj3 (limit$ or cap$)).tw.
120. ((limit$ or cap$) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
121. 119 and 120
122. ((coinsurance or deductible?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament$ or medicat$)).tw.
123. \Deductibles and Coinsurance"/ and 5
124. Fees, Pharmaceutical/
125. Prescription Fees/
126. Capitation Fee/ and 5
127. 108 or 111 or 114 or 115 or 118 or 121 or 122 or 123 or 124 or 125 or 126
128. Drug Information Services/ and (patient? or consumer?).tw. and 2
129. Drug Labeling/ and (patient? or consumer?).tw. and 2
130. Patient Education/ and 3 and (1 or 2)
131. ((educat$ or inform$) adj3 (patient? or consumer?)).tw.
132. ((patient? or consumer?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
133. 131 and 132 and (1 or 2)
134. 128 or 129 or 130 or 133
135. 14 or 18 or 21 or 25 or 29 or 34 or 35 or 62 or 90 or 107 or 127 or 134

Table 3. Search strategies: EMBASE (OVID) to Oct 2008 *(Continued)*

1. (regulat* or requirement? or restrict* or monitor* or control* or reduc* or fix*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

2. (pre-authori#ation* or preauthori#ation* or "prior authori#ation*").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

3. exp Drug/ or prescription/

4. exp health insurance/

5. exp pharmacoeconomics/

6. ((prescrib$ or prescrip$ or substitut$ or generic?) adj3 (drug? or pharmaceut$ or medicines or medicament? or medicat$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

7. 3 or 6

8. reimbursement/ or reimburs*.mp. or rebate?.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

9. 1 or 2 or 4 or 5

10. 9 and 8

11. 10 and 7

12. limit 11 to (human and yr="2005 - 2008")

Table 4. Search strategies: Medline (OVID) to 2005 all pharmaceutical policy areas *(Continued)*

Search strategy: MEDLINE Ovid (Continued)
1. (regulat$ or requirement? or restrict$ or monitor$ or control$).tw.

Table 4. Search strategies: Medline (OVID) to 2005 all pharmaceutical policy areas *(Continued)*

2. (legislation? or law? or act? or policy or policies or politics or reform$ or system? or plan$ or program$ or strateg$).tw. or Policy Making/ or Legislation, Drug/ or Public Policy/ or Health Policy/ or Politics/ or Health Care Reform/
3. (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$).tw. or exp Pharmaceutical Preparation/ or Drug Utilization/
4. (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$).tw. or exp Pharmaceutical Preparation/ or Drug Industry/ or Drug Utilization/
5. (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$).tw. or exp Pharmaceutical Preparation/ or Prescriptions,
Drug/ or Drug Utilization/
6. *Drug Approval/ or (approv$ adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
7. *Licensure/ and 4
8. *Drug Labeling/
9. ((licens$ or registrat$ or label$) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
10. (6 or 7 or 8 or 9) and (1 or 2)
11. *Classication/ and 3 and 2
12. ((classify$ or classication?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw. and 2
13. 11 or 12
14. 10 or 13
15. *Patents/ and 4
16. (patent? adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
17. ((prot$ adj3 (control$ or reduc$ or regulat$ or x$ or restrict$)) and (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
18. (15 or 16 or 17) and (1 or 2)
19. (*Marketing/ or *Marketing of Health Services/ or *Advertising/) and 4
20. ((advert$ or promot$ or market$) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
21. (19 or 20) and (1 or 2)
22. (*Insurance, Hospitalization/ or *Insurance, health, reimbursement/ or *Reimbursement Mechanisms/ or *Reimbursement, disproportionate share/ or *Reimbursement, incentive/) and 5
23. *Insurance, pharmaceutical services/
24. ((reimburse$ or insur$ or (third party adj1 pay$) or benet plan?) adj3 (drug or drugs or pharmaceutic$ or pharmacy or pharmacies or medicines or medicament? or medicat$)).tw.
25. (22 or 23 or 24) and (1 or 2)
26. *Formularies/ and 5
27. *Formularies, Hospital/ and 3
28. ((formulary or formularies or positive list? or negative list?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$ or hospital?)).tw.
29. (26 or 27 or 28) and (1 or 2)
30. Drugs, Essential/
31. (essential adj3 (drug? or pharmaceutic$ or medicine? or medicament?)).tw.
32. ((drug? or pharmaceutic$ or medicine? or medicament?) adj3 list?).tw.
33. 31 and 32
34. 30 or 33
35. ((pre-authori#ation? or preauthori#ation? or prior authori#ation?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
36. *Reminder Systems/ and 5 and 2
37. (reminder? adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw. and 2
38. *Prescriptions, Drug/ and ((continu$ adj3 education) or *Education, Continuing/ or *Education, Pharmacy, Continuing/ or (improv$ or incentive?)).tw. and (1 or 2)
39. (((prescrib$ or prescription?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)) and ((continu$ adj1 education) or (improv$ or incentive?))).tw. and (1 or 2)
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Table 01. Search strategy: MEDLINE Ovid (Continued)
40. (*Guidelines/ or *Practice Guidelines/ or *Guideline Adherence/) and 2 and 5
41. (((guideline? or recommendation?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)) and (disseminat$ or implement$ or complian$ or adherence)).tw. and 2
42. 40 or 41
43. (((generic$ adj3 prescrib$) or (generic$ adj3 prescription?)) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
44. ((local$ or global$) adj3 budget$).tw.
45. (budget$ adj3 (general pract$ or GP? or physician? or doctor?)).tw.

