Interventions to improve spontaneous adverse drug reaction reporting by healthcare professionals and patients

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DOI:
10.1080/14740338.2020.1807003

Interventions to improve spontaneous adverse drug reaction reporting by healthcare professionals and patients: systematic review and meta-analysis

Abstract

Introduction

The aim of this study was to evaluate the effectiveness of interventions used for improving ADR reporting by patients and healthcare professionals.

Areas covered

A systematic review of literature was conducted by searching Medline, Embase and Cochrane Central Register of Controlled of Trials. Meta-analysis of randomised controlled trials (RCTs; n=5)was conducted to estimate the pooled risk ratio for the effectiveness of interventions on ADR reporting rates. Data from observational studies were synthesised using narrative synthesis approach.

Expert Opinion

A total of 28 studies were included. All except one study targeted healthcare professionals using educational, technological, policy, financial and/or mixed interventions. The results showed that financial and face-to-face educational interventions improved quality and quantity of ADR reporting when compared with interventions not involving face-to-face interactions. However, the quality of studies was generally low. Meta-analysis showed a statistically significant 3.5-fold overall increase in reporting of ADRs [RR 3.53; 95% CI (1.77,7.06)] in the intervention group compared to the control. There was a lack of consideration of theory and sustainability in the design of the interventions. There is a need to develop and test theory-based interventions and target patient reporting. More research needs to be conducted in the low-and-middle-income countries.

Study protocol:

Protocol registration ID PROSPERO CRD42019162209 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019162209

Articles highlights

- It is known that up to 94% of adverse drug reactions (ADR) are not reported. Under-reporting delays drug safety signals compromising patient safety.
- There is lack of high quality interventions that aim to increase ADR reporting.
- Limited evidence suggests face-to-face education interventions combined with financial incentives tend to increase ADR reporting by healthcare professionals.

- This systematic review identifies lack of interventions targeted at patients to improve ADR reporting.
- More research studies are needed in low-and-middle-income countries.

Keywords: Adverse Drug Reactions, Drug utilisation, Medication Safety, Pharmacovigilance

Reporting Guidelines

This systematic review and meta-analysis conforms to the PRISMA reporting guideline. A PRISMA checklist has been provided as an electronic supplementary material.

1.0 INTRODUCTION

When a drug is introduced to the market, its safety profile is poorly understood and the spontaneous reporting of adverse reactions remains an essential element for the dissemination of safety signals. An adverse drug reaction (ADR), as defined by the World Health Organisation is 'a response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function' [1]. ADRs are responsible for unplanned hospital admissions and mortality, with elderly and children most likely to suffer ADRs. It is estimated that approximately 1 in 10 admissions of older persons are due to ADRs [2]. There are also economic consequences to the healthcare system. It was reported that ADRs costs the European Union member states and the US approximately €79 billion [3] and $30 billion [4] annually respectively.

One of the main limitations of the spontaneous reporting system of ADRs is under-reporting. A recent systematic review of 37 studies across 12 countries showed that the median under-reporting rate was 94% [5]. Under-reporting delays drug safety signals compromising abilities of national pharmacovigilance centres to generate drug safety signals. Numerous factors contribute to underreporting of ADRs, which include: lack of awareness for the purpose of ADR monitoring and reporting, lack of knowledge on how to use spontaneous reporting of ADRs, restricted access to reporting tools, uncertainty in ADRs associated with many drugs, time constrictions on healthcare professionals and patients, bias due to intensive media coverage of some ADRs, and failure to verify diagnostics reported increases data restriction [6,7].

Pharmacovigilance is an umbrella term encapsulating the systematic detection, reporting, assessment, understanding and prevention of ADRs [8]. Effective and efficient pharmacovigilance systems provide surveillance of marketed medicines, thus are essential to protect the health of the public and limit healthcare costs caused by ADR-related complications. Globally, post-marketing surveillance of medicines is mainly coordinated by national pharmacovigilance centres responsible for collecting and analysing reports of ADRs, making decisions based on the analysis of the reports and alerting prescribers, manufacturers and the public to new risks of ADRs.

The aim of this study was to evaluate the effectiveness of interventions to improve the quantity and quality of spontaneous reporting of ADRs amongst both patients and healthcare professionals. This study will update the evidence presented in a previous systematic review on the topic area [9] which considered published literature until 2010. In addition, the previous review did not consider meta-analysis in their approach to

evidence synthesis. Given evolving international pharmacovigilance regulations, practices and increased emphasis on patient reporting of ADRs, there is a need to update the review to provide researchers, practitioners and stakeholders with up-to-date evidence on the nature and effectiveness of pharmacovigilance interventions.

The primary outcome of the study was the quantity of ADRs reported as a result of the intervention including improvement in the number or rate of reporting. Secondary outcome included the quality of ADR reporting including the nature of ADRs reported (e.g. serious, non-serious ADRs) and completeness of the reports.

2.0 BODY

2.1 Methods

This study adhered to Cochrane guidelines [10] and Preferred Reporting Items for Systematic Review and Meta-Analysis reporting guidelines (PRISMA) [11] to conduct and report the review respectively. A protocol was prepared using Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P, CRD42019162209) [12]. An electronic search of MEDLINE, EMBASE, and Cochrane trials register databases were undertaken using Medical Subject Headings (MeSH) and natural language key words, Boolean operators, truncations (*) and wild cards ($). A search strategy using keywords and Medical Subject Headings was utilised to perform a search (online resource-supplementary material 1). The reference lists of included studies were hand searched to identify any additional references for inclusion. In particular we considered all references within a previous systematic review [9] conducted on the same topic.

2.2 Eligibility criteria

No restrictions to country of origin, publication language were applied. All forms of interventional designs were considered. Literature from year 2000 till August 2019 that sought to improve either a) quality or b) quantity or both of spontaneous ADR reporting were included. Educational research with student participants, interventions not including qualified healthcare practitioners or patients were excluded as well as the interventions related to devices and planned ADR surveillance monitoring programmes, such as those used for mass vaccinations. Abstract only publications including conference abstracts were excluded.

2.3 Screening and selection

Screening was conducted by one pair of researchers (VP, DS; VP, AH) acting independently in three consecutive stages: screening of titles; screening of abstracts; screening of full text against the eligibility criteria.

2.4 Data extraction and quality assessment

A data extraction form was developed based on the review aim, refined, reviewed and piloted. Cochrane risk of bias tool for Randomised Controlled Trials [13] and The Critical Appraisal Skills Programme (CASP) quality assessment tool for cohort study (for all other study designs) was used to assess study quality [14].

2.5 Data Synthesis

The technique for data synthesis varied across different study designs. Data from RCTs (n=5) were combined using random effects meta-analysis. We reported pooled risk ratio (95% CI) to demonstrate the effectiveness of interventions to improve the quantity, i.e. rate of ADR reporting. Relative risk data adjusted for duration of follow-up was extracted and used in meta-analysis, if reported in individual studies. In instances, where the effectiveness of intervention was tested at multiple time-points and time-adjusted relative risk was not reported, the relative risk for last follow-up time point was extracted. Forest plots were produced using RevMan®. Forest plots refer to graphical representation of individual studies in a meta-analysis and allow researchers to graphically identify whether the cumulative evidence in relation to effectiveness of interventions under study favours control or experimental group [15]. In relation to the impact on the quality of ADR reporting, it was not possible conduct a meta-analysis due to heterogeneity in the definition and lack of clarity around seriousness of ADRs and completeness of ADRs.

We did not undertake meta-analysis for non-randomised controlled studies, due to the presence of confounding factors that could affect overall findings and introduce bias [16]. Therefore, a narrative synthesis of the outcomes was undertaken using summary tables extracting data on the rate and quality of ADR reporting.

3.0 Results

A total of 6812 unique titles were screened, of which 28 studies [17-44] fulfilled eligibility criteria for inclusion in the review (online resource- supplementary material 2). Most studies originated from Portugal n=5), followed by Sweden (n=4) and Spain (n=4) (table 1). Only seven of the studies used a randomised controlled design of which five studies used cluster randomisation design. The rest were either quasi experimental, observational pre-post or time series analysis (table 1). All studies focused on healthcare

professionals apart from one study in the UK which also focused on general members of the public. The study focused on patients [22] aimed to assess patterns in reporting of ADRs via the Yellow Card Scheme following a Scottish community pharmacy patient Yellow Card promotional campaign (table 1). A mix of healthcare professionals in various settings was targeted by other studies including physicians, nurses and pharmacists. Four studies exclusively targeted pharmacists (table 1).

3.1 Risk of bias within RCTs

High risk of bias was identified for most of the domains for the included studies (figure 1, online resource- supplementary material 3). In particular, allocation concealment (selection bias), blinding of participants and personnel (performance bias) was not discussed sufficiently in any of the seven trials to allow a judgement [25,27,30,31,34, 38,40]. Therefore there was insufficient information to permit judgment of high or low risk. Selection bias in relation to random sequence generation was high in two studies [30,34] as allocation was by the availability of the intervention and this information was unclear in another study [25]. Contamination between the intervention and control groups could not be ruled out in all of the seven RCTs.

Overall the quality of the non-randomised studies was also considered to be low. Fourteen studies did not include a control group in their study design and where a control group was used, it was often not clear whether the nature of likely ADRs to be reported were identical across both groups in relation to clinical settings and patient demography (online resource- supplemental material 4). There was a general lack of consideration about what factors other than the interventions i.e. confounding factors during the study may have impacted on the observed changes. Development and validation of data collection tools were poorly described. Follow up lacked adequate lag time in studies particularly those adopting educational interventions as evaluation often measured transient impact on knowledge and practice. Sample size of participants or the report numbers were often low compromising the generalisability of the findings.

A lack of standardised definition and classifications of ADRs were observed in the included studies. Classification systems were based on seriousness (serious and non-serious), whether expected and unexpected, and whether labelled and unlabelled (table 1).

