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Educational interventions for health professionals managing COPD in primary care (Protocol)

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Educational interventions for health professionals managing COPD in primary care.
Cochrane Database of Systematic Reviews 2017, Issue 5. Art. No.: CD012652.
DOI: 10.1002/14651858.CD012652.

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[Intervention Protocol]

Educational interventions for health professionals managing COPD in primary care

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Editorial group: Cochrane Airways Group.
Publication status and date: New, published in Issue 5, 2017.

Citation: Liang J, Abramson MJ, George J. Educational interventions for health professionals managing COPD in primary care. *Cochrane Database of Systematic Reviews* 2017, Issue 5. Art. No.: CD012652. DOI: 10.1002/14651858.CD012652.

ABSTRACT

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

To review existing evidence for educational interventions delivered to health professionals managing COPD in the primary care setting.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a 'common, preventable and treatable condition that is characterised by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious gases and particles' (GOLD 2017). Cigarette smoke is the biggest risk factor for the development of COPD, especially in middle-income to high-income countries (Decramer 2012; WHO 2017a). The airflow limitation characteristic of COPD is detected through spirometry testing (GOLD 2017). Diagnosis and assessment of COPD severity are based on the ratio of post-bronchodilator forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC). A ratio < 0.7 suggests airflow limitation consistent with COPD (GOLD 2017). Another approach involves the use of lower limit of normal values as cut-offs for COPD diagnosis, in contrast to the fixed cut-off value of 0.7 (Culver 2012). The four stages of GOLD (Global Initiative for Chronic Obstructive Lung Disease; GOLD I to IV), which categorises patients according to % FEV_1 predicted, are commonly used to assess severity of COPD (GOLD 2017). The ABCD grading system assesses COPD symptoms, along with exacerbation frequency and severity (GOLD 2017).

Prevalence of COPD varies widely from 0.2% to 37% according to country, population, age group analysed and method of diagnosis used (such as spirometry and other classification methods according to symptoms) (Rycroft 2012). The actual prevalence of COPD is likely to be higher than reported in studies owing to widespread underdiagnosis of the condition in some parts of the world (Koblizek 2016). Approximately 80% of COPD cases confirmed by spirometry were previously undiagnosed (Koblizek 2016).

Chronic obstructive pulmonary disease is widely acknowledged as a major health problem associated with substantial burden on morbidity, mortality and healthcare resources (Decramer 2012; Toelle 2013). It is the fourth leading cause of death in the world and is

projected to be the third leading cause by 2030, accounting for 8.6% of deaths globally (WHO 2008). Chronic and progressive respiratory symptoms, such as dyspnoea and cough with sputum production, are frequently experienced by patients with COPD (GOLD 2017). The disease is aggravated by acute exacerbations of the disease, which reduce quality of life in affected patients (Decramer 2003; Doll 2005) and result in extensive use of healthcare services. Potential psychological effects of the condition such as anxiety and depression, along with systemic manifestations and comorbidities (such as ischaemic heart disease, congestive heart failure, diabetes and lung cancer), can contribute to loss of quality of life (Decramer 2012; Doll 2005; Putcha 2015).

Description of the intervention

New developments in therapeutics and changes in the evidence base for treatments occur over time. Treatment guidelines and strategies change accordingly. It is acknowledged that professionals from all health fields should invest in educational opportunities that give them up-to-date knowledge and skills so they can provide best patient care (WHO 2017b). The term 'continuing professional development' (CPD) is used to describe the "process by which health professionals keep updated to meet the needs of patients, the health service, and their own professional development" (Peck 2000). This includes "continuous acquisition of new knowledge, skills, and attitudes to enable competent practice" (Peck 2000). Health professional registration boards and regulatory bodies in many countries mandate CPD for legislated revalidation and recertification of practitioners (Peck 2000). Continuing education (CE) is an integral part of CPD. Types of CE for different health professions are named accordingly, for example, continuing medical education (CME), continuing nursing education (CNE) and continuing pharmacy education (CPE). Recently, continuing interprofessional education (CIPE) has been recognised as a distinct branch of CE (Owen 2013).