Table 4. Search strategies: Medline (OVID) to 2005 all pharmaceutical policy areas *(Continued)*

46. 44 and 45
47. (fundhold$ adj3 (general pract$ or GP? or physician? or doctor?)).tw.
48. 46 or 47
49. 48 and 3
50. *\Pharmacy and Therapeutics Committee"/ and 2 and 5
51. ((drug? or formulary or pharmac$) adj3 committee?).tw. and 2
52. 50 or 51
53. (*Drug Monitoring/ or *Adverse Drug Reaction Reporting Systems/ or (safe$ adj1 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.) and 2
54. *Product Surveillance, Postmarketing/ and 3 and 2
55. 53 or 54
56. 36 or 37 or 38 or 39 or 42 or 43 or 49 or 52 or 55
57. (*Cost Control/ or *Cost Savings/) and 5 and 2
58. ((control$ or containment or curtailment or reduc$ or save or saving) adj3 cost?).tw.
59. (cost? adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
60. 58 and 59 and 2
61. ((control$ or reduc$ or cut$ or regulat$ or negotiat$ or x$) adj3 (price? or pricing)).tw.
62. ((price? or pricing) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
63. 61 and 62 and 2
64. (reference$ adj3 (price? or pricing)).tw.
65. ((price? or pricing) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
66. 64 and 65
67. (index$ adj3 (price? or pricing)).tw.
68. ((price? or pricing) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
69. 67 and 68
70. (maxim$ adj3 (price? or pricing)).tw.
71. ((price? or pricing) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
72. 70 and 71
73. (cost? effect$ adj3 (price? or pricing)).tw.
74. ((price? or pricing) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
75. 73 and 74
76. (reimbursement contract? adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
77. (*Drug Cost/ or *Economics, Pharmaceutical/) and (1 or 2)
78. (*Purchasing, Hospital/ or *Group, Purchasing/) and 3
79. (purchas$ adj3 (group? or join$ or hospital? or shared)).tw.
80. ((group? or join$ or hospital? or shared) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
81. 79 and 80 and 2
82. (procurement$ adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw. and 2
83. (rebate? adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw. and 2
84. 57 or 60 or 63 or 66 or 69 or 72 or 75 or 76 or 77 or 78 or 81 or 82 or 83
85. *Marketing/ or *Marketing of Health Services/ or *Advertising/ or *Licensure/ or *Drug Labeling/
86. Pharmacies/ or Pharmacists/ or (pharmacy or pharmacies or pharmacist? or retailer? or wholesaler? or supplier? or dispens$).tw.

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Table 01. Search strategy: MEDLINE Ovid (Continued)

87. 85 and 86 and 3 and (1 or 2)
88. (advert$ or promot$ or market$).tw.
89. Pharmacies/ or Pharmacists/ or (pharmacy or pharmacies or pharmacist? or retailer? or wholesaler? or supplier? or dispens$).tw.
90. 88 and 89 and 3 and (1 or 2)
91. 87 or 90
92. ((control$ or reduc$ or regulat$ or x$ or restrict$) adj3 prot?).tw.
93. (prot? adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
94. Pharmacies/ or Pharmacists/ or (pharmacy or pharmacies or pharmacist? or retailer? or wholesaler? or supplier? or dispens$).tw.
95. 92 and 93 and 94
96. (generic$ adj3 substitut$).tw.
97. (substitut$ adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
98. 96 and 97
99. (licens$ adj3 (pharmacy or pharmacies)).tw.
100. (((supply or supplies or distribut$ or sale$) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament$ or medicat$)) and (pharmacy or pharmacies or retailer? or wholesaler? or supplier? or dispens$)).tw. and (1 or 2)
101. 91 or 95 or 98 or 99 or 100

