British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2017) **83** 942–952 942

SYSTEMATIC REVIEW

A systematic review of the outcomes reported in trials of medication review in older patients: the need for a core outcome set

Correspondence Jean-Baptiste Beuscart, Institut de Recherche LDRI – CLIP, Université catholique de Louvain; Avenue E. Mounier 72 bte B1.72.02; 1200 Woluwe-Saint-Lambert, Belgium. Tel.: +32 2062 3494; Fax: +32 2062 6881; E-mail: jean-baptiste.beuscart@univ-lille2.fr

Received 21 September 2016; **Revised** 22 November 2016; **Accepted** 22 November 2016

Jean-Baptiste Beuscart[1], Lisa G. Pont[2], Stefanie Thevelin[1], Benoit Boland[3,4], Olivia Dalleur[1,5], Anne W. S. Rutjes[6,7], Johanna I. Westbrook[2] and Anne Spinewine[1,8]

[1]Louvain Drug Research Institute (LDRI), Université catholique de Louvain, Brussels, Belgium, [2]Centre for Health Systems and Safety Research, Australian Institute of Health Innovation, Macquarie University, North Ryde, Australia, [3]Geriatric Medicine, Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium, [4]Institute of Health and Society, Université catholique de Louvain, Brussels, Belgium, [5]Pharmacy department, Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium, [6]CTU Bern, Department of Clinical Research, University of Bern, Switzerland, [7]Institute of Social and Preventive Medicine (ISPM), University of Bern, Switzerland, and [8]Pharmacy department, CHU UCL Namur, Université catholique de Louvain, Yvoir, Belgium

Keywords elderly, medication review, outcomes assessment, randomized controlled trials, systematic review

AIM

Medication review has been advocated as one of the measures to tackle the challenge of polypharmacy in older patients, yet there is no consensus on how best to evaluate its efficacy. This study aimed to assess outcome reporting in trials of medication review in older patients.

METHODS

Randomized controlled trials (RCTs), prospective studies and RCT protocols involving medication review performed in patients aged 65 years or older in any setting of care were identified from: (1) a recent systematic review; (2) RCT registries of ongoing studies; (3) the Cochrane library. The type, definition, and frequency of all outcomes reported were extracted independently by two researchers.

RESULTS

Forty-seven RCTs or prospective published studies and 32 RCT protocols were identified. A total of 327 distinct outcomes were identified in the 47 published studies. Only one fifth (21%) of the studies evaluated the impact of medication reviews on adverse events such as drug reactions or drug-related hospital admissions. Most of the outcomes were related to medication use (n = 114, 35%) and healthcare use (n = 74, 23%). Very few outcomes were patient-related (n = 24, 7%). A total of 248 distinct outcomes were identified in the 32 RCT protocols. Overall, the number of outcomes and the number and type of health domains covered by the outcomes varied largely.

CONCLUSION

Outcome reporting from RCTs concerning medication review in older patients is heterogeneous. This review highlights the need for a standardized core outcome set for medication review in older patients, to improve outcome reporting and evidence synthesis.

DOI:10.1111/bcp.13197

Introduction

Older patients are often exposed to polypharmacy [1, 2]. This increases the risk of adverse drug reactions (ADR) and the cost of medications [3–6]. Performing a medication review has been shown to be an efficient approach to optimize the quality of prescriptions in older patients [7, 8]. Medication review has been defined by the NICE guidelines as "a structured, critical examination of patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimising the number of medication related problems and reducing waste" [9].

Numerous randomized controlled trials (RCT) have been performed to evaluate the impact of medication review on clinical, patient-reported and economic outcomes. Several systematic reviews and meta-analyses have therefore been conducted to summarize the effectiveness of medication review in various settings [7, 8, 10–20]. However, the heterogeneity of outcomes reported in the RCTs has limited the quality of the conclusions of these systematic reviews. Robust meta-analyses could be performed for only a few outcomes, including hospitalization and death [15–17, 21]. For other outcomes, results were essentially summarized in a descriptive way because of heterogeneity in the choice and definition of the outcomes [17–20, 22].

Outcome reporting bias is an under-recognized problem that affects the conclusions in a substantial proportion of systematic and Cochrane reviews [23–25]. This bias has been defined as selection (on the basis of the results) of a subset of the original variables recorded for inclusion in a study publication [26]. In a large unselected cohort of Cochrane systematic reviews, more than half of the reviews did not include full data for the review primary outcome of interest from all eligible trials [23]. Consequently, the updated CONSORT (Consolidated Standards of Reporting Trials) statement has recently recommended the use of identified and well defined outcomes in RCTs. In other fields of medicine, authors have conducted systematic reviews to reveal and quantify the heterogeneity and inconsistency of outcome reporting in a given research area [27–30]. According to the OMERACT (Outcome Measures in Rheumatology) and the COMET (Core Outcome Measures in Effectiveness Trials) guidelines, some of these works have led to the development of core outcomes sets designed to increase the quality of outcome reporting and evidence synthesis in future research [31, 32].

The purpose of this review was to undertake an in-depth analysis of outcome reporting to identify potential heterogeneity in outcomes reported from RCTs and prospective studies of medication review in older patients.

Methods

Study selection

We considered RCT, quasi-RCT, and other prospective interventional studies that investigated the effect of medication review performed in patients aged 65 years or older [33]. This age limit was widely used in trials of medication review during recent decades and corresponds to the WHO age limit to define older people. The following studies were excluded: studies published before 2000; studies predominantly including patients younger than 65 years; retrospective studies; no outcome reported; sample size lower than 50 participants; medication reviews for a specific disease or condition (e.g. chronic heart failure) or as part of a multifaceted approach. By multifaceted approach we meant a complex intervention that contained additional interventions to the medication review (e.g. physiotherapy, nutritional advice, occupational therapy).

Search strategy

We performed a systematic review of published studies. Our starting point was the systematic review published in 2014 by Lehnbom *et al*. [10], the purpose of which was to examine the evidence regarding the effectiveness of medication review to improve clinical outcomes. Lehnbom *et al*. [10] identified 43 studies published before March 2014. As the purpose of the present systematic review was different in nature, we only used the result of the search strategy, i.e. the list of the published studies included in the systematic review. Only the studies complying with our inclusion and exclusion criteria were included. In addition, an update of the literature search using the same strategy/queries was performed for the period of March 2014 and July 2015 (the search strategy from [10] is given in supplementary data). Two reviewers (L.P. and J.B.B.) independently assessed the title and abstracts of studies resulting from the searches. Full texts were investigated for all eligible published studies by two independent reviewers (L.P. and J.B.B.). Any disagreement on the inclusion of a study was resolved by discussion and consensus. A third reviewer (A.S.) was involved if needed.

