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Impact of medicines regulatory risk communications in the United Kingdom on prescribing and clinical outcomes: systematic review, time series analysis and meta-analysis

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Dr Daniel Morales was the principal investigator however in this study no interventions were performed with human subjects/patients and no substances were administered.

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Abstract

Background

Regulatory risk communications are important to ensure medication safety, but their impact is poorly understood. The aim was to quantify the impact of United Kingdom (UK) risk communications on medication use and other outcomes.

Methods

We conducted a systematic review of studies reporting prescribing/health outcome data relevant to UK regulatory risk communication. Data were re-analysed using interrupted time series regression twelve months after each regulatory intervention. Mean changes were pooled using random-effects generic inverse variance examining the following subgroups: drug withdrawals; restrictions/changes in indications; 'be aware' messages without specific recommendations for action; communication via Direct Healthcare Practitioner Communications (DHPCs); communication via drug bulletins.

Results

Of 11,466 articles screened, 40 studies examining 25 UK regulatory risk communications were included. Product withdrawals, restriction in indications and 'be aware' communications were associated with relative mean changes of -78% (95%CI -60% to -96%), -34% (95%CI -12 to -55%) and -11% (95%CI -8% to -15%) in targeted drug prescribing respectively. DHPCs were associated with relative mean changes of -47% (95%CI -27 to -68%) compared to -13% (95%CI -6 to -20%) for drug bulletins. Of seven studies examining unique health outcomes related to the safety concern, risk communications were associated with a mean -10% (95%CI -3 to -16%) decrease in intended and a 7% (95%CI 4 to 10%) increase in unintended health outcomes.

Discussion

UK regulatory risk communications were associated with significant changes in targeted prescribing and potential changes in clinical outcomes. Further research is needed to systematically study the impact of regulatory interventions.

What is already known about this subject?

- Medicine risk communications from regulatory bodies are important to ensure medication safety, but their impact is often poorly understood.
- Existing studies attempting to examine impact vary in their quality and the method of analysis.
- We re-analysed data from a systematic review of studies measuring the impact of United Kingdom (UK) risk communications using a common approach to synthesis and quantify their impact.

What this study adds?

- UK medicine risk communications are associated with significant changes in targeted prescribing, the extent of which varies by method of communication and type of regulatory action.
- Direct Healthcare Practitioner Communications were associated with larger changes in targeted drug prescribing than communication via drug bulletins.
- Risk communications may be associated with significant changes in intended and unintended health outcomes.

Background

Prescribing medications is the most commonly used healthcare intervention, but is not without risk. Serious and fatal adverse drug reactions in hospital are common, and adverse effects of community prescribed medicines are the primary cause of 6.5% of hospital admissions.[1,2] Ageing populations, multimorbidity and guideline recommendations for more intensive control of long-term conditions like hypertension have driven increases in polypharmacy. The proportion of the population dispensed ten or more drugs tripled between 1995 and 2010, and the proportion of patients prescribed drugs with potentially serious drug-drug interactions doubled.[3,4] Improving the safe use of medicines requires multiple strategies, but a key element is the effective communication of new information about the safety of medicines.

Medicine regulators including the European Medicines Agency (EMA), the United States (US) Food and Drug Administration (FDA) and the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) are responsible for safeguarding public health through evaluating the benefit-risk balance of medicines, and alerting prescribers and patients to new safety information. Regulatory responsibility in this area was first established after the safety concerns with thalidomide emerged in the 1950s and 1960s, and remains critically important today, as the recent issues around the risk of congenital anomalies in offspring of women taking sodium valproate during pregnancy shows.[5] Dissemination of new safety information is primarily done via risk communications, which are intended to help healthcare professionals and patients make more informed decisions to minimize potentially avoidable harm.[6] However, risk communications vary in their design and method of dissemination both within and between countries. In most countries, risk communications are disseminated in multiple ways from regular drug bulletins (such as Drug Safety Update in the UK), through to more urgent direct communications with prescribers using Direct Healthcare Practitioner Communications (DHCP) of various kinds. Methods of dissemination have also changed over time, with increasing use of cascaded central alerting systems to improve reach.[7]

However, there are relatively few evaluations of whether regulatory risk communication achieves its intended effect, in terms of changing healthcare behaviour and reducing harm.[8] A previous systematic review examining the impact of FDA risk communications suggests that regulatory risk alerts generally lead to a reduction in targeted medicine use, but with some evidence of unintended changes in prescribing in populations not targeted by communications.[9] However, less is known about the effects of regulatory risk communications in other health care systems, and studies in this field show great

heterogeneity in study design, method of analysis and outcomes chosen.[8] The aim of this study was to systematically review published studies measuring the impact of UK MHRA risk communications, including reanalysis of published time-series data using a single methodological approach to estimate impact on a common scale, and examination of how impact varies with characteristics of risk communications.

Methods

A systematic review of MEDLINE, EMBASE, Scopus and the Cochrane Library was conducted using a pre-specified search strategy (see appendix) to identify all published English language articles evaluating the impact of UK medicines regulatory communications up to 25th October 2017. Identified articles were screened by two reviewers. Reference lists and citations of included studies were searched to identify additional articles. The systematic review protocol was registered on PROSPERO (number CRD42016033621).[10]

Eligibility criteria

To be included in the descriptive analysis, studies had to 1) examine the impact of a UK medicines regulatory risk communication, and 2) provide time-series data for prescribing or clinical outcomes. To be eligible for the meta-analysis, studies were required to provide sufficient data to calculate the change in outcome 12 months following the risk communication using segmented regression analysis. Cross sectional studies were excluded.

Outcomes

The primary outcome of interest was the rate of prescribing of the medicine targeted by the regulatory risk communication. Specified secondary outcomes included: rates of prescribing of substitute medicines; rates of prescribing of the target medicine in a non-target population (so-called 'spillover' effects) and change in intended and unintended health outcomes that were the focus of the safety concern. For example, for non-steroidal anti-inflammatory drugs (NSAIDs) intended and unintended health outcomes could include cardiovascular events and gastrointestinal bleeding respectively.