Table 4. Search strategies: Medline (OVID) to 2005 all pharmaceutical policy areas *(Continued)*

102. *Cost Sharing/ and 5
103. (cost? adj3 (sharing or share)).tw.
104. ((sharing or share) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
105. 103 and 104
106. (out of pocket? adj3 pay$).tw.
107. (pay$ adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
108. 106 and 107
109. ((copay$ or co pay$) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
110. ((prescrib$ or prescription? or pharmaceutic$ or pharmacy or pharmacies or dispens$) adj3 (charg$ or fee?)).tw.
111. ((charg$ or fee?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
112. 110 and 111
113. ((prescrib$ or prescription?) adj3 (limit$ or cap$)).tw.
114. ((limit$ or cap$) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
115. 113 and 114
116. ((coinsurance or deductible?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament$ or medicat$)).tw.
117. *\Deductibles and Coinsurance"/ and 5
118. *Fees, Pharmaceutical/
119. *Prescription Fees/
120. *Capitation Fee/ and 5
121. 102 or 105 or 108 or 109 or 112 or 115 or 116 or 117 or 118 or 119 or 120
122. *Drug Information Services/ and (patient? or consumer?).tw. and 2
123. *Drug Labeling/ and (patient? or consumer?).tw. and 2
124. *Patient Education/ and 3 and (1 or 2)
125. ((educat$ or inform$) adj3 (patient? or consumer?)).tw.
126. ((patient? or consumer?) adj3 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$)).tw.
127. 125 and 126 and (1 or 2)
128. 122 or 123 or 124 or 127
129. randomized controlled trial.pt.
130. controlled clinical trial.pt.
131. intervention studies/
132. experiment$.tw.
133. (time adj series).tw.
134. (pre test or pretest or (posttest or post test)).tw.
135. random allocation/

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Table 01. Search strategy: MEDLINE Ovid (Continued)

136. evaluation studies/
137. evaluat$.tw.
138. comparative studies/
139. (randomized or randomised).tw.
140. (random$ adj1 (allocat$ or assign$)).tw.
141. animal/
142. human/
143. 141 not 142
144. or/129-140
145. 144 not 143
146. 14 or 18 or 21 or 25 or 29 or 34 or 35 or 56 or 84 or 101 or 121 or 128
147. 146 and 145

Table 5. Search strategies: Central, the Cochrane Central Register of Controlled Trials, OVID to Oct 2008 *(Continued)*

1. (generic* or prescribe* or prescrip* or substitut* or drug or drugs or pharmaceutic* or medicines or medicament* or medicat*).ti.

2. (pre-authori#ation* or preauthori#ation* or "prior authori#ation*" or rebate or reimburs* or insur* or third party near pay* or "benefit plan*" or regulat* or requirement* or restrict* or monitor* or control* or reduc* or fix*).ti.

3. 1 and 2

Table 5. Search strategies: Central, the Cochrane Central Register of Controlled Trials, OVID to Oct 2008 *(Continued)*

4. limit 3 to medline records

5. limit 3 to embase records

6. 4 or 5

7. 3 not 6

8. limit 7 to yr="2005 - 2008"

Table 6. Search strategies: Web of Science, ISI to Oct 2008 *(Continued)*

(Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=2005-2008)

1 Topic=((generic* or prescrip* or prescrib* or substitut*)) AND Topic=((drug* or pharmaceut* or medicines or medicament* or medicat*))

2 Topic=((regulat* or requirement* or restrict* or monitor* or control* or reduc* or fix* or pre-authori*ation* or preauthori*ation or "prior authori*ation")) AND Topic=((rebate or reimburs*))

3 #2 AND #1

Table 7. Search Strategies: Worldwide Political Science Abstracts (CSA) to Oct 2008 *(Continued)*

(DE=medications or KW=(prescri* or pharmaceutic* or drug*) or KW=(medicines or medicament* or generic*)) and(KW=(rebate* or reimburs*)) and((DE=((health care costs) or (health care utilization) or (health insurance)) or KW=rationing) or(KW=(regulat* or requirement* or restrict*) or KW=(reduc* or preauthori?ation or pre-authori?ation) or KW=(prior authori?ation)))

Limit: 2005 - 2008

Table 8. Search strategies: EconLit (Ebsco) to Oct 2008 *(Continued)*

Limit 2005 - 2008

S1 reimburs* and (drug* or medication* or prescription*)

