BMJ Open

Development of evidence-based Australian medication-related indicators of potentially preventable hospitalisations: a modified RAND appropriateness method

Gillian E Caughey,[1] Lisa M Kalisch Ellett,[1] Te Ying Wong[2]

To cite: Caughey GE, Kalisch Ellett LM, Wong TY. Development of evidence-based Australian medication-related indicators of potentially preventable hospitalisations: a modified RAND appropriateness method. *BMJ Open* 2014;**4**: e004625. doi:10.1136/bmjopen-2013-004625

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2013-004625).

Received 4 December 2013
Revised 17 March 2014
Accepted 1 April 2014

For numbered affiliations see end of article.

Correspondence to
Dr Lisa Kalisch Ellett;
lisa.kalisch@unisa.edu.au

ABSTRACT

Objective: Indicators of potentially preventable hospitalisations have been adopted internationally as a measure of health system performance; however, few assess appropriate processes of care around medication use, that if followed may prevent hospitalisation. The aim of this study was to develop and validate evidence-based medication-related indicators of potentially preventable hospitalisations.

Setting: Australian primary healthcare.

Participants: Medical specialists, general practitioners and pharmacists. A modified RAND appropriateness method was used for the development of medication-related indicators of potentially preventable hospitalisations, which included a literature review, assessment of the strength of the supporting evidence base, an initial face and content validity by an expert panel, followed by an independent assessment of indicators by an expert clinical panel across various disciplines, using an online survey.

Primary outcome measure: Analysis of ratings was performed on the four key elements of preventability; the medication-related problem must be recognisable, the adverse outcomes foreseeable and the causes and outcomes identifiable and controllable.

Results: A total of 48 potential indicators across all major disease groupings were developed based on level III evidence or greater, that were independently assessed by 78 expert clinicians (22.1% response rate). The expert panel considered 29 of these (60.4%) sufficiently valid. Of these, 21 (72.4%) were based on level I evidence.

Conclusions: This study provides a set of face and content validated indicators of medication-related potentially preventable hospitalisations, linking suboptimal processes of care and medication use with subsequent hospitalisation. Further analysis is required to establish operational validity in a population-based sample, using an administrative health database. Implementation of these indicators within routine monitoring of healthcare systems will highlight those conditions where hospitalisations could potentially be avoided through improved medication management.

Strengths and limitations of this study

- The clinical indicators developed were based on high-level evidence together with expert clinical panel assessment.
- Since the clinical indicators were developed using Australian-specific resources they may need to be adapted for use in other settings.
- This study provides a set of face and content validated indicators of potentially preventable hospitalisations, linking to suboptimal processes of care and medication use with subsequent hospitalisation.

INTRODUCTION

Clinical indicators of potentially preventable hospitalisations are used as a measure of health system performance and quality of healthcare provided to patients.[1 2] Potentially preventable hospitalisations are defined as those hospitalisations that could be prevented with the provision of timely and effective primary care.[3] Medication-related hospitalisations are relatively common. A literature review found that 2–3% of all hospital admissions in the Australian healthcare setting were medication related, with half considered to be potentially preventable.[4] A systematic review of studies from around the world found that a median of 3.7% of all hospital admissions were preventable medication-related admissions.[5] The identification and subsequent reduction of the most common medication-related potentially preventable hospitalisations will improve morbidity and quality of life for patients, safety of the healthcare system and reduce healthcare expenditure.

Clinical indicators of medication-related potentially preventable hospitalisations have been developed which link suboptimal

processes of care with medicine use to assess adverse outcomes including hospitalisation.[2 6–8] The overall incidence of preventable medication-related hospitalisations when measured using these clinical indicator sets has been reported to range between 3% and 20%, depending on the country of the study population and the clinical indicator set used.[9–11] Using the previously developed clinical indicators, the prevalence of potentially preventable medication-related hospitalisations in the Australian healthcare setting between 1 January 2004 and 31 December 2008 was examined. During the 5-year study period there were 44 416 (20.5%) potentially preventable medication-related hospitalisations, equating to 9000 preventable admissions each year.[11] However, in undertaking the study, it became apparent that many of the internationally developed indicators were not relevant or applicable to the Australian healthcare setting. A cross-country comparison between the USA and the UK indicators found that of the 46 indicators assessed, 58% were relevant to the USA but not the UK, and only 41% were deemed to be relevant in the healthcare setting of both countries.[8] Given the significant differences between the USA and the UK healthcare systems to that of Australia, there may be additional indicators, specifically relevant to the Australian healthcare system, that should be examined. Further, the international indicators were developed over 10 years ago and there are likely to be a number of indicators based on new medicines introduced since then.

