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[Intervention Protocol]

Pharmaceutical policies: effects of policies regulating drug marketing

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

Main objective

To assess the effects of policies that regulate drug promotion on drug utilization, coverage or access, healthcare utilization, patient outcomes, adverse events and costs.

Secondary objective(s)

To assess whether the effects of policies that regulate drug promotion to patients/consumers, healthcare professionals, regulators and third-party payers differ according to drug class, clinical indication, target groups and country (high-, middle- or low-income countries).

BACKGROUND

The pharmaceutical industry works to discover new, effective, and safe drugs for the treatment and prevention of specific diseases. In order to offset the substantial development costs in making new treatments commercially available, drug promotion is used to gain a competitive market share, and drive sale volumes and industry profitability (Alves 2019). This involves disseminating information about new treatments (prescription and non-prescription drugs) to relevant targets, including patients, healthcare professionals and regulators. However, conflicts of interest may arise when profits are prioritised over patient care (Jacob 2018).

Description of the condition

The World Health Organization (WHO) defines drug promotion as "all informational and persuasive activities by manufacturers and distributors, the effect of which is to induce the prescription, supply, purchase and/or use of medicinal drugs" (WHO 2004). The pharmaceutical industry invests heavily around the world to promote its products and ultimately increase sales. For example, in 2016 more than USD 26 billion was spent on marketing prescription drugs in the USA (Schwartz 2019). The pharmaceutical industry uses a variety of drug promotion activities to achieve its marketing goals including direct-to-consumer advertising (DTCA), professionally branded advertising, detailing visits by sales representatives, free drug samples, rebranding and educational awareness programs (O'Connor 2014, Schwartz 2019). Drug promotion activities have a range of targets including patients and consumers; healthcare professionals (involved in the prescribing and dispensing of medications); regulators; and third-party payers, such as insurers and other funders (Parker 2018).

The benefits and harms of drug promotion have been widely debated. Supporters of drug promotion argue that it may empower consumers' medical decision-making and even help avert the underuse of effective treatments for diseases that may be poorly recognised or associated with stigma (Kravitz 2005; Ventola 2011). There is some evidence to back up these claims in terms of enhanced interaction between patients and prescribers, as well as increased information-seeking by patients about drugs or their conditions with healthcare professionals (DeFrank 2019). Opponents argue that promotional activities tend to focus on newer and more expensive products and that consumers lack sufficient knowledge to assess the effectiveness and safety of drugs that are promoted through commercially-motivated advertisements leading to overprescribing of unnecessary, and potentially harmful, medications (Donohue 2007). There is evidence to suggest that interactions between prescribers and drug promotion activities from the pharmaceutical industry are associated with inappropriately increased prescribing rates, reduced prescribing quality and increased prescribing costs (Brax 2017; Spurling 2010). Despite this, many physicians consider their interactions with the pharmaceutical industries as neutral, without perceiving potential negative consequences (Austad 2011; Green 2012).

Several studies have questioned the quality of information disseminated by the pharmaceutical industry. Medical journals often contain biased or incomplete information about drugs (Cardarelli 2006; Othman 2009). A systematic review found that studies sponsored by the pharmaceutical industry tended to show more favourable efficacy outcomes compared to non-industry-funded studies (Lundh 2017). Overemphasizing the benefits and minimizing the associated risks can affect the rational use of medicines, particularly when advertising and promotional material are used as an information source by clinicians, patients and members of the public.

Another type of drug promotion involves disease awareness campaigns conducted by the pharmaceutical industry (Mintez 2012; Schwartz 2019). A recent study showed that several of these campaigns in Europe mentioned a drug by brand name, or included the logo or name of the pharmaceutical company (Alves 2018). Benefits of these types of campaigns include increased awareness of the disease leading to earlier diagnosis and treatment and reduced stigma. However, potential negative consequences include the potential for indirect harm through overdiagnosis and unnecessary treatment (Alves 2018; Schwartz 2019).

Increasing concerns over potential harms associated with drug promotion activities have resulted in calls for updated ethical guidance on drug promotion (Parker 2018).