Table 1 to appear here

3.2 Nature of interventions

Educational interventions

Twenty-one studies implemented educational interventions (table 1 and 2). These included passive interventions such as provision of printed training manual about importance of ADR reporting; or the provision of active interventions including telephone interviews, educational workshops, lectures, email reminders, continuing medical education sessions, bulletins, visits to clinics, improving accessibility of the ADR reporting, group sessions and presentations (table 1 and 2).

3.2.1.Technological interventions

Three studies utilised electronic systems or features to increase accessibility of ADR reporting system or to prompt reminders about when to use the system for ADR reporting (table 1 and 2).

3.2.2 *Financial interventions*

Financial provisions used in the interventions included the use of lottery tickets, direct monetary rewards, and additional days off work (table 2).

3.2.3 Policy interventions

Two studies related to evaluation of the impact of new policies aimed at establishing responsibilities and methods for reporting ADRs (table 1 and 2).

3.2.4. Mixed interventions

Mixed nature of interventions were utilised in five studies including a mix of educational, financial, electronic system or policy interventions. A study [19] evaluated novel organisational policy for reporting adverse drug reactions by streamlining the process of reporting and incorporating ADR reporting mechanisms as part of the organisational accreditation documents. Two studies [20,21] focused on the improved regulation for reporting ADRs resulting from antibiotics use. ADR reporting activity of health professionals was included in performance evaluation of the heads of hospital and department in one study [20] (table 1).

3.3 Use of theory

Only three studies used behavioural theory in the development of the intervention [25,38,40]. These studies used complacency; insecurity; diffidence; indifference; and ignorance to define key behavioural barriers and facilitators to reporting ADRs. The use of theory was deemed to have allowed the intervention to be designed to address these knowledge and attitude gaps (table 1).

3.4 Intervention outcomes

Almost all interventions apart from those utilising passive educational approaches showed improvement in the rate of reporting of spontaneous ADRs. However, the unit of measurement and extent of improvement varied across the studies (table 2).

3.4.1 RCTs

All of the seven RCTs [25,27,30,31,34,38,40] included in the review used educational interventions. A study conducted in Portugal included a one hour educational visit by a pharmacist to hospital and community pharmacists as a group session to address the unmet educational need [38]. The study showed that over the 16 months period, adjusted increase in the total ADR reporting rate attributable to the intervention to be 275.63 per 1000 pharmacist-years which accounted to a 5.87 fold (95% CI 1.98- 17.39, p=0.001) increase in reporting rate over 4 months post intervention. Improvement in the serious (10 fold), unexpected (4 fold), high-casualty (9 fold) and new drug-related ADRs (9 fold) were also observed. A sub-group analysis showed that the intervention had no effect on hospital pharmacists and any positive changes were seen only with community pharmacists [38]. Another study in Portugal by the same research group using similar cluster RCT design focused on the physicians using either telephone or workshop interventions [27]. Comparison with the control group showed that the workshop intervention increased the spontaneous ADR reporting rate by an average of 4-fold (relative risk [RR] 3.97; 95% CI 3.86, 4.08; $p < 0.001$) across the 20 months post intervention. Telephone interviews, in contrast was shown to prove less efficient since they led to no significant difference ($p = 0.052$) in the reporting rate and the intervention effect did not last long [27]. Another cluster RCT conducted in Portugal used either telephone interviews (4-12 minutes) or 1 hour workshop workshops to promote ADR reporting amongst hospital and community pharmacists [31]. Outcomes evaluated four months post-intervention showed improvement in ADR reporting rates and quality, although the effects declined over time (table 2).

A cluster RCT conducted in Spain [25] which used an active component (group session 20-25 minutes) and a passive component (educational material) to the physicians delivered by pharmacists. The intervention showed educational intervention increased ADR reporting by 65.4 % (95 % CI 8.2–153.4) over the four month period post intervention. Moreover, the educational intervention had a positive effect on the relevance of reporting, measured as the increase in unexpected reports (2.06, 95 % CI 1.19–3.55) (table 2).

An RCT conducted in Sweden focused on the heads of primary healthcare units which consisted of email communications about the importance of reporting ADR showed no statistically significant effect on the quality or the quantity of ADR reports [34]. Another study in Sweden which used a one-page information letters on three occasions to physicians and nurses in primary healthcare unit did not show a significant increase in the ADR reporting rate (mean number of reports per unit ± standard deviation: 1.0 ± 2.5 vs. 0.7 ± 1.2, P = 0.34), although increase in the number of high quality reports was noticed (table 2) [30].

Five RCTs were included in meta-analysis [25,27,31,38,40]. Two RCTs [30,34]were excluded from meta-analysis because of following two reasons: Firstly, mode of delivery of educational interventions in these trials was passive and lacked face-to-face contact component. Combining interventions with different mode of delivery would have introduced clinical heterogeneity and is not recommended. Secondly, data were not reported in an appropriate format to allow meaningful statistical combination.

The meta-analysis found a statistically significant 3.5-fold overall increase in reporting of ADRs [RR 3.53; 95% CI (1.77, 7.06)] in the intervention group compared to the control (figure 2). Furthermore, approximately a 4-fold increase was noted in reporting of serious ADRs [RR 4.18; 95% CI (1.69, 10.33)] and unexpected ADRs [RR 5.16; 95% CI (2.42, 11.03)] in the intervention group compared to the control (figure 2).

3.4.2 Other study designs

A study in China demonstrated that financial interventions which constituted rewards and penalty led to 855% increase in the number of ADR reported [20]. When combined with additional regulation, the changes were augmented to over 2,000 fold increase. A 379% increase in the number of ADR reports were reported by a study on the financial incentives delivered to patients, pharmacists, physicians and nurses in Saudi Arabia [17] The intervention which consisted of employee of the month award for the most frequent reporter, letters of appreciation, extra annual leave and performance also led to increase in the number of serious ADR reporting. One study which used lottery tickets as an economic inducement showed 59% increase in the ADR reporting rate in the intervention group ($p<0.10$) [39] (table 2).

The two studies utilising electronic reminders showed positive changes in ADR reporting rates and quality. One study [28] investigated electronic reminders to the electronic patient records or to the desktop computers. The hyperlink took participants to an online ADR reporting form. When comparing with the control group, a statistically significant improvement in reporting was noted. However, outcome follow up only lasted until 4

months post-intervention. Another study [35] used an electronic system to facilitate ADR reporting through easy use, automatic input of certain information, and increased accessibility. A positive improvement in the reporting rate by both the physician and pharmacist study participants in the eight months post intervention period were observed (table 2).

Changes in ADR reporting policy alone was shown to only minimally improve ADR reporting practices [19] despite the follow up evaluation was conducted only three months after the introduction of the new policy. Both studies focused on policy/regulatory interventions were specific to a particular clinical setting, Canadian Forces Health Services Group [19] and specific hospitals [21] in China. While one study [19] made a reference to a national policy change, evaluation was limited to the impact on a specific clinical setting (table 2).

A study on the impact of mass public and health professional campaign on the ADR reporting conducted in Scotland showed an improvement in the reporting by members of public, however, the changes were reported to be insignificant [22]. Changes in the physician computer software systems implemented during the same period were deemed to have impacted on the observed positive changes. The comparator geography used in the evaluation was based outside of Scotland (table 2).

In summary, evidence from non-randomised studies showed that interventions involving financial incentives as a standalone or combined with other interventions types often yielded the biggest changes in the ADR reporting rates. Financial interventions reported between 59% and 855% increase in ADR reporting (Table 2). Similar to the findings from RCTs, face-to-face educational interventions showed greater impact on the number and quality of ADR reported than those not involving face-to-face interactions (table 2).Limited impact was reported around the impact of policy interventions. Pharmacovigilance activities aimed at patients were able to produce limited changes in reporting practices.

4.0 Discussion

Spontaneous ADR reporting is key to improving the post-marketing safety of medicines and it is imperative to identify essential features of successful interventions that can be adopted widely. This is the first systematic review incorporating a meta-analysis of the impact of interventions to improve the quality and quantity of spontaneous ADR reporting considering both healthcare professionals and patients. A total of 28 studies were included in the review of which none of the studies satisfied all quality criteria. Most

of the studies were small scale studies conducted within one specific hospital, clinical speciality or a region. There was a lack of a high quality large scale, multi-centre RCTs or pragmatic study designs. Although seven studies used RCT designs, none were assessed to have a low risk of bias. Contamination was likely to exist given communications amongst healthcare professionals across study settings and geography.

A total of 14 included studies in this systematic review did not include any control group. These were often single arm before and after study designs and the results of these studies are less likely to be transferable to other settings. Where control groups were used, data were often collected on the total number and nature of ADRs from other geographical areas or other healthcare settings. There was often a lack of adequate data on the demographics, clinical characteristics and baseline awareness of spontaneous ADR reporting amongst participants.

Most of the included studies included educational interventions to improve ADR reporting. A variety of educational methods were used including reminders, face to face educational sessions and newsletters. While most of these studies were reported to have improved ADR reporting, there was a lack of long-term follow up of the outcomes. The cluster-randomised controlled trials included in the study reported that the impact of interventions observed by the difference in the intervention and control group in the ADR reporting rate lasted for only 12 months after which such difference was no longer significant. While transient impact is easy to realise, sustainability around change in behaviours is often difficult to achieve [45-48]. Interventions that have been designed with implementation in mind from the outset face least barriers to implementation. Capacity building, ongoing monitoring and evaluation and addressing political, contextual and behavioural barriers to implementation have been identified as key factors that can promote sustainability [46].

4.1. *Implications for practice and research*

While a number of evaluations were included in the systematic review, they only represented a very small number of countries. There is a scope to improve spontaneous ADR reporting in middle and low-and-middle income countries (LMIC) given the high contribution to global burden of diseases and increasing medicines use within those regions. Unique barriers may exist in LMICs which includes lack of a non-blame culture and professional hierarchy [24]. Hence in such settings, educational interventions alone may not be sufficient in changing practice.