In addition, we used the search terms from the systematic review to identify RCTs protocols related to medication review on the following RCT websites: WHO international clinical trials registry platform (http://apps.who.int/trialsearch/); EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/ctr-search/search); US Clinical Trials register (https://clinicaltrials.gov). Two independent reviewers (B.B. and J.B.B.) first assessed the titles and subsequently the summaries of the RCTs protocols identified by the queries. Any disagreement on the inclusion of a study was resolved by discussion and consensus. A third reviewer (A.S.) was involved if needed. If protocols had matured to full report publications, the paper was evaluated as mentioned above and added to the set of published studies.

Finally, the search terms from the systematic review were also used to identify relevant Cochrane reviews. A reviewer (J.B.B.) identified the relevant Cochrane systematic reviews and then extracted the eligible original studies in the selected Cochrane systematic reviews. The selection process was checked by a second reviewer (A.S.).

Data extraction

An electronic data extraction form was developed with Epidata software and pilot tested to increase the reliability of the data extractions. All data extractions on outcomes and outcome measurement instruments were performed by two independent reviewers (S.T. and J.B.B. for RCT protocols; L.P. and J.B.B. for published studies). Any disagreement was resolved by discussion and consensus. A third reviewer (A.S.) was involved if needed.

The characteristics of the RCT protocols and the published studies were extracted by one reviewer (J.B.B.) and included: setting (hospital setting, primary care, nursing home); number of patients intended to be recruited (RCT protocols) or actually included (published studies); mean age (published studies only).

Outcomes used to compare the two groups under investigation (in RCTs and prospective before/after studies) or to evaluate the medication review process were extracted: name of the outcome in free text (what was measured in published studies and what was planned to be measured in protocols); primary or secondary outcome. For each outcome, the following data about measurement instrument were extracted from published studies: which instrument was used to measure the outcome (free text); was the method of measurement clearly defined (the reviewer answered "Yes" if they believed that another researcher could reproduce the procedure and its measurement with the explanations provided in the methods section). As the data provided in RCT protocols are often less detailed than in published studies, the data on measurement instrument were extracted when available.

Classification of outcomes into heath domains and subdomains

The classification of the outcomes extracted from the included studies was achieved in several steps. Firstly, 19 predefined subdomains corresponding to the most frequently reported outcomes (e.g. hospitalization, all-cause death) were identified from the systematic review updated in this study [10]. These predefined subdomains were used by the two reviewers to associate each extracted outcome to a subdomain. The reviewers were free to propose a new subdomain if an outcome did not fit with the proposed subdomains. Secondly, a new list of subdomains was drafted on the basis of the predefined and the newly proposed subdomains. A consultation exercise was then performed with experts in clinical pharmacy and geriatricians. The objective was to get consensus on subdomain terms, to avoid major overlaps between subdomains, and to aggregate subdomains into health domains. The OMERACT filter 2.0 was used to organize this classification. A total of 57 subdomains were identified and grouped into eight health domains (Table S1).

Analysis

Quantitative variables were described by median, first and third quartiles, and minimum and maximum because of skewed distributions. Qualitative variables were expressed as frequencies and percentages.

Results

Selection of studies and RCT protocols

In total, 47 published studies [34–80] and 32 RCT protocols were included in this systematic review. Details on the sources, reasons for exclusion, and selection process are presented in Figure 1.

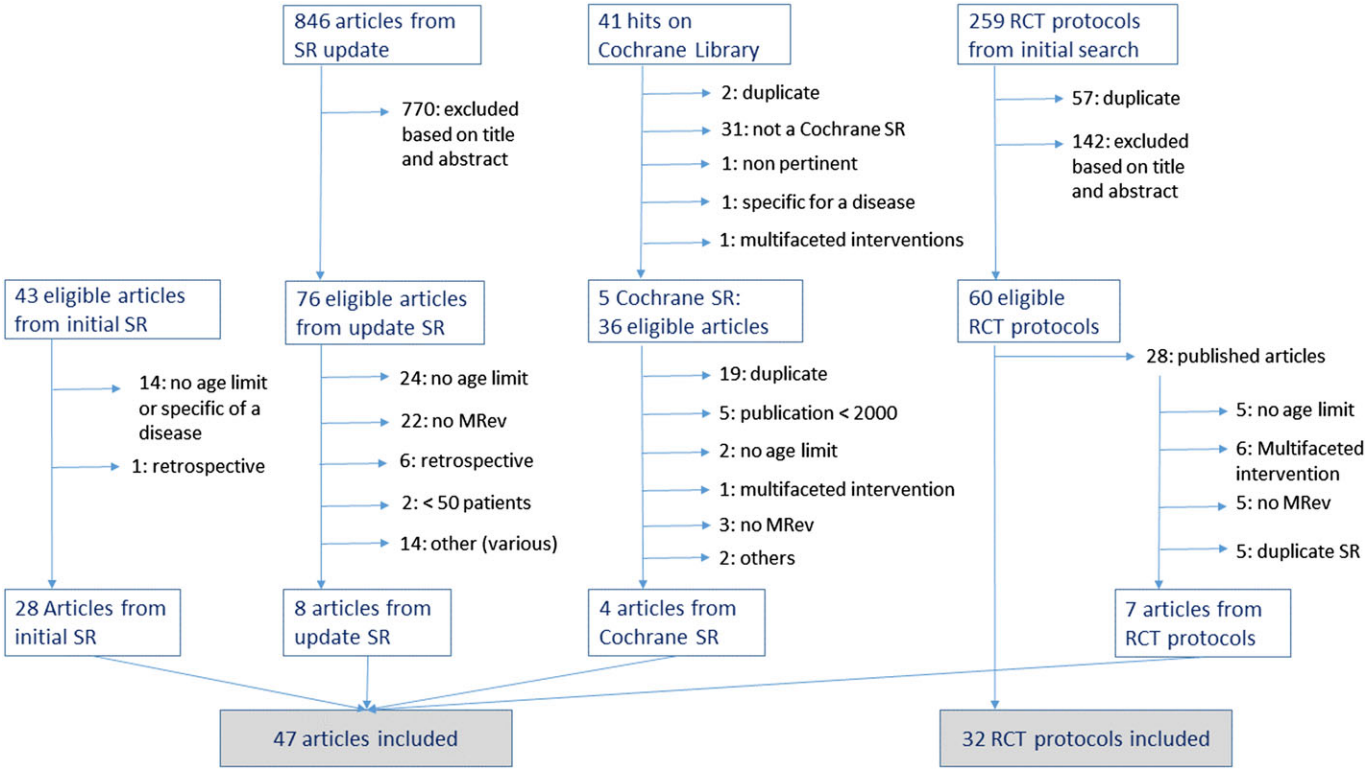

Figure 1

Flowchart of included studies and RCT protocols. RCT, randomized controlled trials; MRev, medication review; SR, systematic review