Description of the intervention

WHO ethical criteria for medicinal drug promotion remain the global standard and should be considered by regulators, governments, and academics when developing regulations and strategies for drug promotion (WHO 1988). WHO ethical criteria provide guidance across a range of promotional activities including advertising, medical representatives, medication samples, promotional symposiums, industry-funded research, packaging, labelling, and other sources of patient information aimed at promoting the rational use of medicines. Despite needing to be updated, these criteria continue to provide important guidance, particularly in countries where local regulation is absent or insufficient (Parker 2018).

Drug promotion regulations are a form of complex intervention and vary substantially between countries for a variety of reasons including political, historical, economic, and cultural reasons. The main purpose of drug promotion regulation is to prevent the dissemination of inaccurate, biased, and misleading information, as well as to promote the rational use of medicines (Ratanawijitrasin 2002). Models to regulate drug promotion include codes of practice and regulations from the pharmaceutical industry, governments and non-governmental organizations (Alves 2019).

The pharmaceutical industry has its own codes of ethics and marketing practices, which can be considered to be a voluntary self-regulatory code with no provisions for sanctions (Alves 2019). Some countries require disclosure of financing to third parties, however, whereby the pharmaceutical industry must declare corporate subsidies and maintain transparency regarding any relationship with relevant stakeholders (Rothman 2011).

In other countries, the government alone establishes criteria through its regulatory agencies to approve and monitor promotional activities and impose fines and sanctions where necessary (Alves 2019; Ratanawijitrasin 2002). A co-regulation approach between industry and government can be adopted, in which some forms of promotion fall under government responsibility, while others are delegated to industry (Alves 2019). Additionally, inspection boards can be introduced, composed

of multiple stakeholders, such as representatives from the government and the pharmaceutical industry, as well as healthcare professional and consumer groups (Ratanawijitrasin 2002).

Policies for regulating drug promotion can also include non-governmental initiatives such as the declaration of potential conflicts of interest by researchers when publishing scientific papers, or by academics when lecturing or speaking publicly (Robertson 2009).

Approaches for regulating drug-promotion activities targeting consumers and patients directly vary across countries. Some countries have no restrictions (Harker 2007); some only allow promotion of over-the-counter (OTC) medicines (Chaar 2017; Schwartzberg 2017); and other countries only allow promotion of medications to healthcare professionals in specific ways, such as through medical journals (Ratanawijitrasin 2002).

This review will focus on policies that regulate drug promotion for prescription drugs and non-prescription drugs (i.e. OTC drugs, including vitamins, nutraceuticals, dietary supplements, herbal products, etc.). We will classify these policies into the following three categories, according to their target.

- Policies that regulate drug promotion to patients, patient organisations, consumers and consumer advocacy groups.

These policies will include any controls relating to promotion of prescription drugs and non-prescription drugs, such as advertising through various media, including print, billboards, radio, television and online.

- Policies that regulate drug promotion to healthcare professionals (involved in the prescribing and dispensing of medications), healthcare students, and healthcare professional associations.

This will include regulations relating to direct payments to healthcare professionals (including student healthcare professionals) and their associations, sales representatives, face-to-face visits, educational and promotional meetings, gifts (including all types of financial gifts such as travel expenses and subscriptions to a journal), advertisements in medical journals and through direct mail, key opinion leaders, discount promotions (e.g. coupons), and free drug samples.

- Policies that regulate drug promotion to regulators and third-party payers (insurers, other funders, profit entities, 'not for profit' entities, governments).

We will include regulations targeting lobbying activities, direct payments and other forms of promotion aimed at regulators, federal government, public insurance agencies, private insurers/insurance companies and other funders.

How the intervention might work

Pharmaceutical policies seek to ensure that the dissemination of information about promotional activities is impartial, reliable, balanced, and up to date (WHO 1988). In 2004, WHO suggested that enhanced government regulation and prescriber education could lead to improvements in drug promotion (WHO 2004). This also could help prevent serious violations (e.g. misleading claims, off-label promotion), and allow patients, consumers, and healthcare professionals to make informed decisions about safe and effective drug use (Lexchin 2012; Zetterqvist 2015).

Some countries have used active means of monitoring drug promotion, which are generally carried out by government (Lexchin 2010). This involves drug regulatory authorities checking whether promotion activities and their materials comply with policies and legislation (Ratanawijitrasin 2002). Other countries use passive means whereby violations are discovered through complaints by consumers or competing companies to the responsible bodies (Ratanawijitrasin 2002).