S2 SU economics of regulation or (reimburs* or pricing or cost* or preauthori?ation or pre-authori?ation or "prior authori?ation")

S3 SU drugs or (medication* or prescription* or pharmaceut* or medicines or generic*)

S4 S3 and S2

S5 reimburs* and S4

S6 S1 not S5

S7 S6 or S1 and (Limiters - Published Date from: 200501-200812; Publication Type: Journal Article)

Table 9. Search Strategies: PAIS International CSA to Oct 2008 *(Continued)*

Search Query #6 (DE=(medicine or drugsor prescriptions) or KW=(prescri* or generic* or pharmaceutical*)) and(KW=(regulat* or requirement* or restrict*) or KW=(monitor* or control* or reduc*) or KW=(fix* or pre-authori?ation or preauthori?ation) or KW=(prior authorization) and DE=(insurance, health)) and(KW=(rebat* or reimburs*))
Date range: 2005 to 2008
Limited to: Journal articles only

Table 10. Search Strategies: International Political Science Abstracts (EBSCO) to Oct 2008 *(Continued)*

S1	prescription* or drug* or medicines or generic* or pharmaceutical*
S2	regulat* or requirement* or restrict* or monitor* or control* or reduc* or pre-authori?ation or preauthori?ation or prior authorization
S3	rebate* or reimburs*
S4	S3 and S2 and S1
S5	S3 and S2 and S1 Limiters - Published Date from: 200501-2008

Table 11. Search strategies: NHS Economic Evaluation Database to Oct 2008 *(Continued)*

1 drugs* OR medicines OR prescrip* OR generic* OR pharmaceut* OR medicament* OR medicat* RESTRICT YR 2005 2008
2 regulat* OR requirement* OR restrict* OR monitor* OR control* OR reduc* OR pre-authori?ation OR preauthori?ation OR "prior authorization"
3 rebate* OR reimburs*
4 #1 AND #2 AND #3 RESTRICT YR 2005 2008

Table 12. Search strategies: SourceOECD to Oct 2008 *(Continued)*

((title/rebat* or title/reimburs*) and title/r*) and year>=2005

Table 13. Search Strategies: International Pharmaceutical Abstracts (OVID) to Oct 2008 *(Continued)*

1. reimbursement.sh.
2. insurance reimbursement.sh.
3. prescriptions.sh.
4. drugs.sh.
5. regulations reimbursement.sh.
6. ((generic$ adj3 prescrib$) or (generic? adj3 prescription) or (generic$ adj3 substitut$)).mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
7. ((prescrib$ or prescription? or substitut$) adj3 (drug? or pharmaceutic$ or medicines or medicament? or medicat$)).mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]

Table 13. Search Strategies: International Pharmaceutical Abstracts (OVID) to Oct 2008 *(Continued)*

8. (regulat$ or requirement? or restrict$ or monitor$ or control$ or reduc$ or fix$).tw. or (pre-authori#ation? or preauthori#ation or "prior authori#ation?").mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]

9. 3 or 4 or 6 or 7

10. 1 or 2 or 5

11. 9 and 10 and 7

12. limit 11 to (human and yr="2005 - 2008")

Table 14. Search Strategies: PubMed to Oct 2008 *(Continued)*

#1 Search regulat*[ti] OR requirement*[ti] OR restrict*[ti] OR monitor*[ti] OR control*[ti] OR reduc*[ti] OR fix*[ti]

#2 Search pre-authorisation* OR pre-authorization* OR preauthorisation* OR preauthorization* OR "prior authorisation" OR "prior authorization"

#3 Search #1 OR #2

#4 Search rebate OR "reimbursement contract*" OR reimburse* OR insur* OR "third party pay*" OR "benefit plan*"

#5 Search "Reimbursement, Disproportionate Share"[Mesh]

#6 Search "Reimbursement, Incentive"[Mesh]

#7 Search "Reimbursement Mechanisms"[Mesh]

#8 Search "Insurance, Health, Reimbursement"[Mesh]

#9 Search #5 or #6 or #7 or #8 or #5

#10 Search prescrib* OR prescrip* OR substitut* OR generic* or drug[ti] OR drugs[ti] OR pharmaceutic*[ti] OR medicine[ti] OR medicines[ti] OR medicament*[ti] OR medicat*[ti]

#11 Search "Pharmaceutical Preparations"[Mesh] OR "Prescriptions, Drug"[Mesh]