Prior studies which developed clinical indicators for potentially preventable medication-related hospitalisations used the Delphi technique,[2 6 8 12 13] which measures consensus among experts using a series of structured surveys.[14 15] Recent studies have highlighted the need for clinical indicators to be evidence based, rather than based on expert consensus only.[11 13 16] Increasingly, the RAND appropriateness method is used in indicator development,[17 18] which develops indicators by combining evidence-based recommendations from clinical guidelines with expert clinical opinion. In addition, recent studies have highlighted the need for clinical indicators to be country specific to reflect current practice within individual healthcare systems.[11 13 16] To date, no evidence-based indicators of medication-related potentially preventable hospitalisations have been developed specific for the Australian setting. The aim of this study was to develop and validate Australian evidence-based medication-related indicators of potentially preventable hospitalisations.

METHODS

A modified RAND appropriateness method was used for the development of medication-related indicators of potentially preventable hospitalisations, which has characteristics of both the Delphi and Nominal Group Techniques, providing a systematic method to combine evidence with expert opinion.[19] It consists of a literature review, assessment of the strength of the supporting evidence base, an initial face and content validity assessment by an expert panel, followed by an independent assessment of indicators by an expert clinical panel across various disciplines, using an online survey.

Identification of existing indicators and development of new indicators

A number of methods were used to systematically identify and develop clinical indicators for medication-related potentially preventable hospitalisations, specific for the Australian healthcare setting. A literature review was conducted to identify all published studies of indicators for preventable medication-related hospitalisations that could be adapted using specific inclusion criteria. Identification and development of additional clinical indicators was based on chronic diseases included in Australia's National Health Priority Areas.[20] In addition, indicators were developed for gastrointestinal disorders, which are associated with high prevalence and morbidity in Australia.[21] Australian treatment and clinical guidelines for these chronic conditions were then examined to identify potential mediation-related issues relevant for the development of clinical indicators for preventable medication-related hospitalisations.

Literature review to identify existing clinical indicators of potentially preventable medication-related hospitalisations

A literature review of all published studies on clinical indicators for preventable medication-related hospitalisations was conducted from January 2001 to December 2012, inclusive. The primary search terms used were 'indicators', 'prevent$ OR avoid$', 'medication OR drug-related', 'hospitalisation OR morbidity' and 'adverse drug event'. MEDLINE (via Ovid) and EMBASE were searched, with results limited to articles published in English and conducted in adults. Studies which developed indicators not associated with the outcome of hospitalisation were excluded. Reference lists of relevant identified studies were further searched to identify additional papers. The following information was extracted from each suitable study: the hospitalisation outcome, the process of care leading to the outcome and references (ie, studies which developed the indicator). Clinical indicators were grouped according to broader chronic disease groupings and similar clinical indicators obtained from different studies were recorded as one clinical indicator.

Predefined inclusion criteria were used to determine the applicability and relevance of previously published clinical indicators to the Australian healthcare setting. Indicators that did not meet one or more of these criteria were excluded from the study.

The inclusion criteria were the following:

1. Strength of supporting evidence must be Grade B or level III or higher, based on the National Health and Medical Research Council (NHMRC) evidence matrix.[22]

2. The medicine must be available in Australia and subsidised under the Schedule of Pharmaceutical Benefits (PBS or RPBS).[23]
3. The process of care must concur with Australian treatment guidelines.
4. The process of care can be identified in Australian electronic health records.

Concordance of the indictors with current Australian treatment and clinical guidelines were identified from the Australian Therapeutic Guidelines,[24] Australian Medicines Handbook[25] and clinical guidelines including cardiovascular disease,[26–30] respiratory conditions,[31 32] diabetes,[33 34] musculoskeletal conditions[35 36] and mental health.[37 38] Where the international clinical indicators differed slightly from Australian guidelines, modifications were developed if appropriate. The guidelines were also searched to determine the level of supporting evidence. The strength of the supporting evidence for each indicator was assessed and categorised into five levels based on current Australian standards, used for guideline development.[39] Only those indicators with level III or greater evidence were included. The WHO International Classification of Diseases (ICD) 10–AM classification was used to identify codes for hospitalisation outcomes.[40]

Development of new clinical indicators of potentially preventable medication-related hospitalisations

Development of new clinical indicators was largely based on those chronic diseases included in Australia's National Health Priority Areas.[20] Chronic obstructive pulmonary disease was included with asthma under the broad disease category of respiratory conditions due to its large disease burden and mortality.[41] Gastrointestinal disorders which are associated with high prevalence and morbidity in Australia, were also included.[21] Clinical indicators for cancer were not developed in this study. Medicine use for cancer is highly specialised and varied depending on the type of cancer, and the development of new medicines for these conditions is a fast evolving area. To develop new indicators treatment and clinical guidelines for each of the conditions were reviewed, with a focus on treatment considerations, medicine class statements and monographs, contraindications, precautions, recommended testing and follow-up. All newly developed indicators were required to meet the inclusion criteria used for previously published clinical indicators, as described above.