Educational activities provided in CE/CPD programs vary in terms of educational media (i.e. format used to deliver educational content, e.g. printed materials, videotapes, audiotapes, podcasts, online materials), method of delivery (e.g. live sessions vs Internet or other technology-based sessions), educational technique (specific educational tools used to deliver media, such as small group learning, lectures and simulation) and exposure (duration and frequency of the activity) (Moores 2009). Activities can be categorised as (1) 'live' or external activities, such as courses, seminars, meetings, conferences and audio and video presentations, (2) internal activities, including practice-based activities, case conferences, grand rounds, journal clubs, teaching and consultation with peers and colleagues, and (3) 'enduring' materials (print, CD-ROM or Web-based materials, with testing or assessment) (Peck 2000). Educational interventions can consist of individual activities or may involve multiple activities, and can be didactic, interactive or a mixture of both (Davis 1999).

How the intervention might work

It is assumed that CE for health professionals improves healthcare practice and, thereby, health outcomes for patients receiving care (Forsetlund 2009). The effectiveness of continuing education can be analysed in three areas: competence, performance and patient health status (Lloyd 1979). Reviews have shown that CE can improve knowledge, performance skills, attitudes and behaviour of health professionals, as well as patient healthcare outcomes (Bloom 2005; Cervero 2015; Robertson 2003). Additionally, more specific reviews of the effectiveness of different CE formats have been conducted. Reviews of online CME have shown positive effects on professional practice and satisfaction (Thepwongsa 2014), and reviews of CE meetings, including conferences, workshops and rounds, have shown beneficial effects on both professional practice and patient healthcare outcomes (Forsetlund 2009). In contrast, didactic presentations and distribution of printed information have been shown to provide little or no benefit in changing physician practice (Bloom 2005).

Despite dissemination of evidence-based guidelines and the availability of resources, evidence still suggests suboptimal management of COPD in primary care. Underutilisation of spirometry in COPD diagnosis is a key problem identified in the primary care setting (Abramson 2012; Walters 2011; Zwar 2011), leading to misdiagnosis and underdiagnosis. Lack of spirometry referral for high-risk patients is a major barrier to improved patient outcomes, as it delays treatment of patients with potential COPD and associated symptoms (Drexel 2011). In addition, adherence to recommended management guidelines by health professionals is poor. Approximately one in four adults 40 years of age or older, with known risk factors for COPD, have airway obstruction consistent with COPD diagnosis (Drexel 2011; Zhou 2010). Even though the prevalence of COPD is high in primary care, the condition remains undertreated compared with less morbid and asymptomatic conditions such as hypertension (Barr 2009). Various studies have identified deviations from recommended pharmacological treatment guidelines by primary care professionals (Glaab 2012; Jones 2008; Price 2014). It is also very common for evidence-based non-pharmacological components of guidelines to be omitted from COPD management (Bourbeau 2008; Johnston 2012; Jones 2008; Price 2014).

Although review authors found good evidence showing benefits for patients with COPD of non-pharmacological management components such as pulmonary rehabilitation, smoking cessation support and vaccinations, these components are commonly absent from COPD management. It is important that health professionals are adequately educated on the benefits of these and their routine use in practice. Smoking cessation is integral, regardless of disease severity (GOLD 2017), with quitting smoking shown to slow rate of lung function decline, preserve remaining lung function and delay onset of disability (Anthonisen 1994; Anthonisen 2002; GOLD 2017; Tashkin 1996). Knowing patients' smoking habits and recording smoking status and smoking information are

essential for identifying high-risk patients and providing appropriate smoking cessation support to delay progression of COPD and worsening of symptoms (Jimenez-Ruiz 2015; Vasankari 2011). Influenza vaccination has been shown to reduce risks of exacerbation, hospitalisation and death among patients with COPD (GOLD 2017; Nichol 1994; Poole 2006), and the incidence of community-acquired pneumonia in younger patients with COPD with FEV_1 < 40% predicted or comorbidities was reduced after pneumococcal vaccination (Alfageme 2006; GOLD 2017).