There is a scope to include community pharmacy, particularly to improve ADR reporting by patients. Community pharmacies are well distributed geographically and are easily accessible by population. For example in England, over 90% of population in England live within a 20-minutes' walk to a community pharmacy and they are well situated to promote ADR reporting by patients [49,50]. Only five included studies used community pharmacy based interventions to improve ADR reporting, of which one only aimed to promote ADR reporting by patients. There is a scope for interventions aimed at patients to be developed, implemented and evaluated. Over a 100 countries have now provisions for ADR reporting by patients [51]. Despite this, a very low awareness amongst patients about their eligibility to report ADRs in eligible countries exist [52].

Interventions as well as outcomes measurement needs to be sustained over time. Continuing professional development models needs to be in place instead of one-off training events. Studies need to build needs assessment and implementation plans as part of the intervention development to promote sustainability.

There was a lack of consideration of behavioural theories in intervention development. There is an accumulation of evidence that theory based interventions are more likely to yield positive and sustainable results compared to pragmatic approaches. There is therefore a need for a well-designed, systematic and comprehensive study of a theoretically derived intervention aiming to optimize ADR reporting by health professionals and patients. The Medical Research Council Framework of Complex Interventions in the UK advises the use of theory and exploratory studies to identify barriers to change while developing complex interventions [53]. It is imperative that future interventions utilise appropriate theories to maximise the success of interventions. These include the use of theoretical domains framework (TDF) [54] and behaviour change taxonomy (BCT) [55]. The various interacting components in behaviour change research makes them challenging to identify the active, effective components within interventions and for others to replicate them. The included studies in these systematic reviews often tend to report mean changes in ADR reporting rates across all participants. It will be worth considering the low or the non-reporters and developing and targeting active ingredients of the interventions to focus on the low and non-reporters.

5.0. CONCLUSIONS

The limited evidence showed that active interventions involving face to face educational approaches, financial incentives and electronic features targeted at healthcare professionals could improve ADR reporting. However, the results need to be interpreted cautiously given the short term evaluation outcomes, dominance of observational

designs and low quality of included studies. While observational studies are allow pragmatic approach to undertaking pharmacovigilance interventional studies, there is a need to develop and test theory based interventions through fully powered randomised controlled trial design, particularly those including patients. Moreover, there is a need for interventions to be developed and tested in countries low-and-middle income countries.

6. Expert opinion

Most of the currently available interventional research studies in relation to improving ADR reporting have relied on educational interventions with measurements of transient outcomes. Future studies need evidence base from LMICs, particularly in relation to addressing policy level, professional, organisational and cultural barriers to spontaneous ADR reporting. While global policy changes allowing patients to report spontaneous ADRs have been welcome, research to capture impact and facilitators of greater patient involvement needs to be undertaken through the use of behaviour change theories.

References

1. World Health Organization. Safety of Medicines - A Guide to Detecting and Reporting Adverse Drug Reactions - Why Health Professionals Need to Take Action. https://apps.who.int/medicinedocs/en/d/Jh2992e/2.html. Accessed 28 June 2020.
2. Oscanoa TJ, Lizaraso F, Carvajal A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. Eur J Clin Pharmcol. 2017; 173(6):759-70.
3. Vilhelmsson A. Consumer narratives in ADR reporting: an important aspect of public health? Experiences from reports to a Swedish consumer organization. Front Pub Health. 2015;1:3:211.
4. Sultana J, Cutroneo P, Trifirò G. Clinical and economic burden of adverse drug reactions. J Pharmcol Pharmacotherp. 2013;4(Suppl1):S73.
5. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29(5):385-96.
6. Molokhia M, Tanna S. Bell D. Improving reporting of adverse drug reactions: systematic review. Clinical Epidem*. 2009*, *1*: 75.
7. De Angelis A, Colaceci S, Giusti A, et al.. Factors that condition the spontaneous reporting of adverse drug reactions among nurses: an integrative review. Journal Nurs Manage*.* 2016; *24*(2):151-163.
8. World Health Organization. Reporting and learning systems for medication errors: the role of pharmacovigilance centers, 2014. Available at: http://apps.who.int/medic inedo cs/documents/s2162 5en/s2162 5en.pdf. Accessed 10 February 2020.
9. Gonzalez-Gonzalez C, Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Strategies to improve adverse drug reaction reporting: a critical and systematic review. Drug Saf 2013. 1:36(5):317-28.
10. Cochrane Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.0.0. The Cochrane Collaboration; 2011. Accessed at www.cochrane-handbook.org. [Accessed 10 July 2020].
11. Moher D, Shamseer L, Clarke M et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Rev. 2015;4[1]:1.
12. Paudyal V, Al-Hamid H, Jalal Z, et al.. Effectiveness of interventions to improve spontaneous reporting of adverse drug reactions: systematic review and meta-analysis. PROSPERO 2019 CRD42019162209 Available At:

https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019162209 [Accessed July 2020].
13. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
14. Critical appraisal skills programme (CASP). CASP Checklist. Available from: http://www.casp-uk.net/casp-tools-checklists. Accessed 01 July 2020.
15. Cochrane Uk. How to read a forest plot? https://uk.cochrane.org/news/how-read-forest-plot. Accessed 01 July 2020
16. Greenland S. A critical look at some popular meta-analytic methods.Am J Epidemiol. 1994 Aug 1; 140(3):290-6.
17. Ali S, Egunsola O, Al-Dossari DS, et al. Adverse drug reaction reporting in a large tertiary hospital in Saudi Arabia: results of an incentive strategy. Ther Adv Drug Saf. 2018;9(10):585-90.
18. Avong YK, Jatau B, Gurumnaan R, et al. Addressing the under-reporting of adverse drug reactions in public health programs controlling HIV/AIDS, Tuberculosis and Malaria: A prospective cohort study. PloS One. 2018;13(8).
19. Roy R, Ma J. Impact of a policy change on pharmacists' reporting of adverse drug reactions. The Can J Hosp Pharm. 2018;71(4):227.
20. Chang F, Xi Y, Zhao J, et al. A time series analysis of the effects of financial incentives and mandatory clinical applications as interventions to improve spontaneous adverse drug reaction reporting by hospital medical staff in China. J Eval Clin Prac. 2017;23(6):1316-21.
21. Fang H, Lin X, Zhang J, et al. Multifaceted interventions for improving spontaneous reporting of adverse drug reactions in a general hospital in China. BMC Pharmacol Toxicol. 2017;1:18(1):49.
22. Aldeyab MA, Noble SC, Cuthbert M, et al. Assessment of the impact of the Scottish public health campaign on patient reporting of adverse drug reactions. Drugs & Thearp Persp. 2016; 1:32(5):209-18.
23. Ríos OM, Gutiérrez LJ, Talavera JO, et al. A comprehensive intervention for adverse drug reactions identification and reporting in a pediatric emergency department. Int J Clin Pharm. 2016; 1:38(1):80-7.
24. Srikanth MS, Adepu R, Nagaraj S. Impact of an educational intervention on knowledge, attitude, and practices of urban community pharmacists towards adverse drug reaction reporting in a South India city. Asian J Pharm Clin Res. 2016;9:140-4.
25. Lopez-Gonzalez E, Herdeiro MT, Piñeiro-Lamas M et al. Effect of an educational intervention to improve adverse drug reaction reporting in physicians: a cluster randomized controlled trial. Drug Saf. 2015;1:38(2):189-96.
26. Biagi C, Montanaro N, Buccellato E, et al. Underreporting in pharmacovigilance: an intervention for Italian GPs (Emilia–Romagna region). Eur J Clin Pharmcol. 2013; 1:69(2):237-44.
27. Herdeiro MT, Ribeiro-Vaz I, Ferreira M, et al. Workshop-and Telephone-Based Interventions to Improve Adverse Drug Reaction Reporting. Drug Saf. 2012;1:35(8):655-65.
28. Ribeiro-Vaz, Santos C, da Costa-Pereira A, et al. Promoting Spontaneous Adverse Drug Reaction Reporting in Hospitals Using a Hyperlink to the Online Reporting Form. Drug Saf. 2012; 1:35(5):387-94.
29. Gerritsen R, Faddegon H, Dijkers F, et al. Effectiveness of pharmacovigilance training of general practitioners. Drug Saf. 2011;1:34(9):755-62.
30. Johansson ML, Hägg S, Wallerstedt SM. Impact of information letters on the reporting rate of adverse drug reactions and the quality of the reports: a randomized controlled study. BMC Clin Pharmacol. 2011;1:14.
31. Ribeiro-Vaz I, Herdeiro MT, Polónia J et al. Strategies to increase the sensitivity of pharmacovigilance in Portugal. Revista de Saude Publica. 2011;12:45:129-35.
32. Gony M, Badie K, Sommet A, et al. Improving adverse drug reaction reporting in hospitals. Drug Saf. 2010; 1:33(5):409-16.
33. Yen YH, Kuo LN, Hsu MH, et al. Evaluation of the electronic adverse drug event management system. J Exper Clin Med. 2010;1:2(6):287-91.