Data extraction

Data were extracted on type of the regulatory action defined as: withdrawal from the market; recommendations to change practice based on a change or restriction of indication; recommendations for additional monitoring; and communications to 'be aware' of new information without explicitly recommending specific action. Data were also extracted on method of dissemination (defined as either

direct via a 'Dear Health Care professional Communication' (DHPC) letter, or indirect via drug bulletins containing safety warnings and other messages about medications); target medicine; population; outcomes evaluated; analytical methods used in the original study; and year of publication.

Data analysis

Descriptive analysis was conducted for all studies examining the topic, type of regulatory intervention and risk communication, outcomes measured and method of analysis used in the original paper. For studies that reported at least 12 months of data post-regulatory intervention, we re-analysed the data using a common approach of interrupted time series (ITS) regression in order to estimate impact on the outcome of interest 12 months following the regulatory intervention. Time-series data were extracted from tables or (if no tabular data were available) from figures using Plot Digitizer v2.6.8. Segmented regression models were then fitted to the time-series data. For these models, the presence of autocorrelation was assessed using the Durbin-Watson statistic and autocorrelation function (ACF) plots and partial autocorrelation function (PACF) plots. When autocorrelation was observed it was managed by fitting a lag value and re-examining the ACF and PACF plots.[11] For all models, the date of the risk communication was used as the pre-specified intervention in the model.

For each risk communication, segmented regression model coefficients were used to estimate a comparable measure of effect. This was the relative change in each outcome 12 months after the date of the risk communication, compared to that predicted by pre-interruption trends before the risk communication.[11] For most regulatory interventions the intended effect was a reduction in the rate of the outcome. For the minority where the intended effect was to increase the rate of the outcome, the reciprocal of the relative change at 12 months was taken in order that results could be directly compared as the 'change in the intended direction'. Estimates of the relative change at 12 months were then pooled using a generic inverse variance method of analysis with random-effects models in Revman v5 grouped by the nature of the regulatory action and by method of dissemination. When multiple studies measured the same regulatory action and outcome using the same source population, a single study was selected for inclusion in the meta-analysis based upon the size of the population studied and duration of data, with sensitivity analyses performed substituting this with the overlapping studies that were included and assessed separately. For this purpose different countries within the UK were not considered the same source population, since risk communication impact is likely to be mediated by differences in NHS organisation. We excluded models with serious non-linearity due to large changes in trend in the pre-intervention period detected through visual inspection of plots.

Risk of bias

Risk of bias was assessed using seven standard criteria for ITS analysis studies recommended by the Cochrane Effective Practice and Organisation of Care group.[12]

Patient and public involvement

No patients or members of the public were involved in the design or conduct of this study.

Results

Overview of studies examining the impact of UK regulatory warnings

Of 11,466 identified articles, 40 studies examining UK medicines regulatory risk communications were included (supplementary figure S1).[13-52] These 40 studies examined the impact of 25 UK regulatory risk communications. Twelve of the 25 risk communications recommended a restriction of or change in medicine indication, eight asked prescribers to 'be aware' of new information about safety without explicit recommendations for action, four related to product withdrawals, and one to both restriction of indication *and* additional monitoring (table 1 and supplementary table S1). Twenty-six of the 40 studies identified examined risk communication impact for only four classes of medication; namely analgesics including NSAIDs (ten studies), SSRI antidepressants (six), combined oral contraceptives (five) and antipsychotics in people with dementia (five), while the remaining 14 studies examined risk communications targeting nine other medication classes (table 2). No studies examined the impact of specialised medicines utilised only in the hospital setting.

Of the 40 identified studies, 35 (87.5%) evaluated the impact of the risk communication on the rate of prescribing of the targeted drug, 26 (65.0%) evaluated the rate of prescribing of non-target (substitute) drugs, and 20 (50.0%) evaluated health outcomes (table 2 and supplementary table S2). Eighteen (45.0%) studies used ITS regression or Joinpoint regression, seven (17.5%) studies used a different method of regression (that did not fully account for the time-series nature of the data), nine (22.5%) studies used simple descriptive statistics only (that did not account for the time-series nature of the data) and seven (17.5%) studies used a descriptive approach without any statistical examination of impact.

Impact of UK regulatory warnings on targeted drug prescribing

Of the 35 studies describing impact on targeted drug prescribing, 24 studies examining 17 unique warning and populations were eligible for re-analysis to estimate the impact on targeted drug

prescribing 12 months following the risk communication and are the focus of the meta-analysis (table 2). The mean number of pre-intervention time points available for analysis was 13.5 (range 6-29). For the primary outcome of rate of targeted drug prescribing by the risk communication, the largest overall reduction in prescribing 12 months after the date of the regulatory risk communication was associated with product withdrawals (mean change -78%, 95%CI -60 to -96%, figure 1 and supplementary figure S2) (of note co-proxamol was a phased withdrawal over two years). Smaller overall reductions were seen for restriction of or change in indication with recommendations for action (mean change -34%, 95%CI -12 to -55%, figure 1) and 'be aware' risk communications highlighting new information but without explicit recommendations for changing prescribing practice (mean change -11%, 95%CI -8 to -15%, figure 1 and supplementary figure S3). When stratified by method of dissemination, the mean effect on targeted prescribing was larger for DHPC than for drug bulletins (mean change -47% [95%CI -27 to -68%] versus -13% [95%CI -6 to -20%] respectively, figure 2). This difference between DHPC and drug bulletin was similar when analysis was restricted only to risk communications notifying of a change of or restriction in indication (mean change -42% [95%CI -20 to -65%] for direct letter vs. -17% [95%CI -3 to -31%] using a drug bulletin) (figure 2 and supplementary figures S4 and S5).

Impact of regulatory risk communications on substitution and spillover effects on prescribing

Twenty six studies (65%) examined impact on other types of prescribing (supplementary table S3). This was most commonly for substitute medicines including prescribing of other NSAIDs (n=5) and analgesics (n=6) for pain, other antidepressants for depression (n=5), other oral antihyperglycaemic agents for diabetes (n=4), and other antipsychotics for dementia (n=3). Risk communications were associated with a mean increase in substitute prescribing of 28% (95%CI 15 to 41%, figure 3).