Initial face and content validity by a convenience sample of pharmacists

An initial face and content validity of the compiled list of indicators was undertaken with a convenience sample of eight clinical pharmacists. Based on the four elements of preventability developed by Hepler and Strand,[42] they were asked the following questions: would you expect most health professionals to

1. Recognise the problem in the process of care?
2. Foresee the potential for hospitalisation associated with the process of care?
3. Know how to change the process of care to reduce the likelihood of hospitalisation?
4. Be able to change the process of care to reduce the likelihood of hospitalisation?

Responses to each of the four elements of preventability were rated on a three-point Likert scale, where '1' indicates disagreement, '2' uncertain or equivocal and '3' agreement, together with comments to allow for feedback or suggestions regarding specific elements or readability. For each indicator, a majority agreement (5/8 or 62.5%) by the convenience sample across all four elements of preventability was required for inclusion in our final list for validation by an expert panel.

Expert panel assembly, survey and analysis

The final list of indicators for validation were grouped into subject categories (cardiovascular disease, diabetes, renal, mental health, respiratory, gastrointestinal and osteoporosis/fracture indicators) and sent to clinical experts for review. Experts were identified as clinical leaders in their field, that included both medical physicians (general practitioners and specialists) and pharmacists (including certified geriatric pharmacists and clinical pharmacists), across Australia from a range of healthcare settings. A total of 352 clinical experts were identified and contacted to be part of the expert clinical panel for validation of the indicators, between December 2012 and March 2013. They were invited to score the indicators using an online survey (SurveyMonkey http://www.surveymonkey.com) on the four elements of preventability, as described above. Participants were not able to respond to the survey more than once. A brief summary of each indicator was provided; the level of evidence for each indicator together with the reference(s) supporting the level of evidence. A priori criteria of consensus for validation for each of the indicators were defined; an average score of 70% or greater agreement by the expert panellists, across all four elements of preventability for each indicator, were deemed to meet requirements for validation of an indicator. As described above, responses to each of the four elements of preventability were rated on a three-point Likert scale, where '1' indicates disagreement, '2' uncertain or equivocal and '3' agreement, together with comments to allow for feedback on each of the individual indicators.

RESULTS

A total of 48 potential indicators across major disease groupings based on level III evidence or greater were developed (table 1), all of which had majority agreement in the initial face and content validity by a convenience sample of eight clinical pharmacists. Of these, 13 were from previously developed medication-related indicators of potentially preventable hospitalisations, 15 were modified to be applicable to the Australian healthcare

Table 1 Australian medication-related potentially preventable hospitalisation clinical indicator set

Number	Hospitalisation outcome	Process of care (preceding hospitalisation)	Level of evidence	Source of indicator: Previously published; not modified	Source of indicator: Previously published; modified for this study	Source of indicator: Newly developed
Cardiovascular indicators						
1	Acute coronary syndrome	1. History of MI (in 2 years prior to admission) 2. Not on aspirin, β-blocker, ACEI or ARB and statin (in 3 months prior to admission)	Aspirin, β-blocker—level I, ACEI/ARB, statin—level II[28]		Changed outcome from just MI; added ACEI/ARB and statin[6 7]	
2	Acute coronary syndrome	1. Patient has coronary artery stent (in 1 year prior to admission) 2. No use of aspirin or clopidogrel (in 12 months prior to admission)	Level I[28]			28
3	CHF	1. History of CHF (in 2 years prior to admission) 2. Not on an ACEI or ARB (in 3 months prior to admission)	Level I[26]		Added ARB for those intolerant to ACEI[6–8]	
4	CHF	1. History of CHF (in 2 years prior to admission) 2. Not on a heart failure indicated β-blocker (in 3 months prior to admission)	Level I[26]			26
5	CHF	1. History of CHF 2. Use of rosiglitazone or pioglitazone (in 6 months prior to admission)	Level I[33]			33
6	CHF	1. History of CHF 2. Use of NSAID (in 3 months prior to admission)	Level I[49]		Removed fluid overload from outcome[2 6–8]	
7	CHF or cardiac ischaemic event	1. History of IHD (in 2 years prior to admission) 2. Use of rosiglitazone (in 6 months prior to admission)	Level I[50]			33
8	CHF and / or heart block	1. History of CHF with heart block or advanced bradycardia (in 2 years prior to admission) 2. Use of digoxin (in 6 months prior to admission)	Level III[51]	6–8		
9	CHF or MI	1. Concurrent use of insulin and rosiglitazone	Level III[50]			33
10	Ischaemic stroke	1. History of chronic AF or ischaemic stroke in 2 years prior to admission) 2. No use of warfarin or aspirin (in 3 months prior to admission)	Level I[30]	8		
11	VTE or stroke	1. History of coronary artery disease or VTE 2. Use of raloxifene	Level II[52]			35
Mental health indicators						
12	Bipolar disorder	1. History of bipolar disorder 2. Use of lithium 3. Drug level not monitored in the previous 3 months	Level I[38]	6 7		
13	Acute confusion	1. Patient aged ≥65 years 2. Use of two or more agents with anticholinergic activity OR use of an agent with high anticholinergic activity	Level III[53]	2		
14	Acute confusion	1. Patient aged ≥65 years 2. Use of multiple psychotropic medications (eg, benzodiazepines, tricyclic antidepressants)	Level III[25 54]	2		