34. Johansson ML, Brunlöf G, Edward C, et al. Effects of e-mails containing ADR information and a current case report on ADR reporting rate and quality of reports. Eur J Clin Pharmacol. 2009; 1:65(5):511-4.
35. Ortega A, Aguinagalde A, Lacasa C et al. Efficacy of an adverse drug reaction electronic reporting system integrated into a hospital information system. Annals Pharmacother. 2008;42(10):1491-6.
36. Pedrós C, Vallano A, Cereza G, et al. An intervention to improve spontaneous adverse drug reaction reporting by hospital physicians. Drug Saf. 2009; 1:32(1):77-83.
37. Tabali M, Jeschke E, Bockelbrink A, et al. Educational intervention to improve physician reporting of adverse drug reactions (ADRs) in a primary care setting in complementary and alternative medicine. BMC Public Health. 2009; 1:9(1):274.
38. Herdeiro MT, Polónia J, Gestal-Otero JJ, et al. Improving the reporting of adverse drug reactions. Drug Saf. 2008; 1:31(4):335-44.
39. Bäckström M, Mjörndal T. A small economic inducement to stimulate increased reporting of adverse drug reactions a way of dealing with an old problem? Eur J Clin Pharmacol. 2006;1:62(5):381-5.
40. Figueiras A, Herdeiro MT, Polónia J, et al. An educational intervention to improve physician reporting of adverse drug reactions: a cluster-randomized controlled trial. JAMA2. 006; 6:296(9):1086-93.
41. Bracchi RC, Houghton J, Woods FJ, et al. A distance-learning programme in pharmacovigilance linked to educational credits is associated with improved reporting of suspected adverse drug reactions via the UK yellow card scheme. Br J Clin Pharmacol. 2005;60(2):221-3.
42. Lata PF, Mainhardt M, Johnson CA. Impact of nurse case manager-pharmacist collaboration on adverse-drug-event reporting. Am J Health-System Pharm. 2004;1:61(5):483-7.
43. Castel JM, Figueras A, Pedrós C, et al. Stimulating adverse drug reaction reporting. Drug Saf. 2003;1:26(14):1049-55.
44. Bäckström M, Mjörndal T, Dahlqvist R. Spontaneous reporting of adverse drug reactions by nurses. Pharmacoepid Drug Saf. 2002;11(8):647-50.
45. Paudyal V, Hansford D, Cunningham S, Stewart D. Pharmacists' perceived integration into practice of over-the-counter simvastatin five years post reclassification. Int J Pharm Prac. 2012;1:34(5):733-8.
46. Shelton RC, Cooper BR, Stirman SW. The sustainability of evidence-based interventions and practices in public health and health care. Ann Rev Pub Health. 2018;1:39:55-76.
47. Todd A, Copeland A, Husband A, Kasim A, Bambra C. The positive pharmacy care law: an area-level analysis of the relationship between community pharmacy distribution, urbanity and social deprivation in England. BMJ Open. 2014;1:4(8):e005764.
48. Stewart D, MacLure K, Paudyal V, Hughes C, Courtenay M, McLay J. Non-medical prescribers and pharmacovigilance: participation, competence and future needs. Int J Clin Pharm. 2013;1:35(2):268-74.
49. Matos C, Härmark L, van Hunsel F. Patient reporting of adverse drug reactions: an international survey of national competent authorities' views and needs. Drug Saf. 2016;39(11):1105-16.
50. Al Dweik R, Stacey D, Kohen D et al.. Factors affecting patient reporting of adverse drug reactions: a systematic review. Br J Clin Pharmacol 2017;83(4):875-83.
51. Craig P, Dieppe P, Macintyre S, et al.. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008; 29;337:a1655.
52. Atkins L, Francis J, Islam R, et al.. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implement Sci. 2017 Dec;12(1):77.
53. Michie S, Richardson M, Johnston M, et al The Behavior Change Technique Taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions, Ann Behav Med. 2013;46(1): 81-95.

Table 1: Characteristics of included studies

Study (author and year)	Aim	Country	Study design	Study setting	Participants/target population intervention including number of participants where stated	Participants/target population control	Follow up duration	Study outcome(s)	ADR classification
Ali et al. 2018[17]	To describe the reporting of ADRs in a tertiary hospital and determine the effect of incentives to healthcare professionals on ADR reporting	Saudi Arabia	Pre-post observational study/ time series	A tertiary hospital	Patients, pharmacists, physicians, nurses and others (n unclear)	No control group	12 months	Quality and quantity of ADRs reported	Serious and non-serious ADRs
Avong et al. 2018[18]	To evaluate pharmacovigilance training model that was designed to improve the reporting of ADRs in public health programs treating the Human Immunodeficiency Virus, tuberculosis and Malaria	Nigeria	Pre-post observational study	health facilities and institutions	Nurses, physicians and pharmacists (n=55 in total)	No control group	12 months	Knowledge gained and the number of ADR reports submitted	Not available
Roy, Ma 2018[19]	To determine whether ADR reporting behaviours of pharmacists improved after release of a revised policy on the reporting of medication incidents	Canada	Pre-post observational study	Canadian Forces Health Services Group	48 pharmacists	No control group	3 months	Quality and quantity of ADRs reported	Not available
Chang et al. 2017[20]	To assess the effectiveness of a financial intervention for improving ADR reporting by physicians in a hospital setting	China	Ecological time series study	Tertiary care university hospital	Physicians and pharmacists (n unclear)	No control group	Time series for eight years	Quantity and quality (serious and new ADRs)	Total, general; new; and serious
Fang et al. 2017[21]	To compare the spontaneous reporting data collected under old and new regulations	China	Ecological time series study	Hospital	Physicians, clinical pharmacists, and nurses (approximate n= 943)	No control group	Time series for eleven years	Quantity of ADR reports and compliance with and clinical utility of reports	Total, serious; and general
Aldeyab et al. 2016[22]	To assess patterns in reporting of ADRs via the Yellow Card Scheme following a Scottish community pharmacy patient Yellow Card promotional campaign	Scotland, UK	Ecological time series study	Healthcare professionals and patients	All inhabitants of Scotland	All inhabitants of the Northern and Yorkshire	12 months	Number and quality of ADR reporting	Overall, total and serious
Ríos et al. 2016[23]	To assess the effectiveness of a pharmacist intervention in a tertiary care paediatric hospital on ADR identification and reporting	Mexico	Quasi-experimental, pre-post test study	Paediatric ED	62 physicians based at the emergency department	No control group	6 months	Total ADRs, those correctly identified & number of s reported	Not classified
Srikanth et al. 2016[24]	To evaluate the impact of the educational program on community pharmacist's knowledge and perception toward ADR reporting	India	Prospective interventional study	Community pharmacies in Mysore, South India	26 practising community pharmacists	No control group	Not stated	Self-reported ADR reporting practices	Not defined
Lopez-Gonzalez et al. 2015[25]	To assess the effect of an educational intervention to improve the quantity and relevance of physician-led spontaneous ADR reporting	Spain	Spatial, cluster RCT	Hospitals and primary care centres	2,120 physicians	3,614 physicians	8 months	Number of reports and the nature of ADRs	serious; unexpected; and high causality (probable)

Biagi et al. 2013[26]	To evaluate whether an e-mail-based monthly drug safety newsletter sent to GPs would affect the quality and quantity of ADR reports	Italy	Prospective interventional study	GPs in three local health authorities	All 737 GPs from the 3 local health authorities	Pooled number of ADR reports from 7 other regions	10 months	Number and quality of reports	Not classified
Herdeiro et al. 2012[27]	To evaluate the results of workshop and telephone based educational interventions on quantity, quality (relevance) and duration of the effect of these interventions	Portugal	Cluster randomised controlled trial	25 hospitals in the Northern region of Portugal	1388 physicians from 4 spatial clusters	5063 physicians from 11 spatial clusters	0- 20months	Reporting quantity; and reporting relevance	Serious; definitive or probable; and unexpected
Ribeiro-Vaz et al. 2012[28]	To evaluate the impact of adding hyperlinks to an online ADR reporting form to hospitals' electronic patient records on the number of spontaneous ADR reports	Portugal	Ecological study	27 hospitals in Northern Portugal	All staff in 16 hospitals)	All staff in 11 hospitals	31 months	Number of reports, seriousness of the ADRs	Categorised into: total; serious or non-serious; and previously known
Gerritsen et al. 2011[29]	To establish whether the use of a practice-based pharmacovigilance training method during GP training leads to an increase of reported ADRs after completion of this training, compared with a lecture-based method	Netherlands	Retrospective cohort study	General practice	Lecture-based: 135 GPs; Practice-based: 124 GPs	No control group	Mean=431 months	Number of reports, quality (documentation level of the reports)	Labelled; and unlabelled
Johansson et al. 2011[30]	To evaluate if repeated one-page ADR information letters affect the reporting rate of ADRs, and the quality of the ADR reports	Sweden	Randomised controlled study	Primary healthcare units	GPs and nurses at 77 primary healthcare units	GPs and nurses) at 74 primary healthcare units	12 months	Number and quality of reports	Serious; unexpected; new drug and not common; all other
Ribeiro-Vaz et al. 2011[31]	To evaluate the results of an educational intervention used to improve the number and relevance of reports of ADRs	Portugal	Cluster randomised controlled trial	Community and hospital pharmacy	All pharmacists in 4 cluster groups (n=364, telephone interviews, n=261; workshop, n=103)	All pharmacists in 11 cluster groups (n=1103)	20 months	Number and Quality of reports	Classified into: total; severe; high level of probability; unexpected
Gony et al. 2010[32]	To assess the effect of regular visits of a Clinical Research Assistant on the improvement of ADR reporting in non-university hospitals	France	Longitudinal study	Non-university hospitals within three areas	All healthcare staff within two regions	All healthcare staff within one region	0- 3 years	The total reporting rate and %of serious ADRs, characteristic of ADRs	Total, spontaneous; solicited, and serious
Yen et al. 2010[33]	To compare the efficiency and influence of an electronic ADR management system with a traditional working model at a medical centre	Taiwan	Ecological time series study	Taipei Medical University Wan Fang Hospital	All healthcare staff at Taipei Medical University - Wan Fang Hospital	No control group	Time series for 6 years	Number of ADR reports	Classified into: total; minor; moderate; severe; fatal
Johansson et al. 2009[34]	To evaluate whether repeated e-mails with attachments containing ADR information can affect the reporting of ADRs and the quality of the ADR reports	Sweden	Randomised controlled study	Primary healthcare units	Staff in 59 healthcare units	58 healthcare units	12 months	The total number of ;quality of ADRs	Serious; unexpected (not in SPC); new (< 2 years on the market) and not common ; and all other reports