#12 Search #10 OR #11

#13 Search #3 AND #9 AND #12

#14 Search #3 AND #9 AND #12 Limits: Entrez Date from 2005/01/01 to 2008/12/31, Humans

#15 Search #14[sb] Limits: Entrez Date from 2005/01/01 to 2008/12/31, Humans

#16 Search #14 pubstatusaheadofprint Limits: Entrez Date from 2005/01/01 to 2008/12/31, Humans

#17 Search #14 pubmednotmedline[sb] Limits: Entrez Date from 2005/01/01 to 2008/12/31, Humans

#18 Search #14 pubmednotmedline Limits: Entrez Date from 2005/01/01 to 2008/12/31, Humans

Table 15. Summary of findings. Effects of restrictions to reimbursement *(Continued)*

OUTCOME	NO OF STUDIES	RELATIVE EFFECT: MEDIAN (RANGE)	QUALITY	COMMENTS

Table 15. Summary of findings. Effects of restrictions to reimbursement *(Continued)*

Target drug use, immediately after introduction	7	-26% (-.04, -92%)	1 study met all 7 criteria, 4 met 6 and 2 met 5	All studies were set in publically funded drug benefit plans: 5 US Medicaid and 2 Canadian provincial plans. One study was reanalysed.
Target drug use, at 2 years after introduction	4	-17% (-9%,-70%)	2 studies met all 7 criteria, 2 met 6	All studies were set in publically funded drug benefit plans: 2 US Medicaid and 2 Canadian provincial plans
Expenditures on target drug or drug class at 6 months after introduction	3	- 57% (-85%, -36%)	2 studies met all 7 criteria, 1 met 6	Studies suitable for reanalysis provided the best estimates of relative effect. All studies were set in publically funded drug benefit plans: 2 Canadian provincial plans and 1 US Medicaid
Expenditures on target drug at 2 years after introduction	2	- 49% (-79%, -18%)	1 studies met all 7 criteria, 1 met 6	Studies suitable for reanalysis provided the best estimates of relative effect. Both studies were set in Canadian provincial publically funded drug benefit plans

WHAT'S NEW

Date	Event	Description
14 October 2019	Amended	A link to a summary for policy-makers was added to the plain language summary

CONTRIBUTIONS OF AUTHORS

MA drafted the original protocol spanning 13 pharmaceutical policy review areas and amended it with comments from an international group of co-athours (Aaserud 2003). Following this general protocol and refining it for restriction to reimbursement policies were MM and CJG. Review authors CJG, MM, PF examined studies for eligibility, extracted data and analyzed the results. CJG drafted the review. MM, AO, CR guided the data analysis planning and implementation. MM, SB assisted with interpretation of the results and clinical relevance. CR conducted a re-analyses of selected ITS studies, where this was warranted. MA and CR commented on the draft of this review. All authors approved the final review for publication.

DECLARATIONS OF INTEREST

PF, CR, PF. None known. MM is employed by the Ministry of Health Services of British Columbia in the position of Co-Director of Research and Evidence Development in Pharmaceutical Services Division, which uses PA policies as part of a suite of policies for managing the cost-effectiveness of its drug benefits program, PharmaCare. CG has previously been under contract to the Pharmaceutical Services Division of the Ministry of Health Services of British Columbia to produce reviews of evidence. MA is employed by Statens legemiddelverk of the Norwegian Medicines Agency which ensures cost-efficient, effective and well-documented use of medicines in Norway.

SOURCES OF SUPPORT

Internal sources

- University of Victoria, Canada, Canada.

  University infrastructure and faculty support

External sources

- British Columbia Medical Association, Canada.
- Canadian Institutes of Health Research, Canada.

  Post-doctoral Fellowship grant

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

New risk of bias criteria were developed by EPOC in the time since the original protocol by Aaserud 2003 was developed. Studies that were originally appraised using older criteria were re-appraised using newer criteria and the GRADE system was not used in compliance with updated Cochrane protocols. Updated searches were performed that were restricted to 'restriction to reimbursment' search terms whereas the original searches which were done across all policy areas used all terms as described by the original protocol (Aaserud 2003).

INDEX TERMS

Medical Subject Headings (MeSH)

Drug Costs; Health Care Costs [legislation & jurisprudence]; Health Services [statistics & numerical data]; Insurance, Pharmaceutical Services [*legislation & jurisprudence]; Prescription Drugs [economics] [*supply & distribution]; Process Assessment (Health Care); Reimbursement Mechanisms [*legislation & jurisprudence]

MeSH check words

Adult; Aged; Humans