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Unbranded advertising of prescription medicines to the public by pharmaceutical companies (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Unbranded advertising of prescription medicines to the public by pharmaceutical companies

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ABSTRACT

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

To assess the effects of unbranded advertising of prescription medicines, conducted by or on behalf of pharmaceutical companies, on consumers' attitudes, knowledge, behaviour, health services use, health outcomes and costs.

BACKGROUND

Direct advertising of prescription drugs to the public, also known as direct-to-consumer advertising (DTCA) (Table 1), is permitted only in the USA and New Zealand. Advertising of products that have prescription-only status is prohibited in the European Union as a public health protection measure. The rationale for prohibition is linked to prescription-only status. These medicines generally treat more complex or serious conditions and have potentially greater toxicity than over-the-counter medicines (Bond 2004; Mintzes 2010). Because the assistance of a health professional is needed to ensure appropriate use, manufacturers may not sell or advertise these products directly to the public. Nevertheless, manufacturers are using an increasing array of techniques to advertise prescription-only medicines to the public both directly and indirectly (Mintzes 1998; Donohue 2007; Gagnon 2008).

There is also evidence of promotional influence on how the media covers health topics (Cassels 2003) and on how the media can play an important role in influencing decisions on health and treatment (Hogue 2012), shaping consumers' information base and opinions about therapeutic options (Haimowitz 2011), and also affecting public policy. Striking examples include, among others, policy decisions being reversed, such as negative reimbursement recommendations for certain cancer drugs after public outcry; or alterations to government priorities and expenditure following intense media coverage of problems in health services provision (such as waiting lists) (Harrabin 2003).

Description of the condition

According to European Union legislation, pharmaceutical companies are permitted to provide general information on health and diseases, but there cannot be any reference, even indirectly, to a specific medicine, unless it is a vaccine (European Parliament and Council 2004). This provision offers companies an alternative promotional approach (Gilbody 2005), that of unbranded advertising (Table 1), also known as 'disease-awareness', 'help-seeking' or 'condition-oriented' advertisements, which discuss a condition but do not mention a specific brand of medicine (Leonardo Alves 2007). The available evidence suggests that these materials draw attention by generating demand for treatments for non-life threatening conditions, by focusing on symptoms and encouraging viewers to see their doctor to obtain further treatment information (Castleberry 2008) or seeking diagnostic testing that will later be associated with a decision to use a medicine. Despite their nature and content, these unbranded campaigns are not governed by specific regulations on pharmaceutical promotion, and regulators are often reluctant to consider them as advertising unless explicit links to branded product information are included (Vitry 2012).

Proponents of unbranded campaigns claim these have an educational role in raising awareness about untreated, underdiagnosed health problems at an earlier stage and prompting consumers to seek care (Tiner 2002; Wielondek 2005). However, questions have been raised about the effects of industry-funded unbranded advertising on healthcare use and health outcomes: such campaigns can increase product awareness and increase physician visits, prescribing and sales, thereby burdening health systems (Gilbody 2005; Mintzes 2012). By generating demand among those who do not necessarily need medical treatment and supporting the use of newer, more expensive products, these campaigns can encourage irrational medicines use and divert resources away from more important conditions, negatively affecting quality and costs of care (Gilbody 2005; Castleberry 2008). In doing so, these campaigns may also inadvertently disadvantage patients and consumers who are in genuine need of treatment (either for the specific disease covered in the campaign, or for other more serious conditions) (Gilbody 2005).

While much research has been done in other areas of traditional drug promotion (e.g. physician-directed, product detailing, drug samples, DTCA), far less is known about how these unbranded campaigns influence both health practitioners and the public. A systematic review can add to a better understanding of the effects of these campaigns by synthesising existing research evidence and providing a comprehensive overview both of what is known about the outcomes of such advertising campaigns and gaps in research evidence.

Any condition affecting consumers for which there is a pharmaceutical treatment available can be the object of unbranded advertising. Any member of the public can be affected. Therefore, this review is not restricted to specific diagnoses, symptoms and consequences. A glossary of key terms is available (Table 1).

Description of the intervention

This review will assess the effects of unbranded advertising involving mass media channels of communication and conducted by sponsors, namely the pharmaceutical company that manufactures, produces or distributes a medicine or a third party acting on their behalf, for a condition treated by a pharmaceutical product (Table 1).

Mass media channels of communication are intended to reach large numbers of people, as defined by Brinn 2010, Bala 2013 and Mosdøl 2015, and are not dependent on person-to-person contact. Unbranded advertising interventions may be made up of one or more components and/or formats. Different formats include: print media (newspapers, magazines, booklets, leaflets, posters and pamphlets), online media (websites and social media), digital technology, and broadcast media (television and radio) as well as outdoor advertising (billboards and banners). Different components include: statements on diagnostic criteria, health outcomes, prevalence rates and symptom recognition; normative statements; images; interactive content such as questionnaires, screening tools or symptoms checkers that a consumer can fill in; recommendations for action (suggestions to seek further information and treatment, e.g. see your doctor); as well as sources substantiating the message being conveyed. The condition highlighted may represent an approved or unapproved (off-label) use of the advertiser's pharmaceutical product (Table 1).

Unbranded advertising generally targets the whole population, but can also focus on specific audiences within the population, such as women (via magazines that target women, for example). There may be differences not only in targeting specific groups but also in responses by gender (men or women), age (older or younger, adults, children), health status (patients with chronic conditions versus other population groups) or socio-economic status. There may also be differences between such advertising in higher-income countries versus low- to middle-income countries, and the characteristics of unbranded advertising may vary across different settings or jurisdictions.