Pedrós et al. 2009[36]	To assess the effectiveness of a multifaceted intervention based on healthcare management agreements for improving spontaneous reporting of ADRs by physicians in a hospital setting	Spain	Time series analysis	A tertiary care hospital	All physicians at the tertiary care hospital	No control group	3 years	Total number of reports; seriousness of reports; and reports of new drugs causing	Serious ; unexpected ; and associated with new drugs
Tabali et al. 2009[37]	To evaluate the impact of an educational intervention and monitoring programme designed to improve physician reporting of ADRs in a primary care setting	Germany	Prospective multicentre observational study	Primary care	38 primary care physicians specialised in CAM	No control group	21 months	Number, quality and completeness of reports	Seriousness (degree of) or non-serious, causality
Herdeiro et al. 2008[38]	To evaluate the effectiveness of educational outreach visits aimed at improving ADR reporting by pharmacists	Portugal	Cluster randomised controlled trial	Hospital and community pharmacies	342 pharmacists	1091 pharmacists	16 months	Total; serious; unexpected; high-causality; and new drug related	Total ADRs; serious s; unexpected s; high-causality s; and new drug related s
Ortega et al. 2008[35]	To analyse the efficacy of an electronic ADR reporting tool, make improvements to increase ADR reporting, and evaluate the impact of these improvements	Spain	Time series analysis	A private tertiary care hospital	All physicinas, pharmacists and nurses at the hospital	No control group	1 year	Total number of reports	Classified into: total number of reports
Bäckström et al. 2006[39]	To assess the effect of a small economic inducement on the rate of spontaneous reporting of ADRs and the attitudes of general practitioners and physicians towards reporting of ADRs	Sweden	Prospective interventional study	Hospitals and primary care centres	Unclear	unclear	6 months	Number of reports; quality and seriousness of the report	Total, serious, and suspected
Figueiras et al. 2006[40]	To evaluate the effectiveness of educational outreach visits for improving ADR reporting by physicians	Portugal	Cluster randomised controlled trial	Hospitals and outpatient centres	n=1388 physicians	n=5063 physicians	16 months	Quantity and quality of reports	All, serious, high causality; unexpected or unlabelled; and for new drugs
Bracchi et al. 2005[41]	To investigate the effect of a distance-learning package linked to educational credits on the rate and quality of spontaneous ADR reporting by general practitioners and pharmacists in Wales	Wales, UK	Prospective interventional study	General practices, community pharmacies	Pharmacists (n=2039) and GPs (n=1745)	The Northern region of England	1-15 months	Rate and quality of spontaneous reports	Total ADRs
Lata et al. 2004[42]	To determine the impact of the integration of nurse case managers into the ADR reporting system on ADR reports	USA	Time series analysis	A small community hospital in rural Wisconsin	All staff at the community hospital who could report ADRs, especially the nurse case managers	No control group	3 years	Number of reports and the number of serious, possible, and preventable	Classified into: total, serious, possible, and preventable
Castel et al. 2003[43]	To measure the effect of the periodical distribution of a bulletin on drug safety issues and of including yellow cards in prescription pads on the rate of ADR reporting	Spain	Time series analysis	All practising physicians within the region	All practising physicians within the catchment area were included	No control group	Time series for 13 years	Total, reporting rate	Total ADRs reported and reporting rate
Bäckström et al. 2002[44]	To investigate whether trained nurses could be a useful source for improving the reporting rate of ADRs in Sweden	Sweden	Prospective interventional study	Geriatric medicine hospitals in northern Sweden	All 117 nurses working at the two geriatric medicine units	All other 50 geriatric departments in hospitals in Sweden	12 months	reporting rate	Labelled/unlabelled; and serious

ADR: adverse drug reaction, GP: general practitioner UK: United Kingdom; USA: United States of America

Table 2: Intervention outcomes

Study ID	Nature of intervention	Details of intervention	What did the control group receive?	Any clinical area of focus	Response rate	ADR reporting pre-intervention (baseline)		ADR reporting post intervention- all time points		% change post intervention and p values where reported	Change in quality of ADR reporting
						control	Intervention	Control	Intervention		
Ali et al. 2018[17]	Financial	Reward system, including public commendation and award	N/A	Not specified	Not reported-	-	167 reports		800 reports	379%	Increase in reporting of the serious ADRs
Chang et al. 2017[20]	Financial	First intervention: Financial incentives including penalty. Second intervention: Financial incentive and strict regulations for antimicrobial agents	N/A	No specific area. Antimicrobials	-	-	Median per month: 3.56±3.60 3.56±3.60 (95% CI 2.42-4.75), and per year was 29 (range 27-72)	-	Post first intervention: 21±13 (95% CI 16.97-25.80) per month, 277 per year. Post second intervention: 56±20 (95% CI 48.81-62.17) per month, 666 per year	Financial +855% Financial plus regulation +2197%	Increase in reporting and serious and new ADRs
Bäckström et al. 2006[39]	Financial	An economic inducement (lottery tickets)	Information about the main purpose of spontaneous reporting of ADRs and feedback.	No specific area	All physicians and general practitioners within the two counties were included	50 reports	39 reports	50 reports	62 reports	59% increase in the intervention group (p<0.10). No significant difference between the reporting rates of the two groups	No significant increase in the number of serious reports in the intervention group compared to the pre-intervention period, or the control group.
Tabali et al. 2009[37]	Educational and financial	consisting of a one-on-one ADR training session and newsletters; telephone reminders; financial incentive	No control group	Complementary and Alternative Medicine.	362 physicians were initially contacted. 38 physicians participated	-	116 reports in total. Median monthly reporting rate of 4.00 (IQR 3.00-7.50)	-	288 reports in total. Overall median monthly reporting rate of 14.00 (IQR 9.50-19.50)	A statistically significant increase of 148% overall (p<0.001). Statistically significant increase through the first 16 months after the intervention (p<0.005) but not in the last 4 months period	The completeness of reports increased significantly (p<0.001). The quality of the reports did not increase significantly (before intervention: kappa 0.15 (95%CI 0.08-0.29), after intervention: kappa 0.43 (95%CI 0.23-0.63)
Pedrós et al. 2009[36]	Educational and financial	Financial incentives, meetings with the pharmacovigilance department, reminder cards	No control group	No specific area	All physicians (not stated how many exactly) at the hospital were included	-	Mean monthly of 3.47 reports (95% CI 1.90-5.03)	-	Significant increase of a mean of 0.74 reports per month (95% CI 0.62-0.86)	-	There were two folds increase in the number of: serious ADRs reported (p<0.001). No significant increase in the number of unknown ADRs (p=0.376); and new drug ADRs (p=0.559).

Fang et al. 2017[21]	Policy/regulatory, financial and educational intervention	New antibiotic regulations, financial incentives; training courses; improvement of the computer system; regular publishing of ADR information; alerts on serious ADRs; and regulation of antibiotic use	N/A	Antimicrobials	All physicians, clinical pharmacists, and nurses at Jinshan hospital were included	557 ADRs in total in the pre-intervention period	-	832 ADRs in total in the post-intervention period	-	No significant difference in the reporting rates between the pre intervention period (0.0128%) and post intervention period (0.011426%) (p=0.8023). Significant increase in total reports between the pre intervention period (n=557) and post intervention period (n=832) (p=0.0086)	There were improvements in reporting compliance in the post intervention period. Increase in reporting of serious ADRs
Roy, Ma 2018[19]	Policy/regulatory intervention	Policy focused on when, how and who should report ADRs	N/A	None	67%	-	47%	-	45%	2%	-
Avong et al. 2018[18]	Educational intervention	A structured Pharmacovigilance training and workshop	N/A	HIV/Tb/Malaria	98.2%	Not reported	1099	805	3000	273%	100% correctness of the report post intervention
Aldeyab et al. 2016[22]	Educational	Posters and leaflets for patients to promote yellow card reporting including display in pharmacy; Information sheets for community pharmacists and received remuneration	No promotional campaign	Herbal medicines, but also all medicines	Intervention group n= 5,295,400 inhabitants; control group n= 8,266,000 inhabitants	Northern and Yorkshire: Patients: 0.004 Community pharmacists: 0.001 GPs: 0.009 ADR	Northern and Yorkshire: Patients: 0.004 Community pharmacists: 0.002 GPs: 0.014	During the promotional period: Scotland: Patients: 0.002 Community pharmacists: 0.002 GPs: 0.007	Only GPs significantly (p=0.001)increased their ADR reporting	-	Observable improvement in reporting for the quality indicators reaction outcome, patient age, patient initials, patient weight and height, and route of administration. No statistics were provided
Ríos et al. 2016[23]	Educational	Educational session including clinic visits, reminders and accessibility of reporting system	No control group	Paediatrics in the emergency department.	All 62 physicians based at the emergency department	-	6.1% of ADRs were reported (does not state the actual number)	-	41.2% of ADRs during the intervention; 41.7% 6 months post the intervention	35.6% (p<0.05)	Not measured
Srikanth et al. 2016[24]	Educational	Participants given a training manual about ADR reporting	No control group	No specific area.	26 pharmacists	7.69% (n=2)		57.69% (n=15)		650%	Intervention improved the participants' knowledge, attitude, and practice towards ADRs and ADR reporting.