Characteristics of the studies and RCT protocols included for data abstraction

The characteristics of the published studies and the RCT protocols included for data abstraction are provided in Table 1. The median number of participants included in published studies and intended to be included in RCTs described in protocols were similar. The studies were performed mainly in Europe, followed by Australia and USA. More recent RCT protocols have mainly been developed in European countries. The median number of outcomes per study or per RCT protocol was seven. This number varied from a single outcome in a published study [69] to 19 distinct outcomes in an RCT protocol [81].

Outcomes identified in the published studies and RCT protocols

The published studies and RCT protocols covered a median of four of the eight health domains identified (range: 1–6 for published studies; 2–7 for RCT protocols). The results are summarized in Figure 2 and detailed per subdomains in Table S2. More than 50% of all outcomes reported in published studies concerned medication use (e.g. the number of drugs, the number of potentially inappropriate medications, or overuse) or healthcare use (e.g. hospitalizations or GP visits). Other health domains such as patient-reported outcomes, geriatric syndromes or costs evaluation were far less frequently investigated. Only one fifth (21%) of the 47 published studies have evaluated the impact of medication reviews on adverse events such as ADR or drug-related hospital admissions. Consequently, only four published studies (9%) had a primary outcome in the adverse event domain.

Outcomes related to medication use were reported by 89% of published studies and 94% of RCT protocols, suggesting an informal consensus on reporting this health domain. However, there was substantial variation in the subdomains used to explore this health domain between studies. Twelve

Table 1

Summary characteristics and demographics of included studies (published studies included 35 randomized controlled trials [RCTs] and 12 prospective studies)

	Published studies (*n* = 47)	**RCT protocols** (*n* = 32)
Number of study participants		
Median	334	300
Interquartile range	[170; 568]	[195; 600]
Range	[50; 7202]	[50; 3685]
Average age		
Median	80	
Interquartile range	[75.7; 82.7]	
Range	[73.5; 86.8]	
Setting		
Hospital	15 (32%)	11 (34%)
Community	19 (40%)	16 (50%)
Nursing homes	13 (28%)	5 (16%)
Country		
EU	28(Belgium 2; Denmark 3; Germany 1; Ireland 3; The Netherlands 1; Spain 2; Sweden 5; UK 11)	25(Belgium 2; France 1; Germany 7; Ireland 2; Italy 1; Netherlands 6; Norway 1; Slovenia 1; Spain 1; Sweden 1; Europe MC 1)
Australia	8	3
USA	7	1
Others	4	3
Year of publication		
2000–2005	14 (30%)	
2006–2010	6 (13%)	
2011–2015	27 (57%)	
Number of outcomes		
Median	7	7
Interquartile range	[5; 10]	[6; 9]
Range	[1; 14]	[2; 19]

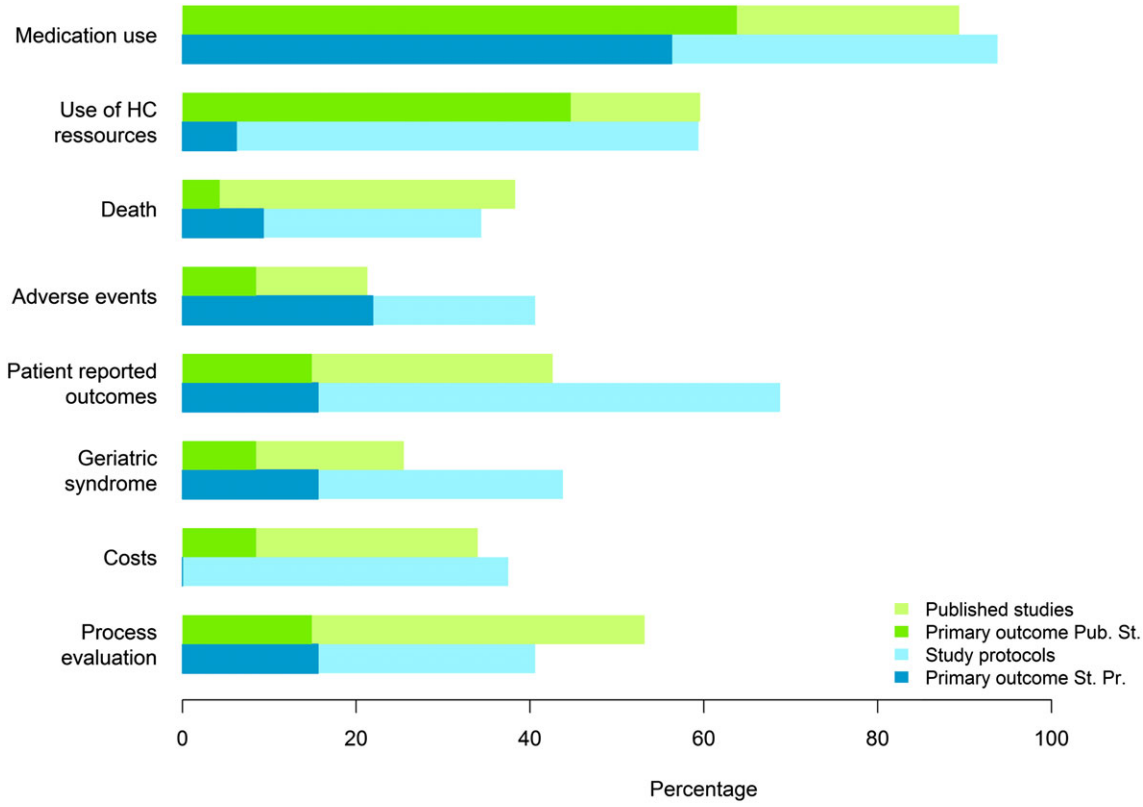

Figure 2

Percentage of health domains covered by the 47 published studies and 32 randomized controlled trial protocols included in the systematic review, according to the outcomes identified. The percentage of studies in which the domain was covered by a primary outcome is given in darker colour. HC, healthcare; Pub. St., published studies; St. Pr., study protocols. For the full list of subdomains contained in each domain, please refer to Table S1

different subdomains were identified and variously measured in the studies. The number of studies using each subdomains varied from only one time ("anticholinergic drug use" in one RCT protocols) to 26 times ("number of drugs" in 17 published studies and nine RCT protocols). Eight of these 12 subdomains were used at least once as a primary outcome in a published study or in an RCT protocol.