Studies have shown beneficial effects of training and education on health professional knowledge and practices surrounding COPD diagnosis and treatment. A one-hour training session on national COPD guidelines provided to hospital physicians was shown to improve the percentage of individuals correctly given a diagnosis of COPD and ability of physicians to correctly grade COPD severity and correctly prescribe COPD treatment (Cai 2015). A four-day spirometry and COPD interactive training programme with Web assistance provided to community pharmacists was shown to improve identification of high-risk individuals and performance of spirometry to identify airflow obstruction (Castillo 2015). Participation in an educational programme on COPD in Denmark primary care was shown to improve FEV_1 recording in patient files, smoking cessation counselling provision, referral to pulmonary rehabilitation and appropriate prescribing of inhaled corticosteroids (Ulrik 2010). Another study looking at a one-day interactive COPD CME/CE programme for 351 primary care clinicians in the United States showed improvement in clinician self-confidence, knowledge of COPD and implementation of clinical change after completion of the programme (Adams 2012).

Why it is important to do this review

The worsening burden of COPD calls for critical review and assessment of the efficacy of different interventions aimed at case finding and diagnosing COPD, controlling COPD symptoms, preventing exacerbations and maintaining quality of life. Education of health professionals involved in the management of COPD may fill existing practice gaps in COPD recognition and management.

Although numerous original studies and reviews have surrounded the effectiveness of educational interventions targeted at patients, less work has been done in reviewing the evidence behind educational interventions targeted at health professionals involved in the management of COPD. Patients are usually extensively treated in the primary care setting (with general practitioners serving as the main health professionals providing care for most patients with COPD (Koblizek 2016)) before moving into secondary and tertiary care as the condition progresses. However, evidence of suboptimal management in the primary care setting has aroused concern, and awareness and use of evidence-based guidelines are known to be low (Adams 2012). Therefore, it is important that primary care health professionals involved in COPD management are clinically up-to-date and well educated so they can provide high-quality primary care services to affected patients (Fletcher 2007).

We will conduct this review to assess the effectiveness of education provided to doctors, and of educational interventions provided to the wide range of health professionals who play important roles in COPD diagnosis and ongoing management. Different healthcare workers provide different components of care to patients with COPD. The roles of nurses, pharmacists and allied health professionals, such as physiotherapists, are becoming increasingly important with availability of new therapeutic agents and increasing awareness of the benefits of pulmonary rehabilitation programmes. Growing interest in COPD management involving interprofessional collaboration among health professions and multidisciplinary team-based care has led to studies investigating both patient-related outcomes and health professional practices (Chavannes 2009; Kruis 2010; Kruis 2014; Zwar 2012). Improving knowledge and skills related to optimal COPD management amongst all health professionals practising in primary care could further improve guideline adherence, health professional practice and patient-related outcomes.

OBJECTIVES

To review existing evidence for educational interventions delivered to health professionals managing COPD in the primary care setting.

METHODS

Criteria for considering studies for this review

Types of studies

We will include cluster randomised controlled trials (cRCTs) with at least two intervention sites and two comparator sites, and randomised controlled trials (RCTs). We will include studies reported as full text, those published as abstract only and unpublished data (where available).

Types of participants

We will include any health professionals involved in the management of COPD in primary care. We will also include studies with health professionals involved in the management of COPD and other medical conditions, provided outcomes in patients with COPD are reported and analysed separately.

Types of interventions

We will include trials analysing the efficacy of educational interventions for COPD management targeted at health professionals in primary care. Educational interventions are defined as interventions aimed at upskilling, improving or refreshing existing knowledge of health professionals in the management of COPD. We will also include trials providing a health professional-targeted educational intervention within a more complex intervention module, provided a discrete analysis of this component is provided. We will compare interventions against no intervention or against printed management guideline dissemination only.