We will analyse, when possible, differences in the effects of unbranded advertising among different target groups. We will compare how the use and effects of unbranded advertising differ between men and women, as there is evidence of greater marketing exposure and effectiveness among women due to their 'healthcare gatekeeper' role in the family (Handlin 2007). In addition, women may be particularly vulnerable to harm arising from prescription drug advertising both for social and biological reasons, as they are more often prescribed drugs and are more susceptible to some harms associated with specific prescription drugs (Mintzes 2010). It will also be relevant to compare the use and effects of the intervention between different types of patients, as patients with chronic conditions have specific information and treatment

needs that differ from other target groups. Since there are reports of promotional activities encouraging the use of medicines outside their approved indications (off-label) (Steinman 2006), we also plan to carry out a subgroup analysis comparing the effects of unbranded advertising encouraging on- and off-label use (Fugh-Berman 2008).

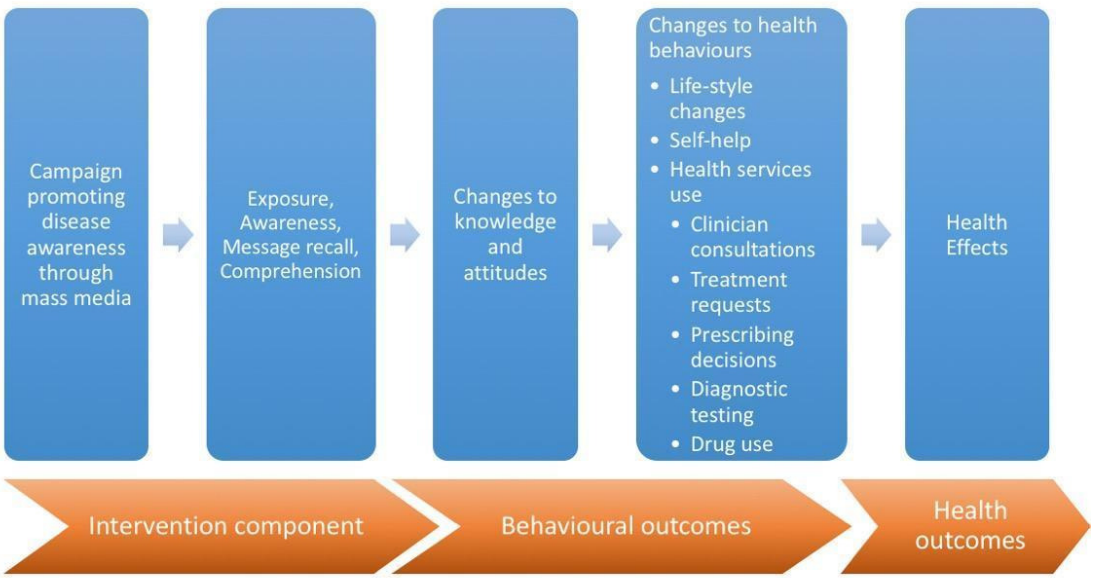
We will compare unbranded advertising with other information or education activities conducted by non-commercial information sources (Table 1); or with no intervention. Non-commercial information or education activities will not be limited to any specific media, but will include print media (newspapers, magazines, leaflets, posters, pamphlets), online media (websites and social media), broadcast media (television and radio) as well as outdoor advertising (billboards and banners). When possible, we will also compare different types of unbranded advertising (for instance traditional media versus social media).

How the intervention might work

Unbranded disease awareness campaigns are often developed and carried out using the concepts and tools from social marketing. Pharmaceutical companies, or third parties acting on their behalf, have an underlying commercial intent to drive the choice for a particular treatment. This unbranded advertising is part of a broader and integrated marketing campaign that aims to increase sales of prescription-only medicines (Mintzes 2012).

Existing studies describe a model whereby advertising to the public affects consumers' awareness of and knowledge about a condition. Consumers are exposed to the unbranded advertising and are stimulated to seek further medical care by consulting their doctors and requesting a pharmaceutical treatment. Consumers' requests trigger the prescription for the advertiser's product by the physician, who has previously been subject to targeted branded advertising (Basara 1996; 't Jong 2004; Hall 2008; Hall 2011). Figure 1 presents a logic model.

Figure 1. Logic model (based on Mosdøl 2015)



Advocates of disease awareness campaigns claim these can educate the public, make consumers aware of otherwise untreated health problems and help them seek effective care at an earlier stage (Tiner 2002; Wielondek 2005). However, concerns have been raised about the content and nature of such campaigns and their potential negative effects. One hypothesis that has been put forward is that advertising campaigns are more misleading than informative (Mansfield 2005; Leonardo Alves 2014).

Unbranded advertising can transform ordinary life experiences into conditions that require medical diagnoses, encourage consumers to seek further medical tests, and misinterpret the evi-

dence about drug benefits and harms (Van Nuland 2010; Schwartz 2013). Also, if such campaigns support the use of newer, more expensive products with least well understood benefit-harm profiles over cheaper, well-known, older medicines, they can encourage irrational medicine use, affecting equity, quality and costs of care (Castleberry 2008).

Campaigns can take place at a single time point, or may be sustained over a longer period. They can also vary in intensity (e.g. extent and frequency of advertising) and reach (e.g. proportion of intended population who see the advertisements).

There are also equity issues associated with the use of unbranded advertising. Gender can influence healthcare access, service utilisation and treatment implementation in different ways, depending on the particular socio-cultural context and region (e.g. lower- and middle-income countries or higher-income countries), and may contribute to the differential impact of unbranded advertising on men and women. In higher-income countries, women may use more health services than men (Bertakis 2000; EU Commission 2009; EU Commission 2011). A similar trend is observed in medicines use, with women using more pharmaceutical products than men and gender targeting in DTCA further reinforcing sexual stereotypes (Mintzes 2012). There is also evidence of a greater exposure to DTCA, along with self-reporting of greater influence, among lower socio-economic groups (Avery 2008). Impact may also be influenced by ability to pay for expensive medicines or available insurance/low co-payments, which differ across socio-economic groups in some countries. It is possible that within lower socio-economic groups, the potential increase in costs resulting from unbranded advertising's encouragement of inappropriate or more expensive treatment choices will have the greatest impact.