This between-subdomain heterogeneity was also observed for the seven other health domains, as detailed in Table S2. For example, seven, 10, and 12 different subdomains were variously used to explore the healthcare use, patient-reported outcome and geriatric syndromes domains, respectively. In total, nearly half of the subdomains (n = 28; 49%) were used by <10% of the 79 selected studies (published studies and RCT protocols). Conversely, only four subdomains were used by a third or more of the 79 selected studies, namely "number of drugs", "hospitalization", "all-cause death", and "health-related quality of life".

Clarity of measurement instrument reported

The total number of outcomes and the specific number of outcomes for which an instrument measurement was clearly described in the methods are presented per health domain in Table 2 and per subdomain in supplementary data (Table S3). In total, the measurement instruments were considered clearly reported in 52–83% of all domains, except for cost outcomes. In the costs domain, the methods most often insufficiently described the source of drug costs or costs related to healthcare use, or the way in which calculations were performed. For medication use, the methods were considered clear in two thirds (65%) of the outcomes. The outcomes most often considered poorly defined were the outcomes "number of drugs" and "drug–drug interactions".

Discussion

This systematic review provides an analysis on which health domains have been and are currently evaluated in published and planned/ongoing studies (RCT protocols) of medication review in older patients. It reveals that there is substantial heterogeneity, as the number of outcomes and the number and type of health domains covered by the outcomes vary from one study to another. Furthermore, it shows that some essential health domains including adverse events and patient-related outcomes have been poorly evaluated in published studies. These results highlight the need for developing a core outcome set for medication review in older patients. Having strong outcome data would help clarifying if and how medication review can be effective, among which population, in which context, and what are the important contextual factors that support positive outcomes.

Table 2

Number of outcomes per health domain with the clarity of the measurement instrument used to measure them, as identified in the published studies or in RCT protocols

	Outcomes				Measurement reproducible[c]			
	Publishedstudies(317 outcomes)		RCTprotocols(240 outcomes)		Published studies		RCT protocols	
	n	%[a]	*n*	%[a]	*n*	%[b]	*n*	%[b]
Medication use	99	31%	51	21%	64	65%	22	43%
Use of HC resources	70	22%	44	18%	43	61%	6	14%
Adverse events	11	3%	17	7%	8	73%	10	59%
Death	18	6%	11	5%	13	72%	2	18%
Patient reported outcomes	32	10%	38	16%	20	63%	31	82%
Geriatric syndrome	24	8%	42	18%	20	83%	29	69%
Costs	21	7%	16	7%	7	33%	4	25%
Process evaluation	42	13%	21	9%	22	52%	3	14%

HC, healthcare

[a] Based on the total number of identified outcomes (*n* = 317 for published studies; *n* = 240 for RCT protocols)

[b] Based on the total number of outcomes identified in the given domain (value is *n* of the column Outcomes

[c]The method of measurement was considered clearly defined if the reviewer believed that another author could reproduce the procedure and its measurement with the explanations given in the method section

Not surprisingly, our results have shown that most studies of medication review in older patients have reported, or planned to report, outcomes related to the medication use domain. These outcomes were often the primary outcomes. However, the 13 distinct subdomains identified in the medication use domain were variously used by authors (Table S2). Despite this heterogeneity between subdomains, several systematic reviews of RCTs have tried to summarize the effect of medication review on such outcomes. Their results showed that medication review is effective in improving drug appropriateness, drug underuse, or potentially inappropriate prescribing, but there were more conflicting results for drug-related problems [7, 8, 18, 20]. Evaluating the effects of medication review on more specific outcomes such as inappropriate use of antipsychotic drugs was limited due to inconsistency in the various definitions of the outcome used across the studies [22]. We identified that clarity in the reporting of the measurement instruments in some domains varied substantially and this impacts upon the extent to which the outcomes from such studies can be accurately interpreted, and may limit the validity of comparison of results across studies.

Our results also show that many published studies have reported outcomes related to the use of healthcare resources domain, mainly hospitalizations. Meta-analyses, however, have failed to identify a significant effect of medication review on hospital admissions, length of hospital stays, or emergency department visits [12, 15–17, 21, 82]. These negative results may have discouraged new studies to use this outcome as a primary outcome. One hypothesis is that these outcomes are influenced by many other factors, which could explain why this outcome is less often used as primary outcome in RCT protocols.

Ten (21%) published studies reported outcomes related to the adverse events domain. This may be due to the difficulty in detecting and adjudicating adverse events prospectively during an RCT. Hence, the effects of medication review on ADR or drug-related hospital admissions remain unclear and have not been assessed by any meta-analysis. Reporting bias of harm outcomes in RCTs and systematic reviews has been identified as an important problem [83]. It seems particularly detrimental that harm outcomes have been so poorly reported in RCTs of medication review, as the purpose of this intervention is actually to manage the risk of prescribed drugs and to reduce the number of drug-related problems. A higher proportion of ongoing studies planned to report adverse events according to their protocols. However, it is uncertain whether this greater focus on these outcomes in protocols will be released in the final studies' results. Outcomes related to costs were also less extensively investigated. The effect of medication review on costs is therefore most often analysed through a narrative approach in systematic reviews [13, 20].

Patient-reported outcomes have been investigated in 43% of published studies and are planned to be investigated in 69% of RCT protocols. Most of these outcomes concern health-related quality of life (Table S2). Very few studies have investigated or will investigate subdomains like drug-regimen complexity or the alignment of drug regimen with patient preference, although these aspects are included in the definition of a medication review [9].