Only four studies examined spill-over effects three of which related to risk communications about SSRIs in children and adolescents with depression and one relating to a risk communication about vigabatrin, where a decrease in prescribing of fluoxetine and lamotrigine was observed respectively.

Impact of UK regulatory warnings on health outcomes

Of 20 studies (50%) describing health outcomes, ten studies covering seven outcomes were eligible for re-analysis to estimate the impact 12 months following the risk communication for: cases of co-proxamol poisoning and deaths from suicide (for the risk communication about co-proxamol withdrawal), cases of hospitalisation for paracetamol poisoning (for the risk communication about the benefit risk of acetylcysteine in paracetamol overdose), rate of self-harm (for the risk communication

about SSRIs in children and adolescents), rate of abortions and of venous thromboembolism (for the risk communication about combined oral contraceptive pills), and rate of admissions with gastrointestinal bleeding or myocardial infarction (for the risk communication about the use of COX2 inhibitors). Using these available data, the regulatory action was associated with a decrease in intended health outcomes 12 months following the risk communication of -10% (95%CI -3 to -16%) and an increase in unintended health outcomes 12 months following the risk communication of 7% (95%CI 4 to 10%) (figure 3 and supplementary figure S6).

Risk of bias

Supplementary table S3 shows the risk of bias for the included studies. Since risk communications are often preceded by academic or other publications reporting new risk, or have additional later actions implemented, most studies were considered to be at high risk of bias because of uncertainty whether the risk communication intervention was independent of other changes. The results of sensitivity analyses substituting with other studies measuring the same regulatory action using the same source population was consistent with the main findings (supplementary table S4).

Discussion

In view of considerable heterogeneity in the analytical methods used in the original studies examining the impact of UK regulatory risk communications (with just over half using no statistical analysis or suboptimal methods not accounting for time trends) we re-analysed data from studies to measure their impact on a common scale (change in outcome 12 months after the risk communication). Regulatory interventions leading to product withdrawals, change of or restriction in indication and general 'be aware' communications were on average associated with a significant ~78%, ~34% and ~11% changes in targeted prescribing in the desired direction respectively at 12 months. Regulatory risk communications using direct letters (DHPCs) were on average associated with greater reductions in targeted prescribing at 12 months (~47%) compared to safety information disseminated using drug bulletins (~17%). Additionally, we found some evidence that risk communications led to substitutions with other drugs, to spillover effects of medicines not targeted by respective risk communications, and potentially to desired intended but also negative unintended health outcomes.

From these data it therefore appears that on average all three types of regulatory intervention and both methods of dissemination studied have significant effects on targeted drug prescribing, although effect sizes differ. Apart from the type of warning and method of dissemination, the heterogeneity in impact

could also be related to multiple factors including differences in clinical context, media coverage, regulatory interventions occurring elsewhere in the world, and public and professional perceptions that some risks are particularly serious, such as in the October 1995 'pill scare' and for the use of antidepressants in children. Variation in impact is an important feature to consider. A previous systematic review including articles published up to 2010 reported that DHPCs, Black Box Warnings and/or Public Health Advisories appeared to have similar patterns of impact, showing an effect in 56%, 57% and 61% of included studies respectively, with no effect in 27%, 21% and 31%, respectively, or a mixed effect in 17%, 21% and 8%, respectively.[53] Similarly, the impact of a DHPC targeting mirabegron prescribing in England demonstrated significant variation in mirabegron prescribing and variation did not change substantively following the DHPC.[54] Our analysis provides a study-average effect of the impact of each type of regulatory action and risk communication. However, variation was observed meaning that other factors are likely to be important in determining their absolute effect although it is possible that relative differences in effect would remain similar.

A strength of this study is the rigorous approach we used to try and identify all relevant published articles. However, it may be that not all relevant studies will be published in peer-reviewed journals that could result in publication bias. We noted widely varying and often inappropriate analysis methods used among identified studies that do not take into account baseline trends, consistent with previous European and US reviews.[8,9] We therefore applied a common method of re-analysis to the extracted data, namely ITS analysis, which is a robust quasi-experimental design to evaluate the effects of policy interventions.[11] A limitation of ITS regression is that it provides evidence on associations but a key assumption is that there is no impact from other interventions occurring around the same time (e.g. publication of high-profile papers which then drive a later regulatory decision, or regulatory action in other countries with resulting media coverage), which in part depend on the data source as not all data sources may be suitable.[55] We therefore considered all included studies as high risk of bias because of uncertainty whether the intervention was independent of other changes. A further limitation is that the relatively small number of studies available meant that we were unable to fully stratify the results, which is important since drug withdrawals (the intervention with the highest impact) are also more likely to be communicated by DHPC (the dissemination method with the highest impact). However, the observed greater impact of DHPC over drug bulletin remained even when restricting the comparison among studies in which the regulatory intervention recommended a change of or restriction in indication only, increasing our confidence in the findings. Two risk communications were sent within 12 months relating to paroxetine and other SSRI use in children and adolescents however sensitivity

analysis excluding this study from the meta-analysis had no significant impact on the effect estimates. Changes in prescribing outcomes for risk communications recommending additional monitoring alone would likely represent an unintended effect. However, only one study where the risk communication recommended additional monitoring was identified and this also involved a restriction in indication. As such, there appears to be limited studies evaluating the impact of additional monitoring recommendations in the UK. Safety decisions taken centrally by member states through the EMA are still disseminated by national competent authorities. However, information about EMA decisions may have been publicized a short time before a formal risk communication emerges. Finally, studies were relatively focused on important but narrow groups of medicines that could impact on the generalisability of results, with a preponderance of studies that examined medicines of wide interest (such as antidepressants) and a clear lack of studies examining specialised medicines used only in the hospitals settings.

A previous systematic review of studies examining the impact of US FDA regulatory interventions reported that communications with recommendations for greater monitoring did not appear to change practice much, and that changes in prescribing were greater in new (incident) medication users compared to continuing (prevalent) users.[9] As with this review, studies in other contexts have most commonly evaluated use of the medicines directly targeted by the regulatory intervention and risk communication.[8,9] Changes in targeted drug prescribing provide an important measure of impact, but the primary aim of pharmacovigilance is in fact to safeguard public health and reduce harm in terms of clinical outcomes related to the targeted drug. Whilst clinical outcomes were only rarely evaluated in studies included in previous reviews [8,9] and in this review, we noted that few studies measured potentially harmful unintended consequences that may occur. In this regard, a balanced accounting of desired and undesired outcomes is generally lacking.