Continued

Table 1 Continued

Number	Hospitalisation outcome	Process of care (preceding hospitalisation)	Level of evidence	Source of indicator: Previously published; not modified	Source of indicator: Previously published; modified for this study	Source of indicator: Newly developed
15	Serotonin toxicity	Use of duloxetine, fentanyl, tramadol, SSRIs, TCAs or venlafaxine concurrently with MAOI or moclobemide, or within 14 days of stopping MAOI	Level III[54]			25
16	Serotonin toxicity	Concurrent treatment with strong CYP1A2 inhibitors (eg, duloxetine) with fluvoxamine	Level III[54]			25
Respiratory indicators						
17	Asthma or COPD	1. History of asthma or COPD 2. Use of a β-blocker eye drops for glaucoma	Level I[55]	8 13		
18	Asthma	1. History of asthma 2. Use of SABA more than 3 times/week or use of LABA 3. No use of inhaled corticosteroids	Level I[32]		Asthma only, Australian guideline specific[7–9]	
19	COPD	1. Moderate to severe COPD with frequent exacerbation 2. Use of long-acting β-agonist or anticholinergic 3. No use of inhaled corticosteroids	Level I[31]		COPD only, Australian guideline specific[7–9]	
20	Asthma or COPD	1. History of asthma or COPD 2. No contraindication to influenza vaccine 3. No influenza vaccination in the previous year	Level I[31 32]			31 32
21	Influenza-related pneumonia	1. Patient aged ≥65 2. No contraindication to influenza vaccine 3. No influenza vaccine in the previous year	Level I[56 57]	2		
22	Pneumococcal pneumonia or sepsis	1. Patient aged ≥65 2. No contraindication to pneumococcal vaccine 3. No pneumococcal vaccine in the previous 6 years	Level III[57 58]	2		
GI indicators						
23	GI bleed, perforation or ulcer or gastritis	1. History of GI ulcer or bleeding 2. NSAID use for at least 1 month 3. No use of gastroprotective agent (eg, PPI)	Level II[36 59]		Added gastroprotective agent[6 7 13]	
24	Chronic constipation or impaction	1. Use of two or more agents with low-to-moderate anticholinergic activity; OR use of a highly anticholinergic agent	Level 1[60]	2		
25	Chronic constipation or impaction	1. Regular use of a strong opioid analgesic (fentanyl, oxycodone, morphine) 2. No concurrent use of a laxative	Level I[61]	8		
26	GI ulcer	1. Patient with dyspepsia 2. PPI not prescribed	Level I[62]			25
27	GI ulcer	1. Patient with a positive test for *Helicobacter pylori* 2. Not prescribed *H pylori* eradication therapy	Level I[63]			25
28	GI ulcer or bleed	1. Patient with osteoarthritis 2. Dispensed long-term NSAIDs (including COX-2) therapy	Level I[64]			36
29	Oesophagitis, oesophageal ulceration or stricture	1. History of oesophageal disorders (active oesophagitis, oesophageal ulceration, stricture or achalasia) 2. Use of alendronate	Level I[65]			25