Types of outcome measures

Primary outcomes

- Proportion of COPD diagnoses confirmed with spirometry
- Proportion of patients with COPD referred to, participating in or having completed pulmonary rehabilitation
- Proportion of patients with COPD prescribed respiratory medication consistent with recommended guidelines

Secondary outcomes

- Proportion of patients with COPD vaccinated against influenza/pneumococcal infection
- Proportion of patients with COPD receiving smoking cessation support
- Health professional knowledge of COPD management
- Health-related quality of life (HRQoL) of patients with COPD, measured on a validated scale
- Frequency of COPD exacerbations (exacerbation defined as requiring emergency department presentation, hospital admission, additional treatment with oral corticosteroids or antibiotics or an unscheduled visit to a healthcare provider)
- Lung function (FEV_1) of patients with COPD
- Patient adherence to medications, including optimal device technique
- Patient satisfaction with care provided by health professional
- Any adverse outcomes (events/effects)

Reporting by trial authors of one or more of the outcomes listed here is not an inclusion criterion for this review.

Search methods for identification of studies

Electronic searches

We will identify trials from the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO, and by handsearching of respiratory journals and conference abstracts. We will search all records in the CAGR using the search strategy presented in Appendix 1. We will search all records in the CAGR using the search strategy provided in Appendix 2.

We will also conduct a search of the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/). We will search all databases from their inception to the present.

Searching other resources

We will check reference lists of included studies and review articles for additional references.

We will search for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and will report within the review the date this was done.

Data collection and analysis

Selection of studies

Two review authors (JL, JG) will independently screen titles and abstracts for inclusion of all potential studies identified through the search and will code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve full-text study reports/publications; two review authors (JL, JG) will independently screen the full texts and identify studies for inclusion, and will record reasons for exclusion of ineligible studies. We will resolve disagreements through discussion, or, if required, we will consult a third review author (MJA). We will identify and exclude duplicates and will collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

We will use a pre-piloted data extraction form to extract study characteristics and outcome data following pilot testing on at least one study in the review. Two review authors (JL, JG) will independently extract the following study characteristics from included studies.

- Trial information: lead and corresponding authors' information, country and date of publication.
- Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and locations, study setting, withdrawals and date of study.
- Participants: numbers enrolled, characteristics of health professional participants (e.g. age, gender, profession, previous experience, number of patients with COPD treated).
- Interventions: description and details of intervention (e.g. type, mode, duration, content, format and delivery of intervention and information about providers).
- Outcomes: primary and secondary outcomes specified and collected and time points reported.
- Notes: funding for trial, reported conflicts of interest of trial authors and additional comments and information.

Two review authors (JL, JG) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a useable way. We will resolve disagreements by reaching consensus or by involving a third review author (MJA). One review author (JL) will transfer data into Review Manager. A second review author (JG) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (JL, JG) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve disagreements by discussion or by consultation with another review author (MJA). We will assess risk of bias according to criteria developed by the Cochrane Effective Practice and Organisation of Care (EPOC) Group (EPOC 2015), including the following.

- Sequence generation.
- Allocation concealment.
- Blinding.
- Baseline characteristics.
- Baseline outcome measurement.
- Incomplete outcome data.
- Selective outcome reporting.
- Protection against contamination.
- Other bias.

We will consider and report when necessary additional biases related to cluster randomised trials.
We will grade each potential source of bias as 'high', 'low' or 'unclear' and will construct a 'Risk of bias' table. We will summarise risk of bias judgements across different studies for each of the domains listed. When information on risk of bias relates to unpublished data or correspondence with a study author, we will note this in the 'Risk of bias' table.
When considering treatment effects, we will take into account the risk of bias for studies that contributed to that outcome.