Regulatory risk communication likely has variable effects because it is a complex intervention in a complex system and the wider health service context may modify the effect of regulatory risk communications that can occur between countries.[56] Antipsychotic prescribing in dementia is an example of this where in England, antipsychotic prescribing also declined in 2007 in the absence of any risk communication, shortly after the publication of National Institute of Health and Care Excellence (NICE) guidance for England and Wales in late 2006.[32] Substitution or spillover effects may also have their own unintended consequences which may reduce or negate the overall net-benefit of regulatory decisions and risk communications, and commonly occur.[57]

Although medicines regulators have made considerable effort to improve their risk communications, there has been little systematic research into how best to design and disseminate them. Similarly, regulators like EMA have developed strategies for measuring the impact of pharmacovigilance. [58] The decision for how certain types of information are communicated are made by committees and can be complex, being made by the MHRA for nationally authorised medicines or the EMA for centrally authorised medicines and some nationally authorised ones. These could be based upon the strength of evidence, the perceived importance of the safety concern, and how likely patients and healthcare professionals are likely to become aware of such risks without specific notifications. Unlike the nature of the risk warning, dissemination methods may have changed over time with increasing use of email and social media that potentially impacts on the speed on knowledge transfer. However, there has been limited robust evaluation of whether previous or new risk communication methods are effective, and if so how effective. For example, although a safety review conducted by the EMA in 2014 recommended measures to better inform women about the risk of congenital anomalies associated with use of valproate during pregnancy, and not to start treatment unless other options were ineffective or could not be tolerated, a subsequent review was undertaken by the EMA in 2018 because of concerns that these measures had not been sufficiently effective.

It is not feasible to randomise clinicians or organisations to *not* receive any risk communication, but since risk communications are disseminated nationwide, it is straightforward to conceive of trials of 'enhanced' compared to 'current' risk communication. There are a number of plausibly effective improvements to risk communication design that could be developed and evaluated, such as more systematic design of risk communications (for example, giving explicit recommendations for alternative action [59] or using health psychology principles to develop more persuasive or action-orientated communications [60]), and ensuring that risk communications come from regulators not pharmaceutical companies to increase their persuasiveness.[61] Similarly, plausibly effective changes to dissemination methods include communicating with prescribers in ways they prefer (UK GPs for example prefer point-of-care alerts and e-mails over electronic communication via mobile apps, text messages or social media [56]), as well as reinforcing messages over time, for example by giving prescribers and organisations feedback about their use of targeted medicines.[62]. Finally, evaluation of informatics support tools to facilitate identification and review of patients could be worthwhile.[63]

Conclusion

Despite the public health importance of pharmacovigilance systems, we found that the literature evaluating the impact of UK risk communications was relatively sparse, narrowly focused on a few medicines and risk communications, did not target specialised medicines used only in the hospital setting and had serious methodological weaknesses, with around half of studies using inadequate analytical methods. Medicines regulatory risk communications in the UK were associated with significant changes in targeted prescribing with some evidence of changes in clinical health outcomes, with communication using DHPCs associated with greater change compared with drug bulletins. Collaborative development and evaluation of new forms of risk communication by regulators, health services and academics could help to optimise impact on public health.

Ethical approval

No approvals were required to conduct this study as it uses published data.

Disclaimer

The views expressed in this article are the personal views of the author(s) and may not be not be understood or quoted as reflecting the views of any particular organisation.

Author contributions

All authors were involved in the design, interpretation of results, writing the manuscript and approved the final draft. CW, TD and BG undertook the search. CW and DM performed the analysis and had full access to the data. DM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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This study was unfunded.

Declaration of interests

All authors have no conflicts of interest to declare.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Figure legends

Figure 1. Impact at 12 months on prescribing of the targeted drug stratified by type of regulatory action communicated by the risk communication.

a. Guthrie 2013 and Stocks 2017 related to ANTIPSYCHOTICS1.

b. Guthrie 2013 and Stocks 2017 related to ANTIPSYCHOTICS2.

Figure 2. Impact at 12 months on prescribing of the targeted drug stratified by method of dissemination.

a. Guthrie 2013 and Stocks 2017 related to ANTIPSYCHOTICS1.

b. Guthrie 2013 and Stocks 2017 related to ANTIPSYCHOTICS2.

Figure 3. Impact at 12 months on substitute prescribing and health outcomes

a) Sandilands 2008 ANALGESIC1. Bedson 2013 ANALGESIC1. Guthrie 2013 ANTIPSYCHOTICS1. Leal 2012 DIABETES1. Wheeler 2009 NSAID1. Watson 2007 HRT1. Mt-Isla 2015 CISAPRIDE. Stocks 2017 ANTIPSYCHOTICS1.

b) Intended: Farmer 2000=venous thromboembolisms COCP. Narayan 2015=hospital admissions for paracetamol poisoning (reciprocal value) ANALGESIC2. Hawton 2012=suicides ANALGESIC1. Wheeler 2009=myocardial infarction NSAID1. Unintended: Shickle 2000=abortions COCP. Wheeler 2008= episodes of self-harm DEPRESSION1. Wheeler 2009=gastrointestinal bleeds NSAID1.

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Table 1. Characteristics of UK regulatory interventions and risk communication within included studies.