Several systematic reviews of medication review identified that inconsistency and imprecision in outcome reporting limited their analyses and conclusions [13, 14, 17, 18, 20, 22]. Our present review has confirmed and extended these findings. While other systematic reviews aimed at pooling and summarizing results on a limited number of outcomes, we have extracted and reported all kinds of outcomes used in this field. Several authors have used hospitalization or mortality toassess the clinical effectiveness of a medication

review [12,15, 16, 21]. However, our results suggest that the choice to perform meta-analyses on these outcomes are probably related to the high proportion of studies reporting these outcomes as opposed to their relevance. In fact, hospitalization or death in older patients with polypharmacy and multimorbidity can be related to many factors other than medications [84, 85]. Incidence of ADR or drug-related hospital admissions may be more relevant to assess the effectiveness of a medication review, but it is indeed much more difficult and time-consuming to detect and adjudicate properly all ADEs or drug-related hospital admissions during an RCT than to record all-causes hospitalizations or mortality.

In summary, our results highlight the need for a core outcome set (COS) for future studies of medication review in older patients. A COS is an agreed standardized collection of outcome variables that should be measured and reported in all trials for a specific condition or clinical area. The development of a COS would tackle the challenge of obtaining a consensus on which outcomes are deemed essential for all stakeholders involved in the management of a given condition, including patients. It has the potential to reduce heterogeneity between trials, lead to research that is more likely to measure relevant outcomes, and enhance the value of evidence synthesis by reducing the risk of outcome reporting bias and ensure that all trials report usable information [86–88]. Moreover, in a second step, the measurement instrument recommended to be used to evaluate each outcome included in the COS can be determined [89]. This aspect may be important as our study has shown that the methods were not clearly detailed in a significant proportion of studies for all categories of domains and subdomains. A consensus on the measurement instrument has also the potential to increase the quality of value of evidence from subsequent systematic reviews and allowing meaningful meta-analyses to be performed. As part of the European Commission-funded OPERAM project, this systematic review will serve as a starting point to developing a COS for clinical trials of medication review in older patients. The OPERAM project will perform a multicentre randomized controlled trial to assess the impact of an intervention to optimize pharmacotherapy and to enhance compliance in 1900 multimorbid patients aged 70 years and older. In order to tackle the challenge of measuring relevant outcomes for these patients, the OPERAM project included the development a COS suitable for all settings.

Some limitations of this review should be mentioned. As the aim of this project was of descriptive nature, we did not perform analytical analyses to formally compare results from published studies and protocol, and had too few studies to evaluate if the between-study variation could be partially explained by the setting (hospitalized *vs*. nursery home *vs*. community dwelling). This systematic review stopped in July 2015, more than one year before its submission. However, the variation in outcome reporting between published studies should not have changed considerably and has been captured indirectly through the analysis of RCT protocols. It seems therefore unlikely that an updated version would have impacted on the results. The selection criteria were those from the initial systematic review by Lehnbom *et al*. [10], which could have influenced the outcomes identified. For example, smaller studies with fewer than 50 subjects, which were excluded from the review, may have reported outcomes that require detailed review of patients or records, such as ADRs or drug-related admissions, more often. Variation between studies was investigated descriptively at the subdomain level but we did not report variation between outcomes in a given subdomain. The outcomes may vary in a subdomain in the way they were reported (e.g. number of potentially inappropriate medications per patient or number of patients with at least one potentially inappropriate medication) or in the way they were measured (e.g. Beers criteria, STOPP criteria, PRISCUS list). Another limitation is that the categorization into domains and subdomains may be somehow arbitrary. We were also reliant upon the descriptions of domains and measures in the published studies and, as we identified, at times these were not clearly described. We used a consultation exercise as other studies or study protocols have [30, 90], as we could not identify an existing framework to guide this process.

Conclusion

This systematic review revealed a significant heterogeneity in outcome reporting in studies of medication review in older patients. Some essential health areas including adverse events and patient reported outcomes have been insufficiently evaluated. We advocate the development of a COS to improve the quality of outcome reporting and evidence synthesis in future research in this important field.

Competing Interests

All authors have completed the Unified Competing Interest form and declare no support from any organization for the submitted work.

This work is part of the project "OPERAM: OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly" supported by the European Union's Horizon 2020 research and innovation programme under the grant agreement No 6 342 388, and by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 15.0137. The opinions expressed and arguments employed herein are those of the authors and do not necessarily reflect the official views of the EC and the Swiss government.

We would like to thank for her invaluable assistance Dr. Elin Lehnbom who participated to the initial workgroup of the study.

Contributors

J.B.B. conceptualized and designed the study, performed the selection of studies and data extraction, carried out analyses and interpretation of data, drafted the initial manuscript, and approved the final manuscript as submitted. L.G.P. designed the study, performed the selection of studies and data extraction, critically reviewed the manuscript and approved the final manuscript as submitted. S.T. performed data

extraction, critically reviewed the manuscript and approved the final manuscript as submitted. B.B. performed the selection of studies, critically reviewed the manuscript and approved the final manuscript as submitted. O.D. participated in study design and critically reviewed the manuscript and approved the final manuscript as submitted. A.R. participated in study design and critically reviewed the manuscript and approved the final manuscript as submitted. J.W. designed the study, critically reviewed the manuscript and approved the final manuscript as submitted. A.S. conceptualized and designed the study, checked the selection of studies and data extraction, carried out interpretation of data, drafted the initial manuscript, and approved the final manuscript as submitted.

References

1 Payne RA, Avery AJ, Duerden M, Saunders CL, Simpson CR, Abel GA. Prevalence of polypharmacy in a Scottish primary care population. Eur J Clin Pharmacol 2014; 70: 575–81.

2 Hovstadius B, Hovstadius K, Astrand B, Petersson G. Increasing polypharmacy - an individual-based study of the Swedish population 2005-2008. BMC Clin Pharmacol 2010; 10: 16.

3 Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, *et al*. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004; 329: 15–9.

4 Ma J, Wang Y, Gao M, Meng Q, Liu J. Adverse drug reactions as the cause of emergency department admission of patients aged 80 years and older. Eur J Intern Med 2012; 23: e162–e163.

5 Conforti A, Costantini D, Zanetti F, Moretti U, Grezzana M, Leone R. Adverse drug reactions in older patients: an Italian observational prospective hospital study. Drug Healthc Patient Saf 2012; 4: 75–80.

6 Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. Ann Pharmacother 2008; 42: 1017–25.

7 Patterson SM, Cadogan CA, Kerse N, Cardwell CR, Bradley MC, Ryan C, *et al*. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev 2014; (10): CD008165.