Lopez-Gonzalez et al. 2015[25]	Educational	An active and a passive approach. The active approach consisting of group sessions, including a presentation	Normal practice	No specific area.	-	31.3/1000 participants	28.1/ per 1000 participants	31.1/1000 participants	39.6/1000 participants	65.4% (95% CI 8.2-153.4). RR 1.65 (95% CI 1.08-2.53, p=0.021)	Non-significant increases in reporting of serious ADRs and High causality ADRs post intervention. Significant increases in reporting of Unexpected ADRs
Biagi et al. 2013[26]	Educational	A monthly newsletter on drug safety was sent to all participants via e-mail for 10 months	Received no newsletter; therefore the ADR reports should be uninfluenced by the intervention	No specific area.	Response rate: 22.8% (n=168)	2.51 reports by GPs per 100,000 inhabitants	0.5 reports by GPs per 100,000 inhabitants	Intervention period Control group: 1.59 reports by GPs per 100,000 inhabitants; 12 months post intervention: 2.21 per 100,000 inhabitants	1.47 reports by GPs per 100,000 inhabitants; 12 months post intervention 0.97 per 100,000 inhabitants	Intervention period: intervention group: rose by 49.2% vs pre intervention control group: increased by 8.8% vs pre intervention. 12 months post intervention period saw reports decrease by 6.4% in the intervention group compared to 4.3% fall in the control group	'Good quality' reports in the pre intervention, intervention, and post intervention periods
Herdeiro et al. 2012[27]	Educational	One intervention group received telephone interviews, and the other received educational workshops	Usual practice	No specific area.	200 physicians received one of the interventions. Participation rate for the workshop was 26.9% (n=118), and 7.9% (n=82) for the telephone interviews	ADR reporting rate per 1000 physician years: Control: 10.3	Baseline ADR reporting rate per 1000 physician years:: Workshop: 10.41 Telephone interview: 19.9	ADR reporting rate per 1000 physician years post-intervention: Overall: Control: 12.0	ADR reporting rate per 1000 physician years: Post-intervention: Overall: Workshop: 52.7 Telephone interview: 22.7	Overall 20 months post intervention, ADR reporting Workshop RR: 3.97; 95%CI 3.86-4.08; p < 0.001) Telephone RR: 1.02; 95% CI 1.00, 1.04	Effect of intervention on reports of serious ADRs: Workshop: RR: 6.84; 95% CI 6.69-6.98; p<0.001 Telephone interview: RR: 0.93; 95% CI 0.91-0.94; p<0.001 Effect of intervention on reports of high-causality ADRs: Workshop: RR: 3.58; 95% CI 3.51-3.66; p<0.001 Telephone interview: RR: 0.75; 95% CI 0.73-0.76; p<0.001
Gerritsen et al. 2011[29]	Educational	One set of graduates undertook lecture-based pharmacovigilance training, while the other undertook practice-based training	No control group	No specific area.	All 259 participants enrolled were included and participated	No baseline or pre-intervention rate given	-	Lecture-based: 2.1 ADR reports per 1000 months of follow up. Practice-based: 6.8 reports per 1000 months of follow up	-	Practice-based trainees made statistically significantly more ADR reports (hazard ratio 2.9; 95% CI 1.4-6.1)	Practice-based trainees submitted significantly higher quality reports (odds ratio 5.0; 95% CI 1.1-23.6).Practice-based trainees submitted significantly more unlabelled ADR reports (odds ratio 3.3; 95% CI 1.1-10.1).

Johansson et al. 2011[30]	Educational	An information sheet (letter)	Usual practice	No specific area	All staff at the primary healthcare units were included.	Mean (SD) number of reports per primary healthcare unit =0.7 (1.1)	Mean (SD) number of reports per primary healthcare unit=0.8 (1.4)	Mean (SD) number of reports per primary healthcare unit (SD)=0.7 (1.2)	Mean (SD) number of reports per primary healthcare unit =1.0 (2.5)	p=0.34	The number of high quality reports was higher in intervention units than in control units (mean(SD) number of reports per unit = 0.5 (0.9) vs. 0.2 (0.6), p= 0.048)
Ribeiro-Vaz et al. 2011[31]	Educational	Either a workshop or a telephone intervention	Received neither intervention. Continued normal practice and so the number and types of ADR reports provided from the controls should not be altered by the intervention.	No specific area	Worksho: 52% participation rate (n=52%). Telephone intervention: 36% (n=94)	All numbers are reports per one thousand pharmacists per month. Control: 1.76	Workshop: 7.65 Telephone intervention: 1.69	4 month control: 3.85 20 month-control: 1.59	Workshop: 4 months: 48.5 20 month: 1.6 Telephone intervention: 4 months: 12.5 20 month: 4.9	Increase ADR reports in both intervention groups compared to control (RR 3.22, 95% CI 1.33-7.80)	No significant change in the number of number of reports with high probability compared to controls. Increase in severe ADR reports in both intervention groups compared to control (RR 3.87, 95% CI 1.29-11.61). Increase in unexpected ADR reports in both intervention groups compared to control (RR 5.02, 95% CI 1.33-18.93).
Gony et al. 2010[32]	Educational	Meetings with healthcare professionals	Received visits from the Clinical Research Assistant	No specific area.	All healthcare professionals at the included administration regions were included.	Reporting rate=number of reports/number of beds Control region: reporting rate 0.3%	First intervention region: reporting rate 11% Second intervention region: reporting rate 3%	Control region: reporting rate 2006=0%; 2007=1%; 2008=1%	number of reports/number of beds First intervention region: reporting rate 2006=23%; 2007=18%; 2008=40% Second intervention region: reporting rate 2006=13%; 2007=13%; 2008=25%	The increase was statistically significant in the first and second intervention regions (both p<0.05). There was no significant change in the control region (no statistics)	-
Johansson et al. 2009[34]	Educational	Emails reminders	Received no emails	No specific area	All staff at the included primary healthcare units were included	89 ADR reports altogether from both the intervention and control primary healthcare units	89 ADR reports altogether from both the intervention and control primary healthcare units	55 reports in total	56 reports in total	Overall a 25% increase in the intervention group, which was statistically significant (p=0.037). No significant difference between the control and intervention group	The proportion of high-quality reports before and after the intervention did not significantly change in the intervention group (36% vs 48%, p=0.11) or the control group (40% vs 36%, p=0.55). The proportion of high-quality reports did not differ between the groups (p=0.53).

Herdeiro et al. 2008[38]	Educational	Educational session, leaflets and reminders	Usual practice	No specific area.	80.7% (n=276) of pharmacists in the intervention group attended the intervention	29.2 reports per 1000 pharmacist years	32.3 reports per 1000 pharmacist years.	Overall: 47.6 4 month: 24.7 16 month: 31.1 per 1000 pharmacist years.	Overall: 326.3 4 month: 570.0 16 month: 114.6	Statistically significant increase in reporting rate (increase=275.6 reports per 1000 pharmacist years; 95% CI 162.15-389.12; RR=5.87, 95% CI 1.98-17.39, p=0.001) compared to the pre intervention period. Significantly more reports than in the control group also (5.49 fold increase, 95% CI 2.37-12.75).	Significant increase for all quality indicators. For serious ADRs (10-fold increase, RR = 9.79; p=0.002), unexpected ADRs (4-fold increase, RR = 4.41; p=0.04), high-causality ADRs (9-fold increase, RR = 8.67; p=0.002), and new drug-related ADRs (9-fold increase, RR = 9.33; p<0.001).
Figueiras et al. 2006[40]	Educational	A continuing medical education multifaceted intervention; this included an out-reach visit, reminder card, and report form	The control clusters did not receive the educational intervention.	No specific area	655 of 1388 physicians (47.2%) in the intervention group attended the intervention	Control group: 11.3 reports per 1000 physician years	Intervention: 7.6 reports per 1000 physician years	All numbers are reports per 1000 physician years. Overall: 14.5 4 month: 13.1 16 month: 15.1	Intervention: Overall: 100.2 4 month: 205.2 16 month: 55.3	The adjusted increase in ADR reporting rates attributable to intervention was 90.19 for total ADRs (95% confidence interval [CI], 54.51-125.87; relative risk [RR], 10.23; 95% CI, 3.81-27.51)	Significant increase for all quality indicators in the control group compared to the intervention group. For serious ADRs RR=6.32 (95% CI 2.09-19.16; p=0.001); for high causality ADRs RR=8.75 (95% CI 3.05-25.07; p<0.001); for unexpected ADRs RR=30.21 (95% CI 4.54-200.84; p<0.001); and for new-drug-related ADRs RR=8.04 (95% CI 2.10-30.83; p=0.002).
Bracchi et al. 2005[41]	Educational	A distance-learning programme in pharmacovigilance	Received no training. Continued normal practice and so the number and types of ADR reports provided from the controls should not be altered by the intervention.	No specific area	13% (n=261) of pharmacists completed and 27% (n=477) of general practitioners completed the module	-	Pharmacists: 297 reports. GPs: 1439 reports	-	Pharmacists: 440 reports. GPs: 2781 reports	Pharmacist ADR reporting increase 92% (p<0.001) compared to the pre intervention period and GP reporting 131%. (p<0.001) pharmacists	Increase in 'appropriate' reports by GPs and pharmacists by 15.6% (p<0.001). 11.5% reduction in the 'appropriate' report 12 months post study

Lata et al. 2004[42]	Educational	The nurse case managers screened patients at admission and follow them through their inpatient stay. They were trained on how to report ADRs	No control group	No specific area	All staff at the hospital who could report ADRs were included.	1998: 2.1 ADR reports per 100 admissions	-	2000: 4.5 ADR reports per 100 admissions 2001: 5.3 reports per 100 admissions	-	None stated.	The number of serious ADRs reported increased and that the nurse case managers were the largest reporter of these
Castel et al. 2003[43]	Educational	Quarterly ADR bulletins and reporting forms attached to prescription pads	No control group	No specific area.	All practising physicians within the catchment area of the Catalan Centre of Pharmacovigilance were included	Not stated	-	Overall mean increase in ADR reports after a bulletin was 11.7 reports. Mean increase in month following bulletin: 12.3 reports (95% CI 7.2-17.4); Following the attachment of reports to prescription pads: monthly reporting rate was 19.8 (95% CI 12.5-27.0)	-	None stated.	-
Bäckström et al. 2002[44]	Educational	Educational interventions including lectures	Received no training. Continued normal practice and so the number and types of ADR reports provided from the controls should not be altered by the intervention	No specific area, other than occurring in geriatric wards	All 117 nurses working at the two geriatric medicine units were invited to attend. Actual participation rate was not given	Not stated	2 reports from the two departments in the year prior to the study	15 reports (0.4 reports per 1000 admissions)	18 reports (11 reports per 1000 admissions)	None stated.	-
Ortega et al. 2008[35]	A new electronic system	It facilitated ADR reporting through easy use, automatic input of certain information, and increased accessibility	No control group	No specific area.	All doctors, nurses and pharmacists at the hospital were included in the study	-	Null reports	-	Phase I: 0.91 yellow card reports per month. Phase II: 1.62 yellow card reports per month	No percentages or statistics stated	Not measured