Assesment of bias in conducting the systematic review

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

Measures of treatment effect

We will analyse dichotomous data as odds ratios and continuous data as mean differences or standardised mean differences (when continuous outcomes are measured on different scales). We will enter data presented as a scale with a consistent direction of effect. We will undertake meta-analyses only when this is meaningful (i.e. if treatments, participants and underlying clinical questions are similar enough for pooling to make sense). Two or more studies must report a similar outcome measure with appropriate extractable data for a meta-analysis to be undertaken. We will include in this meta-analysis studies assessed to have low risk of bias. We will narratively describe skewed data reported as medians and interquartile ranges.
When multiple trial arms are reported in a single trial, we will include only the relevant arms.

Unit of analysis issues

When cluster randomised trials are included, we will consider whether any unit of analysis errors were made. We will extract a direct estimate of the required effect measure from an analysis that properly accounts for the cluster design (Higgins 2011). In the case of trials with multiple arms, we will include in the review only arms that meet the eligibility criteria. If a study includes more than one eligible intervention arm, we will combine all relevant experimental groups to create a single pair-wise comparison, to avoid the problem of including the same group of participants twice in the same meta-analysis. If multiple intervention arms are eligible and are not comparable, we will include each pair-wise comparison separately, but with shared intervention arms divided out approximately evenly among comparisons.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study is identified from an abstract only). When this is not possible, and when missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by performing a sensitivity analysis.

Assessment of heterogeneity

We will visually inspect forest plots and will use corresponding χ^2 and I^2 statistics to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity, we will report this and will explore possible causes by conducting subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study and publication biases.

Data synthesis

We will use a random-effects model and will perform a sensitivity analysis using a fixed-effect model.

'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes: change in proportion of COPD diagnoses confirmed by spirometry, change in proportion of patients with COPD referred to/participating in/having completed pulmonary rehabilitation, change in proportion of patients with COPD prescribed respiratory medication consistent with recommended guidelines, change in proportion of patients with COPD vaccinated against influenza/pneumococcal infection, change in HRQoL, change in frequency of COPD exacerbations, and change in patient satisfaction with health professional care. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to studies that contributed data to meta-analyses for prespecified outcomes. We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and will use GRADEpro software. We will justify all decisions to downgrade or upgrade the quality of studies by using footnotes, and we will make comments to aid readers' understanding of the review when necessary.

Subgroup analysis and investigation of heterogeneity

We will categorise trials according to the nature of interventions. We may consider the following subgroup analyses based on the nature of identified studies.

- Types of healthcare providers (e.g. doctors, nurses, physiotherapists, pharmacists, other health professionals identified through the search).
- Types of education delivered.
- Mode/application forms of education.
- Complexity of intervention (e.g. minimal (fewer than three components) and intensive (three or more components)).

We will use the formal test for subgroup interactions provided in Review Manager (Review Manager (RevMan)).

Sensitivity analysis

We will conduct sensitivity analyses to investigate robustness of effect sizes found in this review under different assumptions. We will consider whether results are sensitive to exclusion of trials judged to have high risk of bias.

ACKNOWLEDGEMENTS

The Methods section of this protocol is based on a template used by the Cochrane Airways Group.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Airways. The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

Julia Walters was the Editor for this review and commented critically on the review.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly

(*Continued*)

AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society (BTS) Winter Meeting	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

Appendix 2. Search strategy to identify relevant trials from the CAGR

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
#2 MeSH DESCRIPTOR Bronchitis, Chronic
#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
#4 COPD:MISC1
#5 (COPD OR COAD OR COBD OR AECOPD):TI,AB,KW
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 MeSH DESCRIPTOR Physicians, Primary Care WITH ED
#8 MeSH DESCRIPTOR Physicians, Family WITH ED
#9 MeSH DESCRIPTOR Nursing Staff Explode All WITH ED
#10 MeSH DESCRIPTOR Health Personnel Explode All WITH ED
#11 MeSH DESCRIPTOR Family Practice WITH ED
#12 MeSH DESCRIPTOR Family Practice WITH ST
#13 MeSH DESCRIPTOR Delivery of Health Care Explode All WITH ST
#14 MeSH DESCRIPTOR Education, Medical Explode All
#15 MeSH DESCRIPTOR Evidence-Based Medicine Explode All WITH ED
#16 MeSH DESCRIPTOR Education, Professional Explode All
#17 MeSH DESCRIPTOR Peer Review, Health Care
#18 MeSH DESCRIPTOR Quality Assurance, Health Care Explode All
#19 MeSH DESCRIPTOR Educational Measurement
#20 MeSH DESCRIPTOR Information Dissemination