Why it is important to do this review

Unbranded advertising of prescription medicines is a grey area in pharmaceutical regulation. Even in countries with strong enforcement of prescription-only status, companies are increasingly running condition-oriented advertising campaigns that aim to stimulate sales of prescription-only medicines. These advertisements do not mention the product's brand name but suggest to viewers to 'ask your doctor'. Unbranded advertising may or may not include that a pharmaceutical company is sponsoring the campaign.

The quality and nature of the information provided in such campaigns is very relevant to inform current and future discussions on pharmaceutical regulation. A proposal for a European directive on information to the general public on medicinal products subject to medical prescription, presented in December 2008, foresaw changes to the regulations on medicines advertising (EU Commission 2008). The proposal contemplated an expanded role for the pharmaceutical industry in the provision of information on prescription medicines directly to the public through the Internet and health-related publications.

The ever-increasing scope and complexity of digital advertising and its span across various media outlets poses a challenge to authorities, which are faced with regulatory frameworks that have not kept abreast with these developments (Gibson 2014).

This systematic review will provide needed evidence to inform current policy discussions on the impact of public unbranded campaigns by the pharmaceutical industry in terms of the research evidence and gaps in knowledge about effects on consumers' attitudes, knowledge, health services use, costs and health outcomes. It is important for these discussions to be informed by the existing body of research evidence, including an understanding of current gaps in knowledge about the effects of this intervention.

There is a Cochrane review on mass media interventions and their effects on health services utilisation (Grilli 2002). The review, however, does not mention unbranded advertising by sponsors and excludes the effects on patient and public attitudes, awareness and knowledge. Moreover, the review also excluded online interventions.

We intend to investigate a specific type of intervention both in terms of the agent that is carrying out the intervention (pharmaceutical manufacturers or other entities or actors that are funded by pharmaceutical manufacturers) and the link to marketing of health products. Due to their commercial intent these interventions are likely to differ systematically from mass media interventions by public health agencies.

Additionally, a systematic review specifically focusing on disease-awareness advertising would provide important background information for regulatory decision-making in this domain. The European Commission has carried out public consultations to canvas opinions on potential legislative changes including on the use of different tools to inform the public about prescription-only medicines; such tools included disease-awareness campaigns. However, no evaluation of the responses to those consultations was produced. The only report published made many assertions concerning outcomes based on varying levels of evidence, contained serious methodological flaws (non-representative sampling; selection bias) and was incomplete (AIM 2007). A rigorous systematic review is therefore needed to shed light on the effects of unbranded advertising.

There are no systematic reviews specifically on this topic as the existing Gilbody 2005 review - now outdated - included both branded and unbranded advertising. The authors did not find any studies that assessed health outcomes. They concluded that while it was clear that DTCA increased prescriptions and market share, there was a void in research of its wider effects. The authors also added that further research on disease awareness campaigns was justified. A number of narrative reviews have examined the issue of disease mongering, including unbranded pharmaceutical advertising (European Parliament 2012; Mintzes 2012).

OBJECTIVES

To assess the effects of unbranded advertising of prescription medicines, conducted by or on behalf of pharmaceutical companies, on consumers' attitudes, knowledge, behaviour, health services use, health outcomes and costs.

METHODS

Criteria for considering studies for this review

Types of studies

We anticipate that few if any randomised controlled trials (RCTs) will have assessed the influence of mass media unbranded advertising sponsored by pharmaceutical companies, especially under conditions of usual advertising exposure. We will therefore include a broader range of study designs in this review, including non-randomised studies, guided by the recommendations from Cochrane Effective Practice and Organisation of Care (EPOC) (EPOC 2013).

We will include the following types of studies:

1) Randomised studies:

- RCTs; and
- cluster-randomised trials, in which the unit of allocation is a specific unit, such as a regional district or institution, rather than an individual.

2) Non-randomised studies:

- quasi-RCTs; these trials attempt randomisation but a non-random type of sequence generation is used, such as day of the week, date or birth, or sequence of entry into trial; and
- controlled before-after (CBA) studies, in which:
  - there are at least two intervention sites and two control sites
  - the timing of the periods for study for the control and intervention groups is comparable (that is, the pre- and post-intervention periods of measurement for the control and intervention groups should be the same); and
  - the intervention and control groups are comparable on key characteristics.

3) Interrupted time series (ITS) studies in which:

- the intervention occurred at a clearly defined point in time, as described by the researchers; and
- there were at least three data points before and three data points after the intervention was introduced.

4) Observational studies:

- controlled cohort studies, in which:
  - a concurrent control group is selected from a similar or the same population as the group with exposure;
  - some form of matching or statistical adjustment is used to minimise the influence of factors other than the exposure of interest; and
  - the cohort consists either of a specific population (e.g. residents of a specified region with advertising exposure; a health insurance database) or of a random sample of a population.

We will only include studies from 1990 onwards as mass media channels have diversified quickly over the last 25 years, changing their nature and type of interventions.

Types of participants

Participants will be members of the public (e.g. consumers) who are exposed to specific unbranded advertising campaigns, with subgroup analyses when possible per demographic group (sex, age, setting), as well as per patient group (people diagnosed with a specific condition). We will exclude studies of health professionals since the regulations governing advertising of prescription-only medicines to health practitioners are substantively different from those governing advertising to the general public.

We will exclude studies on individual patient information provided by healthcare professionals (at a doctor's office, clinic, hospital, health centre, pharmacy) for individual patient information purposes; as well as any material or information provided by a pharmaceutical manufacturer to a healthcare professional for use only by the professional. In addition, unbranded advertising by companies that do not sell prescription-only medicines (e.g. medical device manufacturers, natural health product manufacturers, and food, infant formula, and nutritional supplement companies) will be excluded. Moreover, unbranded campaigns about vaccines will also be excluded.