Code	Risk communication description (date)	Nature of the warning	Dissemination method
Analgesics			
ANALGESIC1	Co-proxamol withdrawal (01/2005)[s1]	Withdrawal	Direct Letter
ANALGESIC2	Benefit risk of acetylcysteine in paracetamol overdose (09/2012)[s2]	Change of indication	Direct Letter
Antidepressants			
DEPRESSION1	Contraindication of Paroxetine in Children and Adolescents for depression (06/2003)[s3]	Restriction to indication	Direct Letter
DEPRESSION2	SSRIs: advice relating to major depressive disorder in children and adolescents (12/2003)[s4]	Restriction to indication	Drug bulletin
Antidiabetics			
DIABETES1	Rosiglitazone and pioglitazone: CVS safety and fracture risk (10/2007)[s5]	Restriction to indication	Drug bulletin
DIABETES2	Rosiglitazone withdrawal (10/2010)[s6]	Withdrawal	Direct Letter
Antipsychotics			
PSYCHIATRY1	Atypical antipsychotics and risk of stroke (03/2004)[s7]	Restriction to indication	Direct Letter
PSYCHIATRY2	Antipsychotics: use in elderly with dementia (03/2009)[s8]	Be aware	Drug bulletin
PSYCHIATRY3	Typical antipsychotics: increased mortality in dementia (12/2008)[s9]	Be aware	Drug bulletin
PSYCHIATRY4	Antipsychotics: initiative to reduce prescribing to older people with dementia (05/2012)[s10]	Be aware	Drug bulletin
Hormone Replacement Therapy			
HRT1	Safety update on long-term HRT (10/2002)[s11]	Restriction to indication	Drug bulletin
HRT2	Safety update on long-term HRT (12/2003)[s12]	Restriction to indication	Drug bulletin
Non-steroidal anti-inflammatory drugs			
NSAID1	Rofecoxib withdrawal (09/2004)[s13]	Withdrawal	Direct Letter
NSAID2	Advice on the use of selective COX-2 and CVS safety (12/2004)[s14]	Restriction to indication	Direct Letter
NSAID3	Updated advice on selective COX-2 inhibitor safety (02/2005)[s15]	Be aware	Direct Letter
NSAID4	Review of evidence on CVS safety of NSAIDs (08/2005)[s16]	Be aware	Direct Letter
NSAID5	Safety of Selective and non-selective NSAIDs (10/2006)[s17]	Be aware	Direct Letter
Combined Oral Contraceptive Pill			
COCP	New advice on oral contraception (10/1995)[s18]	Be aware	Direct Letter
Others			
ASPIRIN1	Use of aspirin in children <12 years of age (06/1986)[s19]	Restriction to indication	Direct Letter
VIGABATRIN1	Vigabatrin: visual field defects (11/1999)[s20]	Restriction to indication/additional monitoring	Drug bulletin
CISAPRIDE1	Cisapride withdrawal (07/2000)[s21]	Withdrawal	Direct Letter
DOSULEPIN1	Dosulepin: measures to reduce fatal overdoses (12/2007)[s22]	Restriction to indication	Drug bulletin
MIDAZOLAM1	Reducing risk of overdose with midazolam injections in adults (06/2009)[s23]	Restriction to indication	Direct Letter
CLOPIDOGREL1	Clopidogrel and proton pump inhibitors: interaction (07/2009)[s24]	Be aware	Drug bulletin
QUININE1	Quinine: not to be used routinely for nocturnal leg cramps (06/2010)[s25]	Restriction to indication	Drug bulletin

Risk communication references = supplementary references s1-s25 in supplementary material. SSRIs=Selective serotonin reuptake inhibitors. CVS=cardiovascular. HRT=Hormone replacement therapy. COX=cyclo-oxygenase enzyme. NSAID=non-steroidal anti-inflammatory drug.

Table 2. Characteristics of impact studies identified by the systematic review.

Study	Code	Behaviour change			Method of analysis in original paper	Included in meta-analysis
		Target drug effects	Non-target drug effects	Health outcomes		
Analgesics						
Sandilands 2008[13]	ANALGESIC1	X	X	X	Descriptive with simple statistics	X
Hawton 2009[14]	ANALGESIC1	X	X	X	Interrupted time series regression	X
Waring 2011[15]	ANALGESIC1	X	X	-	Descriptive without statistics	X
Hawton 2011[16]	ANALGESIC1	-	-	X	Interrupted time series regression	X
Hawton 2012[17]	ANALGESIC1	X	X	X	Interrupted time series regression	X
Bedson 2013[18]	ANALGESIC1	X	X	-	Joinpoint regression	X
Bateman 2014[19]	ANALGESIC2	X	-	X	Descriptive with simple statistics	X
Narayan 2015[20]	ANALGESIC2	-	-	X	Interrupted time series regression	X
Antidepressants						
Martin 2005[21]	DEPRESSION1	X	X	-	Joinpoint regression	X
Murray 2005[22]	DEPRESSION2	X	X	-	Descriptive with simple statistics	-
Wheeler 2008[23]	DEPRESSION1 DEPRESSION2	X	-	X	Joinpoint regression	X
Bergen 2009[24]	DEPRESSION2	X	X	X	Interrupted time series regression	X
Wijlaars 2012[25]	DEPRESSION1 DEPRESSION2	X	X	-	Interrupted time series regression	X
Hernandez 2012[26]	DEPRESSION2	X	X	-	Interrupted time series regression	-
Antidiabetics						
Leal 2012[27]	DIABETES1	X	X	-	Descriptive with simple statistics	X
George 2009[28]	DIABETES1	X	X	-	Descriptive without statistics	-
Hall 2011[29]	DIABETES1	X	X	-	Descriptive with logistic regression	-
Morgan 2014[30]	DIABETES2	X	X	X	Descriptive with Cox regression	-
Antipsychotics						
Guthrie 2013[31]	PSYCHIATRY1 PSYCHIATRY2	X	X	-	Interrupted time series regression	X
Stocks 2017[32]	PSYCHIATRY1 PSYCHIATRY2 PSYCHIATRY4	X	X	-	Interrupted time series regression before and after study	X
Sultana 2016[33]	PSYCHIATRY1 PSYCHIATRY2	X	X	-	Generalized linear models	X
Thomas 2013[34]	PSYCHIATRY3	X	X	-	Interrupted time series regression	X
McIlroy 2014[35]	PSYCHIATRY2	X	-	-	Interrupted time series regression	X
Hormone Replacement Therapy						
Watson 2007[36]	HRT1 HRT2	X	X	-	Descriptive without statistics	X
Martin 2010[37]	HRT1	X	-	X	Joinpoint regression	X
Sharpe 2010[38]	HRT1	X	-	X	Change point regression	X
Non-steroidal anti-inflammatory drugs						
Williams 2006[39]	NSAID1	X	X	-	Descriptive without statistics	-
Wheeler 2009[40]	NSAID1 NSAID2	X	X	X	Joinpoint regression	X
Bedson 2013[18]	NSAID2 NSAID3 NSAID4 NSAID5	X	X	-	Joinpoint regression	X
Combined Oral Contraceptive Pill						
Farmer 2000[41]	COCP1	-	-	X	Descriptive with simple statistics	X
Shickle 2000[42]	COCP1	-	-	X	Descriptive without statistics	X