The monitoring of drug promotion may occur before or after dissemination. In practice, some regulatory agencies cannot review all material due to the large volume that they receive and their limited resources (Mintez 2012). In cases where monitoring only occurs after dissemination, the fines imposed are often not sufficient to prevent illegal or abusive activities (Lexchin 2012). However, recent research suggests that most governments in high-income countries prefer to rely on co-regulation (Alves 2019). Other studies recognise that regulatory systems depend on financing, political will and support from the public and healthcare professionals to successfully regulate drug promotion (Lexchin 2012).

Drug promotion should be conducted in accordance with relevant ethical and regulatory requirements (Jacob 2018). There are nevertheless discrepancies between the policies and practices of drug promotion and law enforcement in different countries (Alves 2019; Zetterqvist 2015). For example although most countries do not allow DTCA, some have poor monitoring and enforcement of these requirements (Mintez 2012). In several countries (both low- and high-income), the financing of regulation and monitoring of drug promotion is insufficient and unstable (Lexchin 2012). This limits the impact of the relevant regulations to promote the rational use of medicine and public health protection (Lexchin 2010).

Why it is important to do this review

Vast and increasing amounts of money are spent on drug promotion activities globally each year (Schwartz 2019); these activities can have both positive and negative influences on consumer and clinician behaviour. Several published reviews have examined the effects of drug promotion on quality, quantity, and cost of physicians' prescribing (Brax 2017; Fickweiler 2017; Spurling 2010). The association between exposure to DTCA and attitudes and quality of pharmaceutical advertisements in medical journals have also been examined (Austad 2011; Kravitz 2005; Othman 2009). We have not, however, identified any previous systematic reviews that address the effects of policies regulating drug promotion.

We anticipate that the results of this review will provide information as to which types of policies are likely to be effective in regulating drug promotion to patients/consumers, healthcare professionals, regulators, and third-party payers.

OBJECTIVES

Main objective

To assess the effects of policies that regulate drug promotion on drug utilization, coverage or access, healthcare utilization, patient outcomes, adverse events and costs.

Secondary objective(s)

To assess whether the effects of policies that regulate drug promotion to patients/consumers, healthcare professionals, regulators and third-party payers differ according to drug class, clinical indication, target groups and country (high-, middle- or low-income countries).

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised trials, non-randomised trials, controlled before-after studies, interrupted time series studies and repeated measures studies. We will include controlled before-after studies if they have at least two intervention sites and two control sites. We will include interrupted time series studies if there is a clearly defined point in time when the intervention occurred and at least three data points before and three data points after implementation of the policy.

Studies will be eligible for inclusion irrespective of their publication status and language of publication.

Types of participants

We will include studies evaluating drug promotion policies that target i) patients, patient organisations, consumers, and consumer advocacy groups; ii) healthcare professionals, healthcare students, and healthcare professional associations; and iii) regulators and third-party payers. For the purpose of this review, consumers can constitute either patients or members of the public at whom drug promotion activities are targeted. Healthcare professionals can be based in any healthcare setting where they have responsibility for the prescribing or supply of drug treatments to consumers. Regulators and third-party payers are defined as private insurers/insurance companies, federal governments, and any other groups with responsibility for funding decisions.

Types of interventions

Policies are defined as laws, rules, guidelines, codes of practice and financial or administrative orders made by governments, non-government organizations (i.e. health workers associations and patient groups) or private insurers.

We will include all policies that regulate drug promotion to consumers, or healthcare professionals or regulators and third-party payers, or any combination of these groups. In the context of this review, drugs are defined as all products that are promoted as a medicine, including prescription and non-prescription drugs, and over-the-counter (OTC) drugs (WHO 1988). We will distinguish between policies that regulate the promotion of prescription and non-prescription drugs (i.e. OTC drugs, including vitamins, nutraceuticals, dietary supplements, herbal products, etc.). We will consider using the individual study's definition/classification of OTC medicines and other forms of supplements.

The interventions of interest for this review will regulate one or more aspects of drug promotion relating to: advertising, medical representatives medication samples, promotional symposia and other scientific meetings, industry-funded research, packaging/labelling, and other sources of patient information (e.g. package inserts, leaflets, booklets), branded gift items, financial gifts, payment of travel costs and meals, direct payment for services, achieving cost subsidy, achieving regulatory approval for use, and recommendations for inclusion in clinical guidelines or drug formularies. We will also include disease awareness and 'ask your doctor' campaigns in which a drug is directly mentioned (Parker 2018; WHO 1988).