Types of interventions

We will include all types of mass media unbranded campaigns conducted by sponsors where there is no direct reference to a pharmaceutical product's brand name. To be eligible, the information provided must be produced by or on behalf of a pharmaceutical company and the intervention must:

1. include mention of a therapeutic drug class; and/or
2. include mention of a condition or disease to be treated with a product; and/or
3. include other information suggesting a visit to a physician to request a treatment with a pharmaceutical product; and/or
4. stimulate diagnostic testing of a condition for which a pharmaceutical treatment is available.

We will define mass media as in other Cochrane reviews (Bala 2013; Brinn 2010; Mosdøl 2015): "Mass media is defined here as channels of communication such as television, radio, newspapers, billboards, posters, leaflets or booklets intended to reach large numbers of people and which are not dependent on person-to-person contact". As recommended by Mosdøl 2015, we will

also include other channels such as campaigns delivered through the Internet, social media and mass distribution through mobile phones.

We will consider a sponsor as any pharmaceutical company that manufactures, produces or distributes a medicine.

We will define advertising as: communication on behalf of a sponsor, or third party acting on its behalf which aims to raise awareness about a specific condition and/or promote or encourage the use of pharmaceutical product(s). This includes both traditional forms of paid communication such as television commercials, and communication in which payment is less explicit, such as online media postings. Advertising is thus not limited to any specific media, but includes print media (newspapers, magazines, leaflets, booklets, posters, pamphlets), online media, broadcast media (television and radio) as well as outdoor advertising (billboards and banners).

We will only consider including studies about hypothetical (i.e. theoretical or experimental, not implemented) unbranded advertising campaigns in our review if the studies are produced or carried out by or on behalf of pharmaceutical companies. Likewise, if the information provided in the study enables us to ascertain that the third party implementing the unbranded advertising campaign is acting on behalf of the sponsor (for instance a patient or user group funded by the sponsor), then that study will be included provided it meets the other inclusion criteria.

We will include studies that compare unbranded advertising with:

- no intervention;
- any information or education activities provided by non-commercial sources;
- branded advertising; or
- another type of unbranded advertising.

We will set no requirements on the minimum length of intervention.

We will exclude:

- interventions by healthcare professionals (at a doctor's office, clinic, hospital, health centre, or pharmacy) for individual patient information purposes;
- any material or information provided by a pharmaceutical manufacturer to the healthcare professional;
- campaigns focusing on vaccination;
- campaigns focusing on medical devices containing no prescription medicine;
- campaigns focusing on over-the-counter medicines (medicines not subject to medical prescription); and
- disease-oriented advertising by companies promoting natural health products, food, infant formula, and nutritional supplements.

Types of outcome measures

We anticipate that the studies included in this review will report a wide variety of outcome measures. The following outcome categories have been identified.

1. Consumer attitudes. This would include positive or negative effects; stigma/acceptance; anxiety/reassurance.
2. Consumer knowledge. This would include accuracy of assessment of disease risks, prognosis, prevalence; knowledge of treatment availability and estimated benefit and harm.
3. Consumer behaviour. This would include both information- and care-seeking behaviours, such as seeking medical advice or visiting the GP or pharmacist), as well as undertaking lifestyle modifications (e.g. quitting smoking, exercise, dietary change).
4. Health services use. This would include effects on health services utilisation such as rates of diagnostic testing (e.g. plasma testosterone levels; bone density; plasma glucose levels); consultations or discussions with healthcare professionals; physician visits in total; physician visits for the advertised condition; other health professional contacts (including pharmacist consultations, mental health professionals etc.); requests for medicines; medicine switches (changes to the pharmaceutical product prescribed).
5. Health service costs, such as: overall costs; medicine use rates (changes in frequency of initiating a new prescription; costs associated with switching from one product to another; changes to the sales volume and to the prescribing volume).
6. Health outcomes associated with a shift in health services use. The outcomes to be assessed include serious adverse events (including hospitalisations and emergency visits); adverse events associated with specific treatments; condition-specific adverse events. No direction of effect is prespecified; shifts in health services use may be associated with either a reduction or an increase in these adverse events.

If more than one outcome measure is available from a study for the same outcome, we will consider the following criteria when selecting an outcome measure.

1. We will select the outcome that has been defined as primary by the study authors.
2. If no primary outcome has been identified, we will choose the outcome measure used in sample size calculations.
3. If no outcome measure is mentioned in the sample size calculations, we will select the most appropriate or relevant outcome measure for the given intervention. This will most likely require further discussion among the authors responsible for data extraction.

Primary outcomes

We have opted to focus mainly on the outcome category of health services use and to select primary outcomes that are objective (not self-reported) and clearly linked to advertising campaigns. Each of these endpoints is also measurable and could be easily combined in a meta-analysis:

1. measures of consumer knowledge;
2. rates of consultations with health professionals; and

3. prescribing rates (including initiation, switching and discontinuation rates).

These outcomes will be measured in terms of the level of change observed and the lag time between the media intervention and the observed effect.

Secondary outcomes

As secondary outcomes of interest, we will include:

1. measures of consumer attitudes on diagnosis and treatment;
2. diagnostic testing rates;
3. fatal and non-fatal serious adverse events, including hospitalisations and emergency visits; and
4. health service costs.

Timing of outcome assessment

We have not established a minimum duration of follow-up for the outcome measures. If data are available, we will present outcomes separately for shorter-term (less than six months) and longer-term follow-up.