Yen et al. 2010[33]	Electronic system, financial	Introduction of an Electronic ADE management system, financial reward	No control group	No specific area	All medical staff	-	108 ADR reports were received	--	394 ADR reports were received	3.6-fold increase (p<0.0001). No statistics given for the total number of reports	The severity difference between before the introduction of the computerised ADR system and after its introduction were significantly different (p<0.001)
Ribeiro-Vaz et al. 2012[28]	Electronic reminders to the electronic patient records or to the computer desktops	The hyperlink took participants to an online ADR reporting form	No hyperlink to an ADR reporting form was added	No specific area.	All staff from 11 hospitals were included	-	Median of 2 ADR reports per month	-	Median of 5 ADR reports per month.	Statistically significant increase in reporting rate (p=0.009)	-

CI: Confidence Intervals, GP: general practitioner N/A: not applicable

Figure 1: Risk of bias assessment

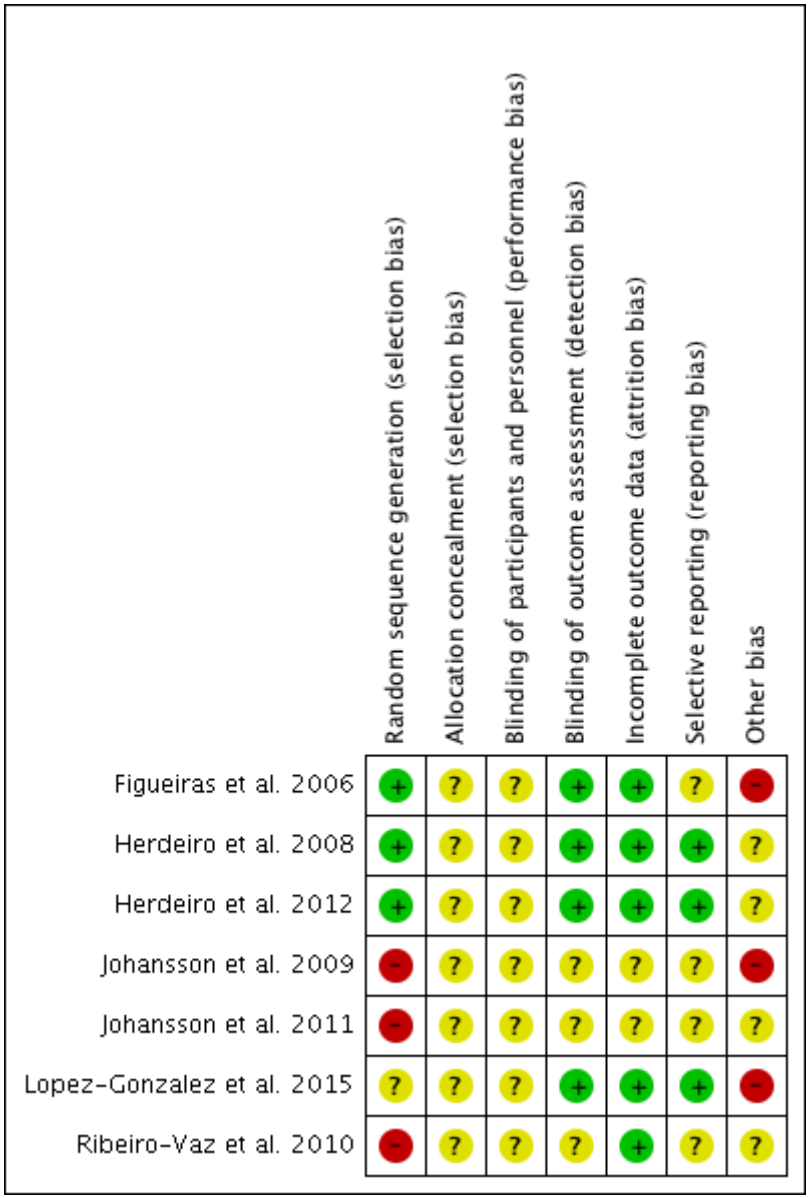
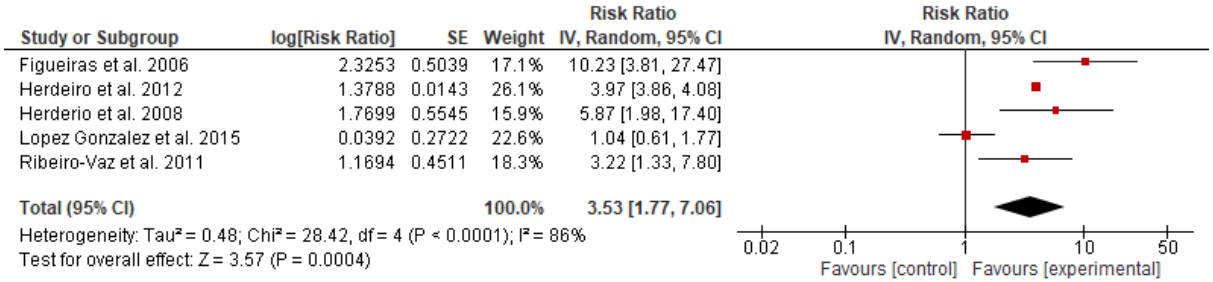

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Figueiras et al. 2006
Herdeiro et al. 2008
Herdeiro et al. 2012
Johansson et al. 2009
Johansson et al. 2011
Lopez-Gonzalez et al. 2015
Ribeiro-Vaz et al. 2010

Figure 2: Forest plots depicting effectiveness of interventions to improve ADR reporting across three outcomes (Overall ADRs, Serious ADRs and Unexpected ADRs)

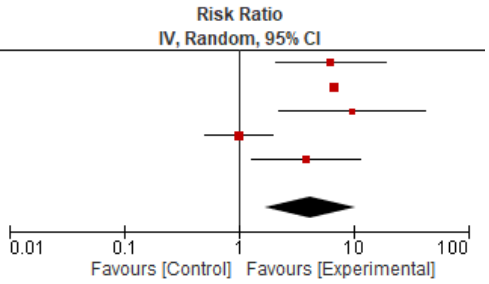
Overall ADRs



Serious ADRs

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Figueiras et al. 2006	1.8437	0.5646	18.5%	6.32 [2.09, 19.11]
Herdeiro et al. 2012	1.9228	0.0113	25.5%	6.84 [6.69, 6.99]
Herderio et al. 2008	2.2814	0.7525	15.2%	9.79 [2.24, 42.79]
Lopez Gonzalez et al. 2015	0	0.3537	22.2%	1.00 [0.50, 2.00]
Ribeiro-Vaz et al. 2011	1.3533	0.5605	18.6%	3.87 [1.29, 11.61]
Total (95% CI)			**100.0%**	**4.18 [1.69, 10.33]**

Heterogeneity: Tau² = 0.83; Chi² = 30.80, df = 4 (P < 0.00001); I² = 87%
Test for overall effect: Z = 3.10 (P = 0.002)



Unexpected ADRs

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Figueiras et al. 2006	3.4082	0.967	10.6%	30.21 [4.54, 201.04]
Herdeiro et al. 2012	1.9228	0.0113	31.2%	6.84 [6.69, 6.99]
Herderio et al. 2008	1.4839	0.7038	15.4%	4.41 [1.11, 17.52]
Lopez Gonzalez et al. 2015	0.7227	0.28	26.8%	2.06 [1.19, 3.57]
Ribeiro-Vaz et al. 2011	1.6134	0.6777	16.0%	5.02 [1.33, 18.95]
Total (95% CI)			**100.0%**	**5.16 [2.42, 11.03]**

Heterogeneity: Tau² = 0.48; Chi² = 21.30, df = 4 (P = 0.0003); I² = 81%
Test for overall effect: Z = 4.24 (P < 0.0001)