For this review, we will include the following comparisons.

- Policies that regulate drug promotion versus no intervention
- One policy to regulate drug promotion versus another policy to regulate drug promotion

Types of outcome measures

For us to include a study in this review it has to include an objective measure from at least one of the following primary or secondary outcome categories.

Primary outcomes

- **Drug utilization, coverage or access:** changes in consumption or sales of medicines, prescription patterns (e.g. overprescription, underprescription, off-label uses, quality of prescription as defined in the included papers) or insurance coverage decisions.

Secondary outcomes

- **Health care utilization:** changes in the use of health services, such as physician office visits per year.
- **Patient outcomes:** health status (mortality, morbidity, hospitalizations, quality of life) or health behaviour (adherence to treatment).
- **Any adverse effects** (unintended consequences): increased inequalities, such as differences in patient outcomes between vulnerable (e.g. low-income) and less vulnerable groups, reduced quality of care (adherence to recommended practice or guidelines), undesirable effects on healthcare providers or increased resource utilization.
- **Costs**: including total and out-of-pocket expenditures on drugs or health care, and catastrophic health expenditures. We will also include costs from the perspective of a third-party payer (insurance, government) for covered medicines.

Search methods for identification of studies

Electronic searches

We will search the following databases for primary studies.

- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library: www.cochranelibrary.com
- EconLit, ProQuest
- MEDLINE, Ovid
- Embase, Ovid
- Global Index Medicus, WHO: www.globalindexmedicus.net
- VHL Regional Portal, Virtual Health Library: bvsalud.org/en
- INRUD Bibliography, International Network for the Rational Use of Drugs: www.zotero.org/groups/659457/inrud_biblio?

We will search the following databases for related systematic reviews and their included studies.

- Epistemonikos, Epistemonikos Foundation: www.epistemonikos.org
- Health Systems Evidence: www.healthsystemsevidence.org/?lang=en
- Health Evidence: www.healthevidence.org

We will use the strategy provided in Appendix 1 to search MEDLINE; and we will adapt it for each of the other databases.

We will not apply any limits on language and we will search all databases from inception to the date of search. We will limit the strategies to appropriate study designs: randomised trials, non-randomised trials, interrupted time series studies and controlled before-after studies. To find as many relevant drug-marketing policy studies as possible, studies that include terms for a policy and those that do not, we will combine terms for drug marketing with terms for relevant study designs mentioned above, but omit any policy terms in the search strategies we will use.

Searching other resources

We will also search the following web sites and databases.

Trial registries

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP): www.who.int/ictrp
- ClinicalTrials.gov, US National Institutes of Health: www.ClinicalTrials.gov

Grey literature

We will conduct a grey literature search of the following web sites to identify studies that are not indexed in the databases listed above.

- Open Grey: www.opengrey.eu
- Grey Literature Report, New York Academy of Medicine: www.greylit.org

And we will:

- review reference lists of all included studies and relevant systematic reviews for additional potentially eligible primary studies;
- contact authors of included studies/reviews to clarify reported published information and to seek unpublished results/data where necessary;
- search the Web of Science Core Collection, Clarivate Analytics, for studies that have cited all included studies.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved through electronic database searching to a reference management database and remove duplicates. Two review authors will independently screen titles and abstracts for inclusion. We will retrieve the full text of potentially relevant references and two review authors will independently assess the full-text articles for inclusion. We will record reasons for exclusion for studies that we exclude following the full-text review. Any disagreements will be resolved through discussion or, if required, by consulting a third review author.

We will list in the 'Characteristics of excluded studies' table, including reasons for exclusion, studies that initially appeared to meet the inclusion criteria but that we later excluded at the full-text review stage. We will collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will also provide any information we can obtain about ongoing studies. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Liberati 2009).

Data extraction and management

Two review authors will independently extract the following information from the included studies using the EPOC standardised data collection form EPOC 2017a and adapt it for study characteristics and outcome data.

- Study design
- Study setting: country, classified according to World Bank income classification: low-, middle- or high-income country (World Bank 2020), key features of the healthcare system and concurrent pharmaceutical policies
- Characteristics of the participants
- Characteristics of the policies
- Main outcome measures and study duration
- Results for the main outcome measures
- Sponsors of the study

We will extract data comprehensively to cover all relevant outcomes and methods reported across studies.