Main outcomes for 'Summary of findings' tables

Bearing in mind their relevance to stakeholders and to decision making, we have opted to select outcomes that are clearly linked to advertising campaigns. These endpoints are also measurable and could be easily combined in a meta-analysis. They are:

1. measures of consumer knowledge of diagnosis criteria, disease prognosis, and treatment outcomes;
2. rates of consultations with health professionals;
3. diagnostic testing rates;
4. prescribing rates;
5. fatal and non-fatal serious adverse events, including hospitalisations and emergency visits; and
6. health service costs.

Search methods for identification of studies

We will obtain the assistance of a research librarian with expertise in Cochrane systematic reviews to prepare the electronic search.

Electronic searches

We will start our electronic search from 1990 (as explained in Types of studies). We will search the following electronic databases.

- The Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, latest issue)
- MEDLINE (OvidSP) (1990 to present)
- Embase (Embase.com) (1990 to present)
- PsycINFO (OvidSP) (1990 to present)
- SCOPUS (1990 to present)
- CINAHL (EBSCOhost) (1990 to present)

There will be no language restrictions during the electronic searches; translation will be organised as needed through university and Cochrane network contacts.

We present the strategy for MEDLINE in Appendix 1.

We will tailor strategies to other databases and report them in the review.

Searching other resources

We expect that many of the studies examining the effects of unbranded advertising will be unpublished, internal market studies held by pharmaceutical companies; therefore the usual strategies to find unpublished studies via clinical trial registries, pharmaceutical company websites and regulatory documents are not likely to be successful. We will search the drug industry documents database (www.industrydocumentslibrary.ucsf.edu/drug) and search studies via US court cases on marketing activities from 1990 onwards as well as Lexis Nexis using the following keywords.

- unbranded AND advert*
- (disease OR condition) AND aware*
- condition-oriented campaigns
- disease-oriented campaigns
- disease awareness campaigns
- unbranded acquisition campaigns
- consumer relationship marketing of prescription-only medicines

We will search reference lists of included studies and relevant systematic reviews. We will also contact experts in the field and authors of included studies for advice as to other relevant studies. Grey literature search methods will include: searching abstracts of world pharmaceutical marketing conferences; contacting industry bodies in key regions (such as EFPIA, IFPMA and PhRMA) as well as searching websites of governmental and non-governmental organisations (in English, French, Spanish, Portuguese, Dutch, Latvian, German and Russian); and citation forward checking from included studies using the Web of Science and Scopus databases.

Data collection and analysis

Selection of studies

Two authors will independently screen all titles and abstracts identified from searches to determine which meet the inclusion criteria. We will retrieve in full text any papers that are identified as being of potential or uncertain relevance by at least one author. Two review authors will independently screen full-text articles for inclusion or exclusion, with discrepancies resolved by discussion and by consulting a third author if necessary to reach consensus.

We will list all potentially relevant papers excluded from the review at this stage as excluded studies, and will provide reasons in the 'Characteristics of excluded studies' table. We will also provide citation details and any available information about ongoing studies, and collate and report details of duplicate publications, so that each study (rather than each report) is the unit of interest in the review. We will report the screening and selection process in an adapted PRISMA flow chart (Liberati 2009).

Data extraction and management

Two review authors will extract data independently from included studies. Two authors will independently assign the outcomes reported in each included study included to the review's outcome categories (see Types of outcome measures) and resolve any differences in categorisation, if they occur, by the involvement of a third author. We will develop and pilot a data extraction form using the Cochrane Consumers and Communication Group data extraction template, and incorporate elements of EPOC data extraction guidance as necessary.

Data to be extracted will include the following items: details of the study (aim of intervention, study design, description of comparison group, participant characteristics and demographics, details of the intervention - such as country, media outlets used, condition/diagnostic/treatment covered, related drug or therapeutic class, duration, primary and secondary outcomes as well as their data and results, sponsorship status (any private funding received by pharmaceutical companies or third parties acting on their behalf, including the name of sponsor, when available), declaration of interests of the authors.

If the focus of a study is an intervention by a patient, consumer or special interest group, we will try to ascertain whether the group receives core or unrestricted funding from a pharmaceutical company, funding for related projects (by subject area), or if the specific campaign is explicitly referred to as being funded by the sponsor, even if conducted by the patient and/or consumer group. If additional information is provided about the details of the funding such as amount or type (core or project funding), these data will be extracted.

Since the quality and accuracy of the information being conveyed is also an important component of the intervention to be taken into consideration, we will also extract, when possible, additional descriptive information, such as numerical data being disseminated, types of risks mentioned and evidence cited to support claims. In addition, should studies examine effects of relevant policy or regulation shifts, these will be noted and extracted.

Outcome data and results of studies will be extracted from included studies during this process. One review author will enter all extracted data into RevMan (RevMan 2014), and a second review author, working independently, will check them for accuracy against the data extraction sheets. We will present details of the included studies in the 'Characteristics of included studies' section.

Assessment of risk of bias in included studies

We will assess and report on the methodological risk of bias of included studies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the guidelines of Cochrane Consumers and Communication, which recommend the explicit reporting of the following individual elements for RCTs: random sequence generation; allocation sequence concealment; blinding (participants, personnel); blinding (outcome assessment); completeness of outcome data, selective outcome reporting; and funding/sponsorship. We will consider blinding separately for different outcomes where appropriate (for example, blinding may have the potential to affect differently subjective versus objective outcome measures). We will judge each item as being at high, low or unclear risk of bias as set out in the criteria provided by Higgins 2011, and provide a quote from the study report and a justification for our judgement for each item in the 'Risk of bias' table.

RCTs will be deemed to be at the highest risk of bias if they are scored as at high or unclear risk of bias for either the sequence generation or allocation concealment domains, based on growing empirical evidence that these factors are particularly important potential sources of bias (Higgins 2011).

We will assess and report quasi-RCTs as being at a high risk of bias on the random sequence generation item of the 'Risk of bias' tool. For cluster-RCTs we will also assess and report the risk of bias associated with an additional domain: selective recruitment of cluster participants.