Wood 1997[43]	COCP1	X	-	X	Descriptive without statistics	-
Flett 1998[44]	COCP1	X	-	X	Descriptive with simple statistics	-
Furedi 1999[45]	COCP1	-	-	X	Descriptive without statistics	-
Others						
Porter 1990[46]	ASPIRIN1	-	-	X	Descriptive with simple statistics	-
Ackers 2007[47]	VIGABATRIN1	X	X	-	Descriptive with simple statistics	-
Mt-Isa 2015[48]	CISAPRIDE1	X	X	-	Descriptive with Poisson regression	X
Deslandes 2016[49]	DOSULEPIN1	X	-	-	ARIMA model	X
Acheampong 2013[50]	QUININE1	X	-	X	Joinpoint regression	X
Thomas 2013[51]	CLOPIDOGREL1	X	X	-	Binary logistic regression	-
Flood 2015[52]	MIDAZOLAM1	X	X	X	Descriptive with simple statistics	-

Bedson 2013 appears twice. Studies were not included in the meta-analysis because they did not provide data to assess impact at 12 months apart from Porter 1990 and Ackers 2007 were models demonstrated non-linearity due to large changes in trend in the pre-intervention period.

ARIMA=Autoregressive Integrated Moving Average

Appendix 1: Search Strategy performed 25th October 2017

MEDLINE search:

1. United Kingdom [MeSH Terms]
2. medicines and healthcare products regulatory agency [Title/Abstract]
3. mhra [Title/Abstract]
4. European Agency for the Evaluation of Medicinal Products [Title/Abstract]
5. European Medicines Agency [Title/Abstract]
6. EMA [Title/Abstract]
7. EMEA [Title/Abstract])
8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. Regulatory risk [Title/Abstract]
10. advisory [Title/Abstract]
11. advisories [Title/Abstract]
12. alert [Title/Abstract]
13. alerts [Title/Abstract]
14. Risk communication [Title/Abstract]
15. Regulatory reports [Title/Abstract]
16. Risk alerts [Title/Abstract]
17. Warning [Title/Abstract]
18. Warnings[Title/Abstract]
19. CAB[Title/Abstract]
20. Current Awareness Bulletins [Title/Abstract]
21. Update[Title/Abstract]
22. Central Alerting System [Title/Abstract]
23. CAS [Title/Abstract]
24. Adverse Drug Reaction Reporting Systems [Title/Abstract]
25. Drug Prescriptions [mesh]))
26. 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25
    INCLUDE 8 AND 26

Scopus search:

1. medicines and healthcare products regulatory agency [Title/Abstract/Keywords]
2. mhra [Title/Abstract/Keywords]
3. European Agency for the Evaluation of Medicinal Products [Title/Abstract/Keywords]
4. European Medicines Agency [Title/Abstract/Keywords]
5. EMEA [Title/Abstract/Keywords]
6. 1 OR 2 OR 3 OR 4 OR 5
7. advisory [Title/Abstract/Keywords]
8. advisories [Title/Abstract/Keywords]
9. 7 OR 8
10. United Kingdom [Title/Abstract/Keywords]
11. 9 AND 10
12. 6 OR 11
13. Regulatory risk [Title/Abstract/Keywords]
14. alert [Title/Abstract/Keywords]
15. alerts [Title/Abstract/Keywords]
16. Risk communication [Title/Abstract/Keywords]
17. Regulatory reports [Title/Abstract/Keywords]
18. Risk alerts [Title/Abstract/Keywords]
19. Warning [Title/Abstract/Keywords]
20. Warnings [Title/Abstract/Keywords]
21. Current Awareness Bulletins [Title/Abstract/Keywords]
22. Update [Title/Abstract/Keywords]
23. Central Alerting System [Title/Abstract/Keywords]
24. Adverse Drug Reaction Reporting Systems [Title/Abstract/Keywords]
25. Drug Prescriptions [Title/Abstract/Keywords]
26. 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25

    INCLUDE 12 AND 26

Embase search:

1. medicines and healthcare products regulatory agency [Title/Abstract]
2. mhra [Title/Abstract]
3. European Agency for the Evaluation of Medicinal Products [Title/Abstract]
4. European Medicines Agency [Title/Abstract]
5. EMA [Title/Abstract]
6. EMEA [Title/Abstract]
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
8. advisory [Title/Abstract]
9. advisories [Title/Abstract]
10. 8 OR 9
11. United Kingdom [Title/Abstract]
12. 10 AND 11
13. 7 OR 12
14. Regulatory risk [Title/Abstract]
15. alert [Title/Abstract]
16. alerts [Title/Abstract]
17. Risk communication [Title/Abstract]
18. Regulatory reports [Title/Abstract]
19. Risk alerts [Title/Abstract]
20. Warning [Title/Abstract]
21. Warnings [Title/Abstract]
22. CAB [Title/Abstract]
23. Current Awareness Bulletins [Title/Abstract]
24. Update [Title/Abstract]
25. Central Alerting System [Title/Abstract]
26. CAS [Title/Abstract]
27. Adverse Drug Reaction Reporting Systems [Title/Abstract]
28. Drug Prescriptions [Title/Abstract]
29. 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28
    INCLUDE 13 AND 29

Cochrane Library search:

1. United Kingdom [Mesh]
2. medicines and healthcare products regulatory agency
3. mhra
4. European Agency for the Evaluation of Medicinal Products
5. European Medicines Agency
6. EMA
7. EMEA
8. 2 OR 3 OR 4 OR 5 OR 6 OR 7
9. 1 OR 8
10. Regulatory risk
11. advisory
12. advisories
13. alert
14. alerts
15. Risk communication
16. Regulatory reports
17. Risk alerts
18. Warning
19. Warnings
20. CAB
21. Current Awareness Bulletins
22. Update
23. Central Alerting System
24. CAS
25. Adverse Drug Reaction Reporting Systems
26. 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25
27. Drug Prescriptions [Mesh]
28. 26 OR 27