If a study presents results on the same outcome several times (e.g. by using different units) or across a large number of medicine groups, we will choose what we consider to be the most important outcomes (drug utilization, coverage or access, healthcare utilization, patient outcomes, adverse effects, costs) as specified by the study authors or based on discussions among the review authors.

Where key data are missing from the study reports, we will attempt to contact the authors to obtain such information. Where multiple reports of the same trial are published, we will extract data from those we deem to be most complete.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each included study using the criteria suggested by the EPOC group (EPOC 2017b) and other recommendations (Higgins 2020; Sterne 2016). We will resolve any disagreements by discussion or by involving a third review author. We will judge each potential source of bias as high, low, or unclear and provide a justification for our judgment in the 'Risk of bias' table.

The assessment domains for randomised trials and non-randomised trials are:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- incomplete outcome data;
- blinded assessment of primary outcomes;
- selective outcome reporting;

- other risk of bias.

The assessment domains for controlled before-after studies are:

- baseline measurement of outcomes;
- baseline characteristics of studies using second site as control;
- follow-up of providers or decision makers;
- follow-up of health care consumers;
- reliable primary outcomes measures;
- blinded assessment of primary outcomes;
- protection against contamination;
- other risk of bias.

The assessment domains for interrupted time-series and repeated measures studies are:

- intervention independent of other changes;
- appropriate data analysis;
- shape of effect pre-specified;
- intervention unlikely to affect data collection;
- blinded assessment of primary outcome(s);
- completeness of data set (complete outcome data addressed);
- reporting selective reliable primary outcome measures;
- other bias.

For controlled interrupted time series studies and controlled repeated measures studies, we will assess the time series part of the studies independently from the control part, using the above-described criteria for interrupted times series and repeated measures studies. We will assess the control series part of the study using the controlled before-after criteria above. Specifically, for interrupted time series studies we will use methodological recommendations to guide our assessments (Jandoc 2015).

Measures of treatment effect

Trials and controlled before-after (CBA) studies

We will report relative effects for randomised, non-randomised and CBA studies. In the case of CBA studies, we will report adjusted relative effects. For dichotomous outcomes we will report, if possible, the relative risk (RR) adjusted for baseline differences in the outcome measure, that is the RR post-intervention/the RR pre-intervention. For continuous outcomes, we will report, if possible, the relative change adjusted for baseline differences in the outcome measure, that is the absolute post-intervention difference between groups minus the absolute pre-intervention difference between groups, divided by the post-intervention level in the control group.

Interrupted time series (ITS), and repeated measure (RM) studies

Our preferred analysis method for ITS and RM studies will be regression analysis with time trends before and after the intervention, adjusted for autocorrelation and periodic changes, or auto regressive integrated moving average (ARIMA) analysis or other techniques that adjusted for autocorrelation and secular trends (Ramsay 2003).

We will present results for the outcomes as changes along two dimensions: change in level; and change in slope.

Change in level, which is the immediate effect of the policy, is measured as 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.

Change in slope, which is the change in the trend from pre-intervention to post-intervention, reflects the long-term effect of the intervention. As interpretation of the change in slope could be difficult, we will choose the long-term effects similarly to the immediate effects.

We will present the effects after six months as the fitted value for the six-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. We will report the effects after one year and after two years in the same way if the study measured it. For pharmaceutical expenditures, we will also calculate the savings after six months, one year and two years as the area between predicted and actual expenditure curves.

Given that policy changes are often announced some months prior to official implementation, we will define a transition phase as the six months from official announcement.

If the included ITS and RM studies state a different transition phase, we will use the study's definition. All results will exclude the transition phase data.

If papers with ITS design do not provide an appropriate analysis or reporting of results, but present the data points in a scanable graph or table, we will reanalyse the data using methods described in Ramsay 2003.

For controlled ITS studies, we will present the difference between the relative changes of the intervention and the control groups.

In an RM design, the data are repeated outcome measures from many individual patients. If a study does not report appropriate results, we will not reanalyse the data from the summary graphs, because no estimate of within-patient variability can be obtained from the summary graphs and any reanalysis would underestimate or overestimate the standard error of the effect sizes. Therefore, for RM studies we will present the results reported in the original papers only.