EPOC guidance recommends using the same nine criteria for assessment of risk of bias for RCTs, non-randomised controlled trials, and controlled before-after studies (EPOC 2015a). In addition to the above domains identified in the RCT 'Risk of bias' tool, as per EPOC guidance, we will assess the following: whether baseline outcome measurements are similar, whether baseline characteristics are similar, and whether the study was adequately protected against contamination.

We will report CBA studies as being at high risk of bias on both the random sequence generation and allocation sequence concealment items. We will exclude CBA studies with sites that are not reasonably comparable at baseline.

We will assess and report on the following items for ITS studies: intervention independence of other changes; prespecification of the shape of the intervention effect; likelihood of intervention affecting data collection; blinding (participants, personnel); blinding (outcome assessment); completeness of outcome data, selective outcome reporting; and other sources of bias such as seasonality.

Other methodological aspects to consider in ITS that could lead to biased results are autocorrelation and non-stationarity. Autocorrelation measures whether data collected close together in time are correlated with each other. For instance, prescription patterns closer to each other may be more similar. Non-stationary data show an underlying trend that is unrelated to the intervention. We will identify both aspects and when present, we will assess whether

they have been adjusted for.

For controlled cohort studies, we will use the recently developed Cochrane 'Risk of bias' assessment tool for non-randomised studies of interventions (ROBINS-I 2016). This includes an assessment of whether or not the study authors have adequately adjusted for a set of prespecified confounders. Potential confounders are defined as factors associated both with likelihood of exposure to unbranded advertising and to measured outcomes. Based on research on branded DTCA (Mintzes 2012), key identified confounders include age (younger versus older adults), sex, and socioeconomic status and/or insurance status/price sensitivity.

We will also include risk of bias associated with the source of funding (Lundh 2012). This is especially important in an analysis of unbranded advertising by pharmaceutical companies as a commercial sponsor may have a strong incentive for a specific result.

Should any of the studies to be included be authored or co-authored by members of the review author team, data extraction and assessment of risk of bias of those studies will be undertaken by two members of the author team not involved in the primary publication.

In all cases, two authors will independently assess the risk of bias of included studies, with any disagreements resolved by discussion to reach consensus or by third review author adjudication if consensus is not reached. We will contact study authors for additional information about the included studies, or for clarification of the study methods as required. We will incorporate the results of the 'Risk of bias' assessment into the review through standard tables, and systematic narrative description and commentary about each of the elements, leading to an overall assessment the risk of bias of included studies and a judgment about the internal validity of the review's results. We will report risk of bias for multiple study designs (RCTs, CBA studies, ITS studies) using EPOC's suggested table (EPOC 2015b). ROBINS-I 2016 will be used for controlled cohort studies.

Measures of treatment effect

In RCTs, for dichotomous outcomes, we will analyse data based on the number of events and the number of people assessed in the intervention and comparison groups. We will use these to calculate the risk ratio (RR) and 95% confidence interval (CI), using a random-effects model for meta-analysis. For rare outcomes (< 1%) a Peto odds ratio (OR) will be used. For continuous measures, we will analyse data based on the mean, standard deviation (SD) and number of people assessed for both the intervention and comparison groups to calculate mean difference (MD) and 95% CI. If the MD is reported without individual group data, we will use this to report the study results. If more than one study measures the same outcome using different tools, we will calculate the standardised mean difference (SMD) and 95% CI using the inverse variance method in Review Manager 5.

For CBA studies, we will calculate effect measures for dichotomous outcomes (RR) and for continuous outcomes (relative % change post intervention).

For ITS studies, we will look into the change in level of the outcome at the first point after the introduction of the intervention, and the post-intervention slope minus the predicted outcome based on the pre-intervention slope only (EPOC 2013b). We will calculate these estimates from regression models adjusting for autocorrelation. If an ITS study has not reported an appropriate analysis but provides the data points, we will consider re-analysing the data using segmented time series regression techniques (Ramsay 2003; EPOC 2013).

For controlled cohort studies we will use generic inverse variance analysis, based on the logs of hazard ratios (HR) and OR and the standard error of log HR or OR, adjusted for confounding factors.

Unit of analysis issues

If cluster-RCTs are included we will check for unit of analysis errors. If errors are found, and sufficient information is available, we will re-analyse the data using the appropriate unit of analysis, by taking account of the intracluster correlation (ICC). We will obtain estimates of the ICC by contacting authors of included studies, or impute them using estimates from external sources. If it not possible to obtain sufficient information to re-analyse the data we will report effect estimates and annotate 'unit of analysis error'.

Dealing with missing data

We will attempt to contact study authors to obtain missing data (participant, outcome, or summary data). Unsuccessful attempts to retrieve data will be duly reported (i.e. no data available; did not reply; did not provide data). For participant data, we will, where possible, conduct analysis on an intention-to-treat basis; otherwise data will be analysed as reported. We will report on the levels of loss to follow-up and assess this as a source of potential bias. For missing outcome or summary data we will impute missing data where possible and report any assumptions in the review. We will investigate, through sensitivity analyses, the effects of any imputed data on pooled effect estimates.

Assessment of heterogeneity

We will report on the rationale behind any decision to pool or not to pool studies after assessing clinical and methodological heterogeneity, and considering characteristics of participants, interventions, comparisons and outcomes.

Where studies are considered similar enough (based on consideration of populations, interventions and outcomes, and study methodology) to allow pooling of data using meta-analysis, we will assess the degree of heterogeneity by visual inspection of forest plots and by examining the Chi^2 test for heterogeneity. Heterogeneity will be quantified using the I^2 statistic. An I^2 value of

50% or more will be considered to represent substantial levels of heterogeneity, but this value will be interpreted in light of the size and direction of effects and the strength of the evidence for heterogeneity, based on the P value from the Chi² test (Higgins 2011). Where we detect substantial clinical, methodological or statistical heterogeneity across included studies we will not report pooled results from meta-analysis but will instead use a narrative approach to data synthesis. In this event we will attempt to explore possible clinical or methodological reasons for this variation by grouping studies that are similar in terms of populations, intervention features and outcomes, and study methodology to explore differences in intervention effects.