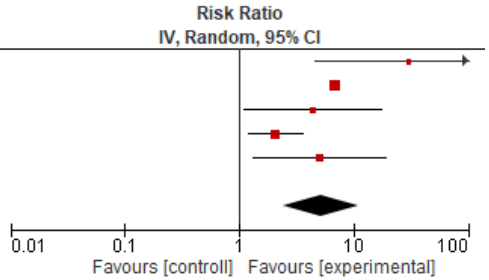


Figure legends

Figure 1: Risk of bias assessment

Legends not applicable

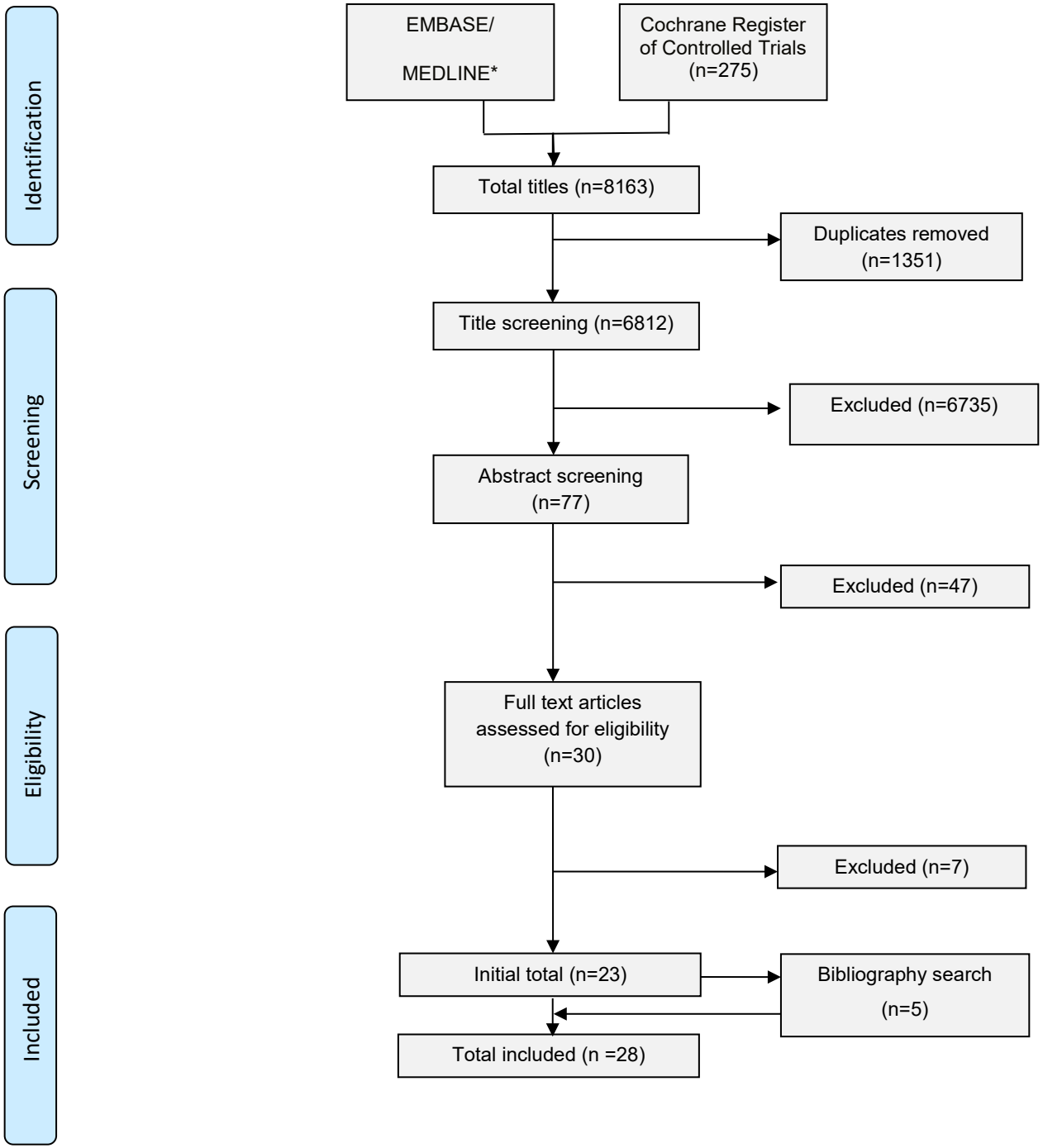
Figure 2: Forest plots Forest plots depicting effectiveness of interventions to improve ADR reporting across three outcomes (Overall ADRs, Serious ADRs and Unexpected ADRs)

Legends not applicable

Supplementary material 1: MEDLINE AND EMBASE search strategy

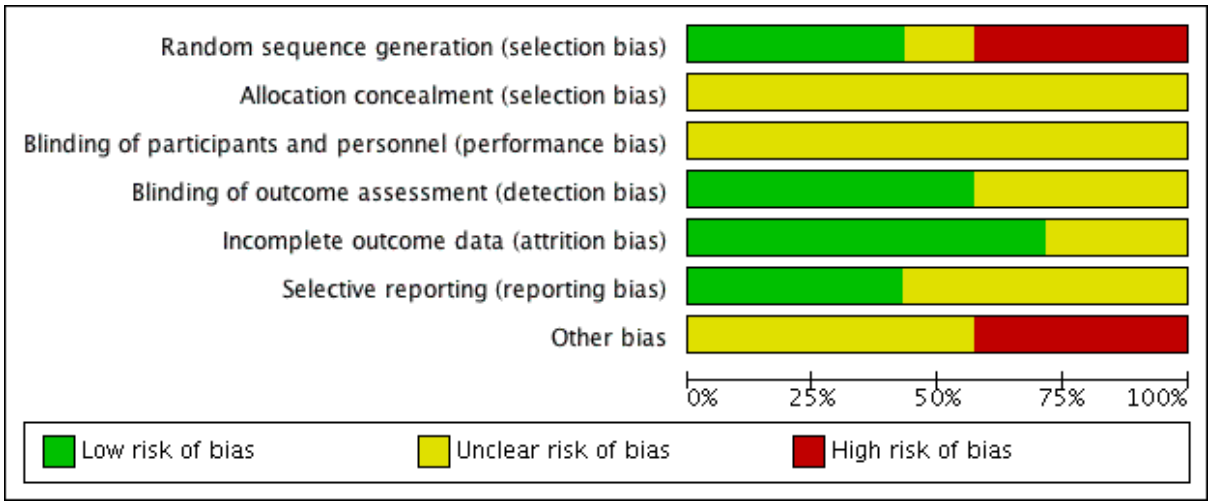
1 adverse drug reaction$ report*.mp.
2 adr report*.mp.
3 adverse drug event$ report*.mp.
4 side effect$ report*.mp.
5 pharmacovigilance.mp.
6 improv*.mp.
7 motivat*.mp.
8 incentiv*.mp.
9 increas*.mp.
10 service$.mp.
11 interven*.mp.
12 educat*.mp.
13 train*.mp.
14 feedback.mp.
15 help.mp.
16 system.mp.
17 modif*.mp.
18 chang*.mp.
19 trend*.mp.
20 1 or 2 or 3 or 4 or 5
21 6 or 7 or 8 or 9 or 17 or 18 or 19
22 10 or 11 or 12 or 13 or 14 or 15 or 16
23 20 and 21 and 22
24 remove duplicates from 23
25 limit 24 to english language
26 limit 25 to yr="2000 -Current"

Supplement 2: PRISMA flowchart


Identification
Screening
Eligibility
Included
EMBASE/
MEDLINE*
Cochrane Register of Controlled Trials (n=275)
Total titles (n=8163)
Duplicates removed (n=1351)
Title screening (n=6812)
Excluded (n=6735)
Abstract screening (n=77)
Excluded (n=47)
Full text articles assessed for eligibility (n=30)
Excluded (n=7)
Initial total (n=23)
Bibliography search (n=5)
Total included (n =28)

PRISMA: Preferred reporting items for systematic reviews and meta-analysis; *databases searched concurrently

Supplement 3: Risk of bias assessment (review level)



Supplementary material 4

Quality assessment of non-randomised studies

	Did the study address a clearly focused issue?	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors?	Have they taken an account of the confounding factors in the design and/or analysis?	Was the follow up of subjects complete enough?	Was the follow up of subjects long enough?	Are the results precise?	Do you believe the results?	Do the results of this study fit with other available evidence?
Aldeyab et al. 2016	Yes	Yes	Yes	Yes	Can't tell	Can’t tell	No	No	Can’t tell	Can’t tell	Yes
Avong et al. 2018	Yes	Yes	Yes	Yes	Can't tell	Can’t tell	Can’t tell	Can’t tell	Yes	Yes	Yes
Roy and Ma 2018	Yes	Yes	Yes	Yes	Can't tell	Can’t tell	Yes	Yes	Yes	Yes	Yes
Chang et al. 2017	Ye	Yes	Yes	Yes	Can't tell	Can’t tell	Yes	Yes	Yes	Yes	Yes
Fang et al. 2017	Yes	Yes	No	Yes	Can't tell	Can’t tell	Yes	Yes	Can’t tell	Yes	Yes
Rios et al. 2016	Yes	Yes	Yes	Yes	Can't tell	Can’t tell	Yes	Yes	Yes	Yes	Yes
Baker et al. 2015	Yes	Yes	Can’t tell	Yes	Can't tell	Can’t tell	Yes	Yes	Yes	Yes	Yes
Srikanth et al. 2015	Yes	Can’t tell	Can’t tell	No	Can't tell	Can’t tell	Yes	No	Can’t tell	Yes	Yes
Biagi et al. 2013	Yes	Yes	Yes	Yes	Can't tell	Can’t tell	No	No	No	Can’t tell	Yes
Gerritsen et al. 2011	Yes	Yes	Yes	Yes	Can't tell	Can’t tell	yes	yes	Yes	Yes	Yes
Ribeiro-Vaz et al. 2011	Yes	Yes	Yes	Yes	can't tell	Can’t tell	Yes	yes	Yes	Yes	yes
Gony et al. 2010	Yes	Yes	Can't tell	can't tell	Can't tell	Can’t tell	Yes	Yes	Yes	Yes	Yes
Yen et al. 2010	Can’t tell	Yes	Yes	Yes	Can't tell	Can’t tell	Yes	Yes	Yes	Yes	Yes
Pedros et al. 2009	yes	Yes	Yes	Yes	Can't tell	Can’t tell	yes	Yes	Yes	Yes	Yes
Tabali et al. 2009	Yes	Yes	Yes	Yes	Can't tell	Can’t tell	Yes	Yes	Yes	Yes	Yes
Ortega et al. 2008	Can't tell	Yes	can't tell	Yes	Can't tell	Can’t tell	Yes	Yes	Yes	Can't tell	Can't tell
Backstrom et al.2006	Yes	Yes	Yes	Yes	Can't tell	Can’t tell	Yes	Yes	Can’t tell	Yes	Yes

Bracchi et al. 2005	Yes	No	Yes	Yes	Can't tell	Can’t tell	No	No	Yes	Yes	Yes
Lata et al. 2004	Can't tell	Yes	Can’t tell	Yes	Can't tell	Can’t tell	Yes	Yes	Yes	Ye	Yes
Castel et al 2003	Yes	Yes	Yes	Yes	Can't tell	Can’t tell	Yes	Yes	Yes	Yes	Yes
Backstrom et al.2001	Yes	Yes	Yes	Yes	Can't tell	Can’t tell	Yes	No	Can’t tell	Can’t tell	Yes

Supplementary material 5

PRISMA Checklist[1]

Section/topic	#	Checklist item	Reported Y/N/NA and page number or section in the manuscript
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Y, title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Y, structured abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Y, introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Y, aim
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Y, page x
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Y, methods
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Y, methods/ data sources
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Y, Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Y, methods
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Y, methods/data extraction

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Y, methods/data extraction
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Y, methods/risk of bias and quality assessment
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Y, methods/data synthesis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Y, methods/data synthesis

Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Y, results/discussion
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Y, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Y Tables 1 and 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Y, Figures 2 and 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Yes, figures 4,5 and 6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA, methodological

			systematic review
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Y, results/risk of bias, quality assessment
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Y, results
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Y, discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Y discussion
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Y, Online submission system

[1]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.doi:10.1371/journal.pmed1000097

NA: Not applicable