We will estimate the effect of the intervention using risk ratio/risk difference for dichotomous data, together with the appropriate associated 95% confidence interval and mean difference or standardised mean difference for continuous data, together with the 95% appropriate associated confidence interval (Higgins 2020). We will ensure that an increase in scores for continuous outcomes can be interpreted in the same way for each outcome, explain the direction to the reader, and report where the directions were reversed, if this was necessary.

Unit of analysis issues

We will perform analysis at the same level as the allocation to avoid unit-of-analyses errors. If there is a unit-of-analysis error in the reported analysis for a study and there is insufficient information to reanalyse the data, we will contact the authors to obtain the necessary data. If these data are not available, we will not report

95% confidence interval (95% CI) or P values for which there is a unit-of-analysis error.

Dealing with missing data

If necessary, we will contact study authors in order to verify key study characteristics and obtain missing outcome data or any other absent data we deem to be important.

If we are not able to obtain missing data, however, we will report the available results provided they are not likely to be misleading.

Assessment of heterogeneity

If we find a sufficient number of studies for which we judge participants, policies, comparisons and outcomes to be sufficiently similar, we will conduct a meta-analysis (Borenstein 2009).

We will assess the extent of the heterogeneity among results of comparable studies using forest plot, I^2 statistic and the Chi^2 test.

We will assess potentially unimportant heterogeneity as an I^2 result between 0% and 40%, moderate heterogeneity as 30% to 60%, substantial heterogeneity as 50% to 90% and considerable heterogeneity as 75% to 100% (Higgins 2020). If we identify substantial heterogeneity, we will explore it by prespecified subgroup analysis.

Assessment of reporting biases

We will attempt to contact study authors, asking them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results. If we are able to pool more than 10 studies, we will create a funnel plot to visually explore the risk of publication bias, interpreting the results with caution (Sterne 2011).

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Data synthesis

We will group studies into the three categories of interventions or policies (policies addressed to patients/consumers; healthcare professionals (prescribers and dispensers); and regulators and third-party payers).

We will prepare a table for each category of intervention including the following information: study identification, characteristics of the intervention, drug use, healthcare utilization, patients' outcomes, adverse events, adherence, equity and resource utilization (costs).

We will undertake meta-analyses for studies that report comparisons (interventions, comparisons and outcome measures) that are sufficiently similar that an average effect across those studies would be meaningful.

For randomised trials, non-randomised trials and controlled before-after studies, we will record the number of events (in the case of health outcomes) and the total number in each group (for risk ratio), or mean and standard deviation (SD) in each group (for mean difference (MD), for instance in the case of drug utilization). All outcome effects will be shown with their associated 95% CI. Anticipating heterogeneity across studies, we will use a random-effects model for any meta-analysis. Data synthesis will be performed using the Cochrane statistical software, Review Manager 5 (Review Manager 2014).

If it is not possible to synthesize the data from the included studies, we will undertake a structured narrative synthesis following the EPOC guidance on this topic (EPOC 2017c). For each category of intervention, we will describe the range of effects found in the studies and, if possible, the mechanisms through which the interventions were intended to affect specific outcomes.

Subgroup analysis and investigation of heterogeneity

When investigating heterogeneity, we will consider the following potential effect modifiers: differences in the type of the policy, differences in the settings (low-, middle- and high-income countries), differences in the drug classes, difference in the condition (chronic disease, acute diseases or palliative care), differences in characteristics of the targets (e.g. sex, age, health status and education or socioeconomic status), differences in the type of health professional involved (using individual study's definition/classification of targeted healthcare professional group).

We will carry out subgroup analyses only if there are sufficient numbers of studies per outcome and we will use Review Manager 2014 to estimate subgroup differences (e.g. using the Chi^2 test for subgroup differences).

Sensitivity analysis

We will perform sensitivity analyses to assess the robustness of our conclusions and explore its impact. This will involve the following.

- Restricting the analysis to studies with a low risk of bias; when there are studies with differing risks of bias, excluding studies with a high risk or uncertain risk of bias.
- Imputing missing data and discussing it.

Summary of findings and assessment of the certainty of the evidence

We will grade the confidence in the available estimates of effects using the GRADE framework (Balshem 2011; Guyatt 2008), and GRADEpro software (GRADEpro GDT 2020). Two review authors will independently assess the certainty of the evidence (high, moderate, low, and very low) using the following five GRADE considerations.