Assessment of reporting biases

We will assess reporting bias qualitatively based on the characteristics of the included studies (e.g. if only small studies that indicate positive findings are identified for inclusion), and if information that we obtain from contacting experts and authors or studies suggests that there are relevant unpublished studies.

If we identify sufficient studies (at least 10) for inclusion in the review we will construct a funnel plot to investigate small study effects, which may indicate the presence of publication bias. We will formally test for funnel plot asymmetry, with the choice of test made based on advice in Higgins 2011, and bearing in mind when interpreting the results that there may be several reasons for funnel plot asymmetry.

Data synthesis

Studies of different designs will be analysed separately. When possible, we plan to analyse RCTs, quasi-RCTs and cluster-RCTs jointly. We will decide whether to meta-analyse data based on whether the interventions in the included trials are similar enough in terms of intervention type, comparison and outcome measures to ensure meaningful conclusions from a statistically pooled result. Due to the anticipated variability in populations and intervention types of included studies, we will use a random-effects model for meta-analysis.

We plan to meta-analyse the data obtained from CBA and/or ITS studies, whenever possible, using a generic inverse-variance weighted average. If we are unable to pool the data statistically using meta-analysis we will conduct a narrative synthesis of results. We will group the data based on the category that best explores the heterogeneity of studies and makes most sense to the reader (i.e. by interventions, populations or outcomes). Within each category we will present the data in tables and narratively summarise the results.

We will carry out separate meta-analysis of controlled cohort data if these are possible, for example if studies with similar enough designs, interventions, and outcomes are found for results to be meaningfully combined. In this case we will use generic inverse variance to combine OR or HR and maintain the authors' adjustments for potential confounders.

Should meta-analysis not be possible, we will provide descriptive statistics for CBA, ITS and controlled cohort studies. Descriptive statistics could include median effect sizes, inter-quartile ranges or other measures, and this information could be presented graphically using bar charts or other approaches.

We plan to conduct the following comparisons:

- Unbranded advertising versus no advertising
- Unbranded advertising versus branded advertising
- Unbranded advertising from sponsors or parties acting on their behalf versus information and education activities from non-commercial sources
- Comparisons between different types of unbranded advertising (for instance, traditional unbranded advertising versus unbranded advertising in social media)
- Comparisons between unbranded advertising campaigns for two different drugs

Subgroup analysis and investigation of heterogeneity

In the presence of sufficient numbers of studies, subgroup analyses may be conducted to explore heterogeneity, using a significance test for interactions for subgroup differences and an I^2 statistic. We plan to carry out a priori subgroup analyses for effects of on- and off-label campaigns if possible, and will contact authors to obtain additional data to carry out these subgroup analyses if the results have not been reported separately in the primary study. Mixed (on and off) campaigns will be subject to a second level of coding for primary message on- or off-label and will be classified based on the primary message. We will test for interaction effects between subgroups of on- and off-label use, and present the results of subgroup analyses. If outcomes do not differ, however, we will calculate the combined effects as well and will present these outcomes. If there are significant interaction effects (Chi² for interaction effects < 0.05), we will present subgroup outcomes separately.

The other factors we may also consider for exploratory subgroup analyses are:

- intervention characteristics:
    - type of media used (online versus all other types of media);
    - length and intensity of intervention;
    - multiple media versus single media; and
    - setting (lower-/middle-income countries versus high-income countries, as per World Bank country income levels);
- influences of age and gender;
- chronic conditions versus other conditions; and
- influence of type of prescriber (medical practitioners versus other healthcare professionals).

In the event that substantial clinical, methodological or statistical heterogeneity across studies precludes meaningful combining of

data, we will attempt to explore possible clinical or methodological reasons for this variation by grouping studies that are similar in terms of target groups, intervention characteristics, methodological features or other factors to explore differences in intervention effects.

Sensitivity analysis

Sensitivity analyses will be conducted to determine the robustness of the results. These may include but are not restricted to undertaking both fixed-effect and random-effects meta-analyses, excluding outlier studies or excluding poorer quality studies to explore the robustness of results. In addition, any methodological decisions undertaken during the course of the review (e.g. combining different study designs; imputation of missing data) will be subjected to sensitivity analyses.

'Summary of findings' table

We will prepare a 'Summary of findings' table to present the results of meta-analysis, based on the methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). We will present the results of meta-analysis for the major comparisons of the review, for each of the major primary outcomes, including potential harms, as outlined in Types of outcome measures. We will provide a source and rationale for each assumed risk cited in the table(s), and will use the GRADE system to rank the quality of the evidence using the GRADEprofiler (GRADEpro) software (Schünemann 2011). If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table format, such as that used by Chan 2011.

Ensuring relevance to decisions in health care

The review will inform current policy discussions on the impact of public unbranded campaigns by the pharmaceutical industry in terms of the research evidence, and gaps in knowledge, about effects on consumers' attitudes, knowledge, health service use, costs and health outcomes. It is important for these policy discussions to be informed by the existing body of research evidence, including an understanding of current gaps in knowledge about effects of this intervention.

The review will receive feedback from at least one consumer referee in addition to a content expert as part of Cochrane Consumers and Communication's standard editorial process.