8 Meid AD, Lampert A, Burnett A, Seidling HM, Haefeli WE. The impact of pharmaceutical care interventions for medication underuse in older people: a systematic review and meta-analysis. Br J Clin Pharmacol 2015; 80: 768–76.

9 Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes | Guidance and guidelines | NICE. Available at https: //www.nice.org.uk/guidance/ng5 (last accessed 31 May 2016).

10 Lehnbom EC, Stewart MJ, Manias E, Westbrook JI. Impact of medication reconciliation and review on clinical outcomes. Ann Pharmacother 2014; 48: 1298–312.

11 Hatah E, Braund R, Tordoff J, Duffull SB. A systematic review and meta-analysis of pharmacist-led fee-for-services medication review. Br J Clin Pharmacol 2014; 77: 102–15.

12 Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. Cochrane Database Syst Rev 2016; 2: CD008986.

13 Graabæk T, Kjeldsen LJ. Medication reviews by clinical pharmacists at hospitals lead to improved patient outcomes: a systematic review. Basic Clin Pharmacol Toxicol 2013; 112: 359–73.

14 Forsetlund L, Eike MC, Gjerberg E, Vist GE. Effect of interventions to reduce potentially inappropriate use of drugs in nursing homes: a systematic review of randomised controlled trials. BMC Geriatr 2011; 11: 16.

15 Wallerstedt SM, Kindblom JM, Nylén K, Samuelsson O, Strandell A. Medication reviews for nursing home residents to reduce mortality and hospitalization: systematic review and meta-analysis. Br J Clin Pharmacol 2014; 78: 488–97.

16 Thomas R, Huntley AL, Mann M, Huws D, Elwyn G, Paranjothy S, *et al*. Pharmacist-led interventions to reduce unplanned admissions for older people: a systematic review and meta-analysis of randomised controlled trials. Age Ageing 2014; 43: 174–87.

17 Holland R, Desborough J, Goodyer L, Hall S, Wright D, Loke YK. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. Br J Clin Pharmacol 2008; 65: 303–16.

18 Alldred DP, Kennedy MC, Hughes C, Chen TF, Miller P. Interventions to optimise prescribing for older people in care homes. Cochrane Database Syst Rev 2016; 2: CD009095.

19 Geurts MME, Talsma J, Brouwers JRBJ, de Gier JJ. Medication review and reconciliation with cooperation between pharmacist and general practitioner and the benefit for the patient: a systematic review. Br J Clin Pharmacol 2012; 74: 16–33.

20 Viswanathan M, Kahwati LC, Golin CE, Blalock SJ, Coker-Schwimmer E, Posey R, *et al*. Medication therapy management interventions in outpatient settings: a systematic review and meta-analysis. JAMA Intern Med 2015; 175: 76–87.

21 Hohl CM, Wickham ME, Sobolev B, Perry JJ, Sivilotti MLA, Garrison S, *et al*. The effect of early in-hospital medication review on health outcomes: a systematic review. Br J Clin Pharmacol 2015; 80: 51–61.

22 Thompson Coon J, Abbott R, Rogers M, Whear R, Pearson S, Lang I, *et al*. Interventions to reduce inappropriate prescribing of antipsychotic medications in people with dementia resident in care homes: a systematic review. J Am Med Dir Assoc 2014; 15: 706–18.

23 Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, *et al*. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. BMJ 2010; 340: c365.

24 Hart B, Lundh A, Bero L. Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses. BMJ 2012; 344: d7202.

25 Page MJ, McKenzie JE, Kirkham J, Dwan K, Kramer S, Green S, *et al*. Bias due to selective inclusion and reporting of outcomes and analyses in systematic reviews of randomised trials of healthcare interventions. Cochrane Database Syst Rev 2014; 10: MR000035.

26 Hutton JL, Williamson PR. Bias in meta-analysis due to outcome variable selection within studies. J R Stat Soc Ser C Appl Stat 2000; 49: 359–70.

27 Wylde V, Bruce J, Beswick A, Elvers K, Gooberman-Hill R. Assessment of chronic postsurgical pain after knee replacement: a systematic review. Arthritis Care Res 2013; 65: 1795–803.

28 Potter S, Brigic A, Whiting PF, Cawthorn SJ, Avery KNL, Donovan JL, *et al*. Reporting clinical outcomes of breast reconstruction: a systematic review. J Natl Cancer Inst 2011; 103: 31–46.

29 Rodgers S, Brealey S, Jefferson L, McDaid C, Maund E, Hanchard N, *et al*. Exploring the outcomes in studies of primary frozen shoulder: is there a need for a core outcome set? Qual Life Res 2014; 23: 2495–504.

30 Hopkins JC, Howes N, Chalmers K, Savovic J, Whale K, Coulman KD, *et al*. Outcome reporting in bariatric surgery: an in-depth analysis to inform the development of a core outcome set, the BARIACT Study. Obes Rev 2015; 16: 88–106.

31 Wylde V, MacKichan F, Bruce J, Gooberman-Hill R. Assessment of chronic post-surgical pain after knee replacement: development of a core outcome set. Eur J Pain 2015; 19: 611–20.

32 Potter S, Holcombe C, Ward JA, Blazeby JM, BRAVO Steering Group. Development of a core outcome set for research and audit studies in reconstructive breast surgery. Br J Surg 2015; 102: 1360–71.

33 Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions, Vol. Version 5.1.0 . The Cochrane Collaboration, 2011.

34 Gillespie U, Alassaad A, Henrohn D, Garmo H, Hammarlund-Udenaes M, Toss H, *et al*. A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older: a randomized controlled trial. Arch Intern Med 2009; 169: 894–900.

35 Mortimer C, Emmerton L, Lum E. The impact of an aged care pharmacist in a department of emergency medicine. J Eval Clin Pract 2011; 17: 478–85.

36 Spinewine A, Swine C, Dhillon S, Lambert P, Nachega JB, Wilmotte L, *et al*. Effect of a collaborative approach on the quality of prescribing for geriatric inpatients: a randomized, controlled trial. J Am Geriatr Soc 2007; 55: 658–65.

37 Lisby M, Thomsen A, Nielsen LP, Lyhne NM, Breum-Leer C, Fredberg U, *et al*. The effect of systematic medication review in elderly patients admitted to an acute ward of internal medicine. Basic Clin Pharmacol Toxicol 2010; 106: 422–7.

38 Hellström LM, Bondesson A, Höglund P, Midlöv P, Holmdahl L, Rickhag E, *et al*. Impact of the Lund Integrated Medicines Management (LIMM) model on medication appropriateness and drug-related hospital revisits. Eur J Clin Pharmacol 2011; 67: 741–52.