- Risk of bias
- Consistency of effect
- Imprecision
- Indirectness
- Publication bias

We will resolve any disagreements on certainty ratings by discussion and provide justification for decisions to downgrade or upgrade the ratings using footnotes in the table. We will use plain language statements to report these findings in the review (EPOC 2018).

We will summarise the findings in a 'Summary of findings' table(s) for the main intervention comparison(s) and include the most important outcomes (drug utilization, coverage or access; health

care utilization; patient outcomes; any adverse effects; costs) in order to draw conclusions about the certainty of the evidence within the text of the review. If during the review process, we become aware of an important outcome that we failed to list in our planned 'Summary of findings' table(s), we will include the relevant outcome and explain the reasons for this is the section 'Differences between protocol and review'.

We will consider whether there is any additional outcome information that we were not able to be incorporate into meta-analyses and note this in the comments and state if it supports or contradicts the information from the meta-analyses. If we are unable to meta-analyse the data, we will summarise the results in the text.

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APPENDICES

Appendix 1. MEDLINE search strategy

MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 30, 2020, Ovid

#	Searches	Results
1	(drug marketing or pharmaceutical marketing).ti.	155
2	Drug Industry/	32974
3	Prescription Drugs/	5768
4	Nonprescription Drugs/	6040
5	Behind-the-Counter Drugs/	18
6	PharmaceuticalPreparations/	53283
7	DrugPrescriptions/	27556
8	or/2-7	118535
9	Marketing/	5434
10	Marketingof Health Services/	14698
11	Advertising as Topic/	14560
12	Direct-to-Consumer Advertising/	249
13	Gift Giving/	1590

(Continued)

14	Consumer Health Information/	3630
15	Information Dissemination/	16291
16	Mass Media/	10839
17	or/9-16	62185
18	PracticePatterns, Physicians'/	58596
19	Disclosure/	13424
20	or/18-19	71886
21	8 and 17	5187
22	2 and 20	1348
23	21 or 22	6068
24	((drug? or pharmaceutical? or medicine? or medical or medication) and (marketing or promot* or advertis* or advertiz*)).ti.	5159
25	((drug? or pharmaceutical? or medicine? or medical or medication) adj3 (marketing or promot* or advertis* or advertiz*)).ab,kf.	8363
26	((drug industr* or pharma* industr* or medical industr* or drug compan* or pharma* compan* or medical compan*) and (mass media or health information or gift? or free sample? or medication sample? or drug sample? or visit*)).ti,ab,kf.	588
27	24 or 25 or 26	13108
28	23 or 27	17567
29	randomizedcontrolled trial.pt.	502862
30	controlledclinical trial.pt.	93587
31	multicenter study.pt.	268858
32	pragmaticclinical trial.pt.	1338
33	non-randomized controlled trials as topic/	641
34	interrupted time series analysis/	807
35	controlledbefore-after studies/	488
36	(randomis* or randomiz* or randomly).ti,ab.	885037
37	groups.ab.	2028061
38	(trial or multicenter or multi center or multicentre or multi centre).ti.	256209
39	(intervention? or effect? or impact? or controlled or control group? or (before adj5 after) or (pre adj5 post) or ((pretest or pre test) and (posttest or post test)) or quasi-	9498870

(Continued)

	experiment* or quasi experiment* or pseudo experiment* or pseudoexperiment* or evaluat* or time series or time point? or time trend? or repeated measur*).ti,ab.	
40	or/29-39	10583988
41	expAnimals/	23058646
42	Humans/	18374680
43	41 not (41 and 42)	4683966
44	(review or meta analysis or news or comment or editorial).pt.	4040806
45	cochrane database of systematic reviews.jn.	14727
46	comment on.cm.	838650
47	(systematic review or literature review).ti.	153785
48	or/43-47	8563004
49	40 not 48	7479382
50	28 and 49	5180
51	1 or 50	5301

HISTORY

Protocol first published: Issue 11, 2020

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Conceiving the protocol: LCL; IF

Designing the protocol: LCL; IF; CAC; CC

Co-ordinating the protocol: LCL

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- No sources of support supplied

External sources

- Monash University, Monash Department of Clinical Epidemiology - Cabrini, Australia

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