INCLUDE 9 AND 28

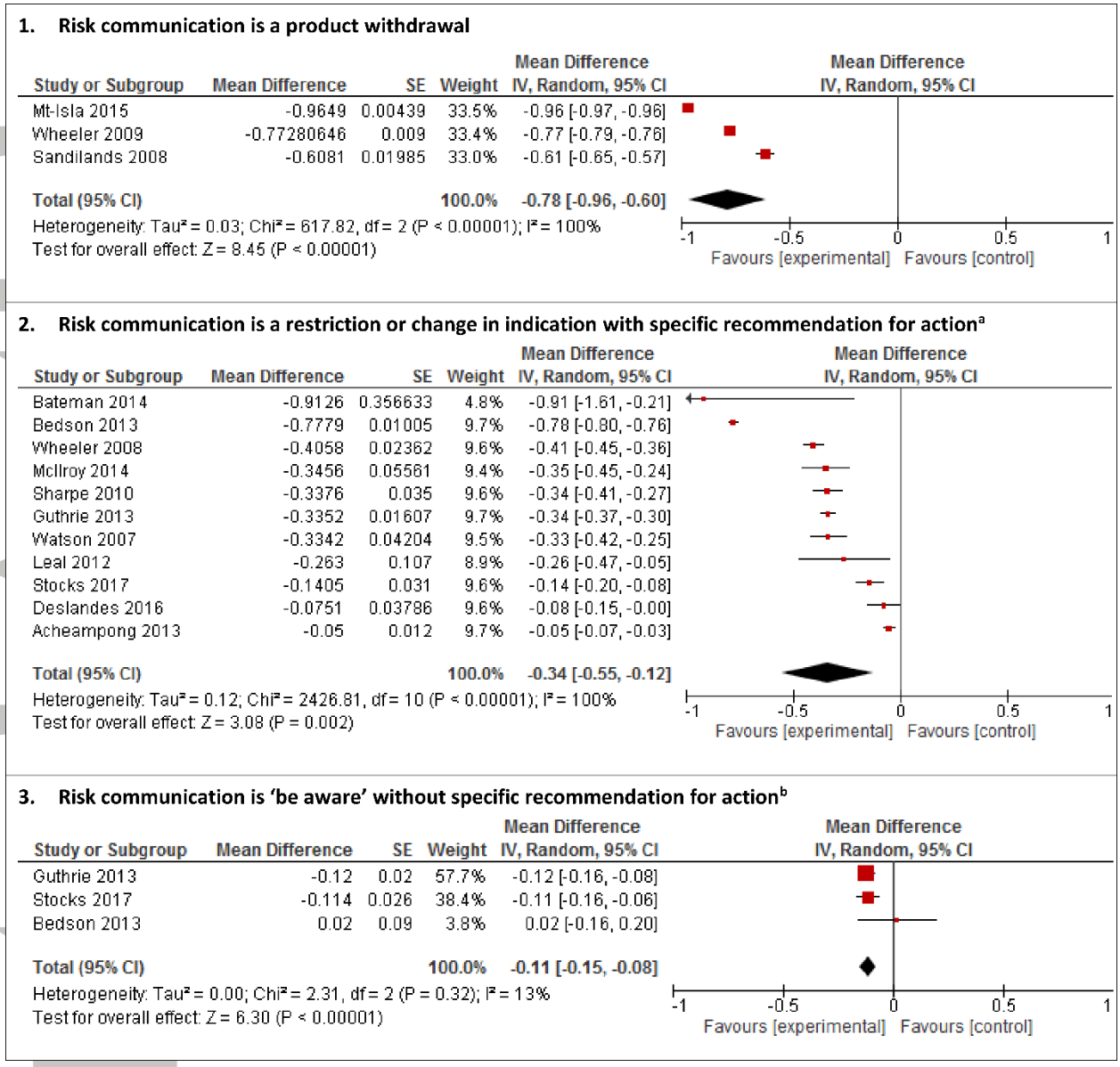

Figure 1. Impact at 12 months on prescribing of the targeted drug stratified by type of regulatory action communicated by the risk communication.

a. Guthrie 2013 and Stocks 2017 related to ANTIPSYCHOTICS1.

b. Guthrie 2013 and Stocks 2017 related to ANTIPSYCHOTICS2.