#21 MeSH DESCRIPTOR Quality Improvement
#22 MeSH DESCRIPTOR Mentors
#23 MeSH DESCRIPTOR Translational Medical Research
#24 MeSH DESCRIPTOR Clinical Protocols
#25 MeSH DESCRIPTOR Practice Guideline
#26 MeSH DESCRIPTOR Health Knowledge, Attitudes, Practice
#27 MeSH DESCRIPTOR Inservice Training Explode All
#28 MeSH DESCRIPTOR Computer-Assisted Instruction
#29 MeSH DESCRIPTOR Professional Practice Explode All
#30 MeSH DESCRIPTOR Guideline Adherence
#31 MeSH DESCRIPTOR Quality Indicators, Health Care Explode All
#32 MeSH DESCRIPTOR Clinical Competence
#33 #7 or #8 or #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 or #26 or #27 or #28 or #29 or #30 or #31 or #32
#34 MeSH DESCRIPTOR Health Personnel Explode All
#35 nurs*
#36 doctor*
#37 physician*
#38 General NEXT Practitioner* or GP:ti,ab
#39 family NEXT practitioner*
#40 physician*
#41 pharmacist*
#42 physiotherapist*
#43 physical* NEXT therapist*
#44 (health* OR medical*) NEAR3 (profession* OR staff* or work* or personnel*)
#45 clinician*
#46 #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45
#47 MeSH DESCRIPTOR Education Explode All
#48 MeSH DESCRIPTOR Teaching Explode All
#49 educat* or train* or instruct* or teach*
#50 professional* NEXT development*
#51 CPD:ti,ab
#52 CME:ti,ab
#53 mentor*
#54 "best practice"
#55 "peer review"
#56 "quality assurance"
#57 guideline*
#58 #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57
#59 #46 and #58
#60 #6 and (#33 OR #59)

CONTRIBUTIONS OF AUTHORS

JL wrote the first and subsequent drafts of the protocol. All review authors contributed to the design of the protocol and provided comments on protocol drafts.

JL, JG and MJA will be involved in screening of eligible studies and data extraction. JL will perform data entry. JL will write the first and subsequent drafts of the full review. All review authors will provide comments on review drafts.

DECLARATIONS OF INTEREST

Dr Johnson George and Prof Michael J Abramson are chief investigators on a National Health and Medical Research Council (NHMRC) Partnership Project titled 'RADICALS'. Jenifer Liang is a PhD scholar working within the RADICALS research project. The RADICALS study receives in-kind support from its partnership organisations: Lung Foundation Australia (LFA), Boehringer Ingelheim Pty Ltd (BI) and Eastern Melbourne Primary Health Network (EMPHN). These organisations have no involvement in the proposed review, nor have they influenced our decision to undertake this systematic review. Dr George and Prof Abramson have held investigator-initiated research grants from Pfizer and BI for unrelated research. Prof Abramson undertook an unrelated consultancy for AstraZeneca. He has received support for conference attendance from BI and Sanofi. Dr George has received in-kind support from Vitalograph®, the manufacturers of COPD-6™, for unrelated research.

SOURCES OF SUPPORT

Internal sources

- Victorian College of Pharmacy Foundation Board, Australia.

Miss Liang is the recipient of the Cyril Tonkin Scholarship administered in 2014 by the Victorian College of Pharmacy Foundation Board at Monash University (Parkville campus), Australia.

External sources

- No sources of support supplied