39 Browne C, Kingston C, Keane C. Falls prevention focused medication review by a pharmacist in an acute hospital: implications for future practice. Int J Clin Pharmacol 2014; 36: 969–75.

40 Bergqvist M, Ulfvarson J, Karlsson EA. Nurse-led medication reviews and the quality of drug treatment of elderly hospitalized patients. Eur J Clin Pharm 2009; 65: 1089–96.

41 Schmader KE, Hanlon JT, Pieper CF, Sloane R, Ruby CM, Twersky J, *et al*. Effects of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly. Am J Med 2004; 116: 394–401.

42 Gallagher P, O'Connor M, O'Mahony D. Prevention of potentially inappropriate prescribing for elderly patients: a randomized controlled trial using STOPP/START criteria. Clin Pharmacol Ther 2011; 89: 845–54.

43 Krska J, Cromarty JA, Arris F, Jamieson D, Hansford D, Duffus PR, *et al*. Pharmacist-led medication review in patients over 65: a randomized, controlled trial in primary care. Age Ageing 2001; 30: 205–11.

44 Nazareth I, Burton A, Shulman S, Smith P, Haines A, Timberal H. A pharmacy discharge plan for hospitalized elderly patients – a randomized controlled trial. Age Ageing 2001; 30: 33–40.

45 Zermansky AG, Petty DR, Raynor DK, Freemantle N, Vail A, Lowe CJ. Randomised controlled trial of clinical medication review by a pharmacist of elderly patients receiving repeat prescriptions in general practice. BMJ 2001; 323: 1340–3.

46 Sellors J, Kaczorowski J, Sellors C, Dolovich L, Woodward C, Willan A, *et al*. A randomized controlled trial of a pharmacist consultation program for family physicians and their elderly patients. CMAJ 2003; 169: 17–22.

47 Naunton M, Peterson GM. Evaluation of home-based follow-up of high-risk elderly patients discharged from hospital. J Pharm Pract Res 2003; 33: 176–82.

48 Sturgess IK, McElnay JC, Hughes CM, Crealey G. Community pharmacy based provision of pharmaceutical care to older patients. Pharm World Sci 2003; 25: 218–26.

49 Holland R, Lenaghan E, Harvey I, Smith R, Shepstone L, Lipp A, *et al*. Does home based medication review keep older people out of hospital? The HOMER randomised controlled trial. BMJ 2005; 330: 293.

50 Lenaghan E, Holland R, Brooks A. Home-based medication review in a high risk elderly population in primary care – the POLYMED randomised controlled trial. Age Ageing 2007; 36: 292–7.

51 Fiss T, Dreier A, Meinke C, van den Berg N, Ritter CA, Hoffmann W. Frequency of inappropriate drugs in primary care: analysis of a sample of immobile patients who received periodic home visits. Age Ageing 2011; 40: 66–73.

52 Bryant LJM, Coster G, Gamble GD, McCormick RN. The General Practitioner–Pharmacist Collaboration (GPPC) study: a randomised controlled trial of clinical medication reviews in community pharmacy. Int J Pharm Pract 2011; 19: 94–105.

53 Elliott RA, Martinac G, Campbell S, Thorn J, Woodward MC. Pharmacist-led medication review to identify medication-related problems in older people referred to an Aged Care Assessment Team: a randomized comparative study. Drugs Aging 2012; 29: 593–605.

54 Furniss L, Burns A, Craig SK, Scobie S, Cooke J, Faragher B. Effects of a pharmacist's medication review in nursing homes. Randomised controlled trial. Br J Psychiatry 2000; 176: 563–7.

55 Roberts MS, Stokes JA, King MA, Lynne TA, Purdie DM, Glasziou PP, *et al*. Outcomes of a randomized controlled trial of a clinical pharmacy intervention in 52 nursing homes. Br J Clin Pharmacol 2001; 51: 257–65.

56 King MA, Roberts MS. Multidisciplinary case conference reviews: improving outcomes for nursing home residents, carers and health professionals. Pharm World Sci 2001; 23: 41–5.

57 Crotty M, Halbert J, Rowett D, Giles L, Birks R, Williams H, *et al*. An outreach geriatric medication advisory service in residential aged care: a randomised controlled trial of case conferencing. Age Ageing 2004; 33: 612–7.

58 Zermansky AG, Alldred DP, Petty DR, Raynor DK, Freemantle N, Eastaugh J, *et al*. Clinical medication review by a pharmacist of

elderly people living in care homes – randomised controlled trial. Age Ageing 2006; 35: 586–91.

59 Patterson SM, Hughes CM, Crealey G, Cardwell C, Lapane KL. An evaluation of an adapted U.S. model of pharmaceutical care to improve psychoactive prescribing for nursing home residents in Northern Ireland (Fleetwood Northern Ireland Study). J Am Geriatr Soc 2010; 58: 44–53.

60 Pope G, Wall N, Peters CM, O'Connor M, Saunders J, O'Sullivan C, *et al*. Specialist medication review does not benefit short-term outcomes and net costs in continuing-care patients. Age Ageing 2011; 40: 307–12.

61 Lapane KL, Hughes CM, Daiello LA, Cameron KA, Feinberg J. Effect of a pharmacist-led multicomponent intervention focusing on the medication monitoring phase to prevent potential adverse drug events in nursing homes. J Am Geriatr Soc 2011; 59: 1238–45.

62 Milos V, Rekman E, Bondesson Å, Eriksson T, Jakobsson U, Westerlund T, *et al*. Improving the quality of pharmacotherapy in elderly primary care patients through medication reviews: a randomised controlled study. Drugs Aging 2013; 30: 235–46.

63 Blalock SJ, Casteel C, Roth MT, Ferreri S, Demby KB, Shankar V. Impact of enhanced pharmacologic care on the prevention of falls: a randomized controlled trial. Am J Geriatr Pharmacother 2010; 8: 428–40.

64 Meredith S, Feldman P, Frey D, Giammarco L, Hall K, Arnold K, *et al*. Improving medication use in newly admitted home healthcare patients: a randomized controlled trial. J Am Geriatr Soc 2002; 50: 1484–91.

65 Dalleur O, Boland B, Losseau C, Henrard S, Wouters D, Speybroeck N, *et al*. Reduction of potentially inappropriate medications using the STOPP criteria in frail older inpatients: a randomised controlled study. Drugs Aging 2014; 31: 291–8.