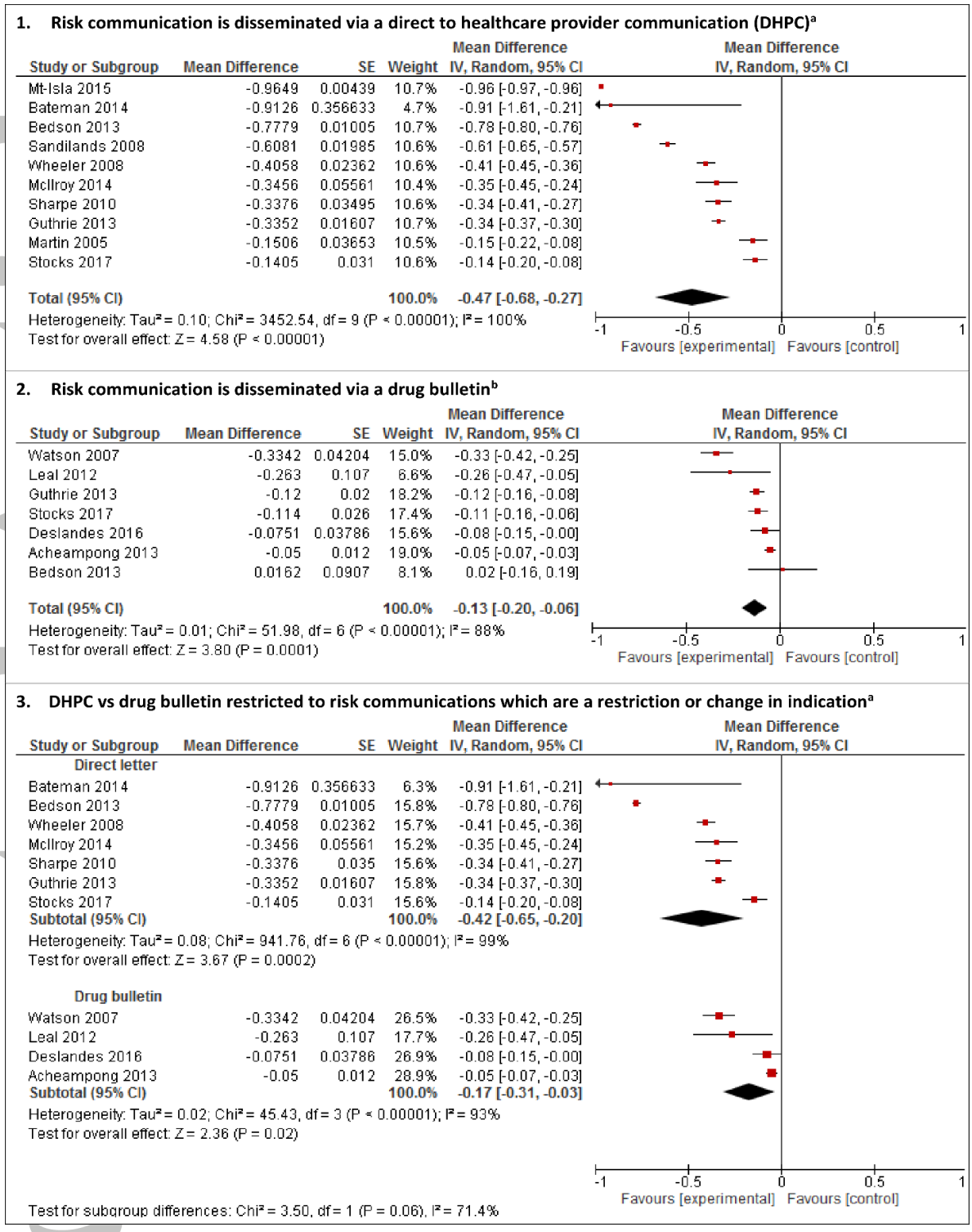

Figure 2. Impact at 12 months on prescribing of the targeted drug stratified by method of dissemination.

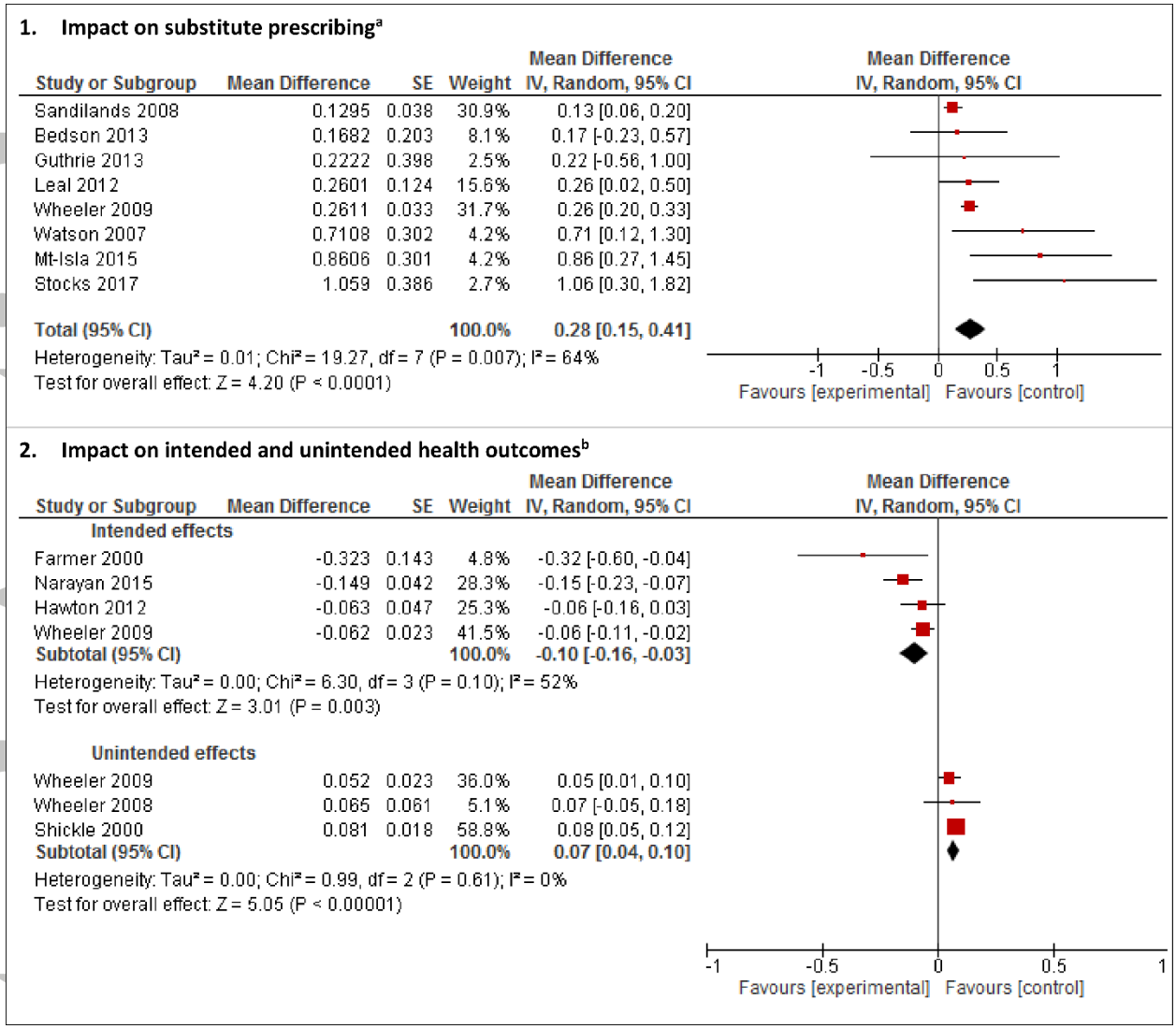

Figure 3. Impact at 12 months on substitute prescribing and health outcomes.