This protocol has also been reviewed by members of an advisory consumer panel - Ilaria Passarani and Signe Mezinska - whom we thank for their input and contribution.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Glossary of key terms

Key term	Definition
Branded direct-to-consumer advertising of prescription medicines (DTCA)	Advertising that includes a product's brand name. In the USA, this includes two types of advertising described by the Food and Drug Administration: 1) 'full product advertising', which includes the product name and health claims. Such advertising must also include information on the drug risks; 2) reminder advertising, which states the product's name but makes no health claims. In the USA, this advertising is not allowed for drugs with boxed warnings of serious risks
Unbranded advertising of prescription medicines	Any paid advertising campaign, in any media, by a pharmaceutical manufacturer, with a focus on a condition treated by one or more of its products, but without any mention of brand or generic names
Off-label promotion	The term 'off-label promotion' refers to promotion of a medicine for an unapproved use. This type of promotion is generally illegal. Physicians may prescribe a medicine for any use, whether it is approved or not, but manufacturers may not promote medicines for off-label use
Mixed promotion (both on- and off-label)	'On-label promotion' refers to promotion for approved uses. 'Off-label promotion' is for unapproved uses. Mixed promotion is for both types of uses
Generic drugs or generics	Generic drugs or generics are medicines that have no brand name or registered trademark. Once the patent for a medicine expires, other manufacturers may produce the medicine, and these products are generic drugs
Direct-to-consumer advertising	Direct-to-consumer advertising (DTCA) refers to advertising of prescription-only medicines aimed at the public. Such advertising is fully legal only in two countries, the USA and New Zealand

Table 1. Glossary of key terms (*Continued*)

Non-commercial information sources	We define a non-commercial information source to be any public or private entity, institution, non-government organisation, foundation or society involved in distributing information about health and treatment which does not derive a commercial gain from inducing the prescription, supply, purchase and/or use of pharmaceutical products, either directly or indirectly
Third party acting on behalf of pharmaceutical company	Any public relations consultancy, marketing company, professional society, think tank, patient and consumer group, key opinion leader, medical practice or hospital, which has been hired or funded by a pharmaceutical company to promote specific pharmaceutical products

APPENDICES

Appendix 1. MEDLINE search strategy

1. prescription drugs/
2. (prescription adj (drug* or medicin* or medication* or pharmaceutic*)).ti,ab,kw
3. drug industry/
4. (sponsor* or awareness or campaign*).ti,ab,kw.
5. (1 or 2 or 3) and 4
6. ((compan* or corporat* or industry) adj10 sponsor*).ti,ab,kw
7. (drug* or medicin* or medication* or pharmaceutic* or prescription*).mp
8. 6 and 7
9. 5 or 8
10. exp marketing/
11. (market* or adverti*).ti,ab,kw.

(*Continued*)

12. (health adj (promotion or education or communication)).mp
13. campaign*.ti,ab,kw.
14. public relations/
15. persuasive communication/
16. (public relation* or publicity or public information or (communication adj (program* or strateg*)) or positive framing).ti,ab,kw
17. mass media.mp.
18. or/10-17
19. 9 and 18
20. (prescri* and (market* or adverti* or promot* or campaign* or public relations or publicity or mass media or sponsor*)).hw,ti
21. disease awareness.ti,ab,kw.
22. (unbranded or nonbranded or non-branded or condition brand* or condition orient* or disease orient*).ti,ab,kw
23. (consumer relation* marketing or sponsored advert*).ti,ab,kw
24. ((disease specific or informational or help seeking) adj5 (adverti* or DTC* or campaign*)).ti,ab,kw
25. (drug* or medicin* or medication* or pharmaceutic* or prescription*).mp
26. or/21-24
27. 25 and 26
28. 19 or 20 or 27

CONTRIBUTIONS OF AUTHORS

- TLA: title registration proposal drafting, protocol drafting.
- AMT: title registration proposal review, protocol review and input into final draft.
- AP: protocol review and input into final draft.
- HGML: title registration proposal review, protocol review.
- LP: protocol review and input into final draft.
- EP: protocol review and input into final draft.
- BM: title registration proposal drafting, protocol drafting and review, input into final draft.

DECLARATIONS OF INTEREST

Teresa Leonardo Alves: None known.

AK Mantel-Teeuwisse: Aukje Mantel-Teeuwisse is the Managing Director of the WHO Collaborating Centre for Pharmaceutical Policy & Regulation, which receives no direct funding or donations from private parties, including the pharmaceutical industry. Research funding from public-private partnerships, e.g. IMI, TI Pharma (www.lygature.org), is accepted under the condition that no company-specific product or company-related study is conducted. The Centre has received unrestricted research funding from public sources, e.g. Netherlands Organisation for Health Research and Development (ZonMW), the Dutch Health Care Insurance Board (CVZ), EU 7th Framework Program (FP7), Dutch Medicines Evaluation Board (MEB), and Dutch Ministry of Health.

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HGM Leufkens: Bert Leufkens is Chair of the Dutch Medicines Evaluation Board and the Scientific DIrector of the WHO Collaborating Centre for Pharmaceutical Policy & Regulation. The Centre receives no direct funding or donations from private parties, including the pharmaceutical industry. Research funding from public-private partnerships, e.g. IMI, TI Pharma (www.lygature.org), is accepted under the condition that no company-specific product or company-related study is conducted. The Centre has received unrestricted research funding from public sources, e.g. Netherlands Organisation for Health Research and Development (ZonMW), the Dutch Health Care Insurance Board (CVZ), EU 7th Framework Program (FP7), Dutch Medicines Evaluation Board (MEB), and Dutch Ministry of Health.

Lorri Puil: None known.

Elita Poplavska: None known.

Barbara Mintzes: Barbara Mintzes has acted as an expert witness on behalf of plaintiffs in Canadian class action suits on postmenopausal hormone therapy and breast cancer, and testosterone therapy and cardiovascular risks.

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Internal sources

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External sources

- No sources of support supplied

NOTES

This protocol is based on standard text and guidance provided by Cochrane Consumers and Communication (CCCG 2014).