66 Trygstad TK, Christensen D, Garmise J, Sullivan R, Wegner S. Pharmacist response to alerts generated from Medicaid pharmacy claims in a long-term care setting: results from the North Carolina polypharmacy initiative. J Manag Care Spec Pharm 2005; 11: 575–83.

67 Pit SW, Byles JE, Henry DA, Holt L, Hansen V, Bowman DA. A Quality Use of Medicines program for general practitioners and older people: a cluster randomised controlled trial. Med J Aust 2007; 187: 23–30.

68 Kwint HF, Faber A, Gussekloo J, Bouvy ML. Effects of medication review on drug-related problems in patients using automated drug-dispensing systems: a pragmatic randomized controlled study. Drugs Aging 2011; 28: 305–14.

69 Gnjidic D, Le Couteur DG, Abernethy DR, Hilmer SN. A pilot randomized clinical trial utilizing the drug burden index to reduce exposure to anticholinergic and sedative medications in older people. Ann Pharmacother 2010; 44: 1725–32.

70 Touchette DR, Masica AL, Dolor RJ, Schumock GT, Choi YK, Kim Y, *et al*. Safety-focused medication therapy management: a randomized controlled trial. J Am Pharm Assoc 2012; 52: 603–12.

71 Frankenthal D, Lerman Y, Kalendaryev E, Lerman Y. Intervention with the screening tool of older persons potentially inappropriate prescriptions/screening tool to alert doctors to right treatment criteria in elderly residents of a chronic geriatric facility: a randomized clinical trial. J Am Geriatr Soc 2014; 62: 1658–65.

72 Ahmad A, Nijpels G, Dekker JM, Kostense PJ, Hugtenburg JG. Effect of a pharmacist medication review in elderly patients discharged from the hospital. Arch Intern Med 2012; 172: 1346–7.

73 Lisby M, Bonnerup DK, Brock B, Gregersen PA, Jensen J, Larsen ML, *et al*. Medication review and patient outcomes in an orthopedic department: a randomized controlled study. J Patient Saf 2015; [Epub ahead of print].

74 Chan DC, Chen JH, Wen CJ, Chiu LS, Wu SC. Effectiveness of the medication safety review clinics for older adults prescribed multiple medications. J Formos Med Assoc 2014; 113: 106–13.

75 Jódar-Sánchez F, Malet-Larrea A, Martín JJ, García-Mochón L, López Del Amo MP, Martínez-Martínez F, *et al*. Cost-utility analysis of a medication review with follow-up service for older adults with polypharmacy in community pharmacies in Spain: the conSIGUE program. Pharmacoeconomics 2015; 33: 599–610.

76 Lenander C, Elfsson B, Danielsson B, Midlöv P, Hasselström J. Effects of a pharmacist-led structured medication review in primary care on drug-related problems and hospital admission rates: a randomized controlled trial. Scand J Prim Health Care 2014; 32: 180–6.

77 Mestres C, Hernandez M, Llagostera B, Espier M, Chandre M. Improvement of pharmacological treatments in nursing homes: medication review by consultant pharmacists. Eur J Hosp Pharm 2015; 22: 207–11. doi:10.1136/ejhpharm-2014-000508.

78 O'Sullivan D, O'Mahony D, O'Connor MN, Gallagher P, Cullinan S, O'Sullivan R, *et al*. The impact of a structured pharmacist intervention on the appropriateness of prescribing in older hospitalized patients. Drugs Aging 2014; 31: 471–81.

79 Paquin AM, Salow M, Rudolph JL. Pharmacist calls to older adults with cognitive difficulties after discharge in a Tertiary Veterans Administration Medical Center: a quality improvement program. J Am Geriatr Soc 2015; 63: 571–7.

80 Westberg SM, Swanoski MT, Renier CM, Gessert CE. Evaluation of the impact of comprehensive medication management services delivered posthospitalization on readmissions and emergency department visits. J Manag Care Spec Pharm 2014; 20: 886–93.

81 Cooperation for Improved Pharmacotherapy in Home-dwelling Elderly People Receiving Polypharmacy - The COOP Study - Tabular View - ClinicalTrials.gov. Available at https: // clinicaltrials.gov/ct2/show/record/NCT02379455 (last accessed 10 August 2016).

82 Page AT, Clifford RM, Potter K, Schwartz D, Etherton-Beer CD. The feasibility and effect of deprescribing in older adults on mortality and health: a systematic review and meta-analysis. Br J Clin Pharmacol 2016; 82: 583–623.

83 Saini P, Loke YK, Gamble C, Altman DG, Williamson PR, Kirkham JJ. Selective reporting bias of harm outcomes within studies: findings from a cohort of systematic reviews. BMJ 2014; 349: g6501.

84 Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012; 380: 37–43.

85 Tooth L, Hockey R, Byles J, Dobson A. Weighted multimorbidity indexes predicted mortality, health service use, and health-related quality of life in older women. J Clin Epidemiol 2008; 61: 151–9.

86 Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, *et al*. Developing core outcome sets for clinical trials: issues to consider. Trials 2012; 13: 132.

87 Idzerda L, Rader T, Tugwell P, Boers M. Can we decide which outcomes should be measured in every clinical trial? A scoping review of the existing conceptual frameworks and processes to develop core outcome sets. J Rheumatol 2014; 41: 986–93.

88 Kirkham JJ, Gargon E, Clarke M, Williamson PR. Can a core outcome set improve the quality of systematic reviews? A survey of the Co-ordinating Editors of Cochrane Review Groups. Trials 2013; 14: 21.

89 Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, *et al*. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epidemiol 2014; 67: 745–53.

90 MacLennan S, Bekema HJ, Williamson PR, Campbell MK, Stewart F, MacLennan SJ, *et al*. A core outcome set for localised prostate cancer effectiveness trials: protocol for a systematic review of the literature and stakeholder involvement through interviews and a Delphi survey. Trials 2015; 16: 76.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13197/suppinfo

Table S1 Names of the health domains and subdomains used to classify the outcomes extracted from the studies included in the systematic review, according to the OMERAT filter 2.0 classification

Table S2 Health domains and subdomains covered by the outcomes identified in the 47 published studies and 32 randomized controlled trial protocols included in the systematic review

Table S3 Number of outcomes per health domain and subdomains with the clarity of the measurement instrument used to measure them, as identified in the published studies or in randomized controlled trial protocols

Appendix S1 Search strategy