Continued

Table 1 Continued

Number	Hospitalisation outcome	Process of care (preceding hospitalisation)	Level of evidence	Source of indicator: Previously published; not modified	Source of indicator: Previously published; modified for this study	Source of indicator: Newly developed
Osteoporosis/fracture indicators						
30a	Osteoporosis or fracture	1. Use of systemic corticosteroids for at least 3 months 2. No osteoporosis prophylaxis (women: no use of HRT, bisphosphonate, teriparatide, selective oestrogen receptor modulators or strontium; men: no use of bisphosphonate or teriparatide)	Level I[66]		Removed dose[8 13]	
30b	Osteoporosis or fracture	1. This indicator is the same as above, but for male patients	Level I[66]		Removed dose[8 13]	
31	Fracture	1. Female patient 2. History of osteoporosis or fracture 3. No use of HRT, bisphosphonate, teriparatide, selective oestrogen receptor modulators or strontium	Level I[35]		Changed from history of fall[6]	
32	Fracture	1. Male patient 2. History of osteoporosis or fracture 3. No use of bisphosphonate or teriparatide	Level II[35]		Changed from history of fall[2]	
33	Fracture	1. Patient aged ≥65 years 2. History of osteoporosis 3. Patient not receiving adequate levels of calcium and vitamin D	Level III[35]	[2]		
34	Fracture	1. Patient on high dose inhaled corticosteroid (≥400 μg fluticasone daily or equivalent) for more than 1 year 2. Bone mineral density not measured in the previous 24 months	Level II[35]			[25]
35	Fracture	1. Patient aged ≥65 years 2. Use of a falls-risk medicine (eg, long-acting hypnotic or anxiolytic, tricyclic antidepressant)	Level I[67]		Included all falls-risk medicines[6–8]	
36	Arrhythmia	1. Concurrent use of calcitriol with digoxin 2. Calcium concentration not monitored in the previous 3 months	Level III[68]			[25]
37	Hypercalcaemia	1. Use of calcitriol 2. Plasma calcium concentration not monitored in the previous 3 months	Level III[69]			[25]
Renal indicators						
38	Renal failure or nephropathy	1. History of diabetes 2. Microalbuminuria and plasma creatinine not monitored in the previous 12 months 3. Patient not on ACEI or ARB	Level II—monitoring, Level I—ACE/ARB use[70]			[70]
39	Renal failure	1. NSAID use for >3 months 2. Serum creatinine not monitored in the previous 12 months	Level II[36]		Changed monitoring from 3 to 12 months[6 8]	
40	Renal failure	1. Use of lithium 2. Serum creatinine not monitored in previous 6 months	Level III[38]	[6 7]		
41	Urinary retention	1. History of BPH 2. Use of an anticholinergic agent	Level III[25]	[6 7]		

Continued

Table 1 Continued

Number	Hospitalisation outcome	Process of care (preceding hospitalisation)	Level of evidence	Source of indicator: Previously published; not modified	Source of indicator: Previously published; modified for this study	Source of indicator: Newly developed
42	Urinary retention	1. Use of two or more agents with anticholinergic activity OR use of a highly anticholinergic agent	Level III[25]		Combined to one indicator[2]	
Diabetes indicators						
43	Hyperglycaemia/ hypoglycaemia	1. Use of an oral hypoglycaemic agent 2. HbA1c level not monitored in the previous 6 months	Level I[34]		Added hypoglycaemia as outcome[2 6]	
44	Hypoglycaemia	1. Use of a long-acting oral hypoglycaemic agent (glibenclamide or glimepiride) 2. HbA1c level not monitored in the previous 6 months	Level I[34]		Added HbA1c monitoring[2]	
45	Hyperglycaemia or hypoglycaemia	1. Use of insulin 2. HbA1c level not monitored in the previous 6 months	Level I[34]			34
46	Hyperglycaemia or hypoglycaemia	1. Use of insulin or oral hypoglycaemic medicines 2. Use of medicines that may increase or decrease blood glucose concentration 3. HbA1c level not monitored in the previous 6 months	Level I[33]			33
47	Hypoglycaemia	1. Use of glibenclamide or glimepiride 2. Renal function not monitored in the previous year	Level II[33]			33
48	Cardiovascular disease	1. History of diabetes 2. Not on lipid lowering drug	Level II[71]			71

ARB, angiotensin receptor blocker; BPH, benign prostatic hyperplasia; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; HbA1c, glycated haemoglobin; HRT, hormone replacement therapy; IHD, ischemic heart disease; LABA, long-acting β agonist; MAOI, monoamine oxidase inhibitor; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, transluminal coronary angioplasty; VTE, venous thromboembolism.

setting and 21 were newly developed. These were then sent to the expert clinical panel for full validation and were independently assessed by 78 expert clinicians (22.2% response rate). Of the respondents, 32% were medical physicians and 68% were pharmacists.

The expert panel considered 29 of these (60.4%) to be sufficiently valid based on the a priori developed criteria (table 2). The majority of these (72.4%, n=21) were based on level I evidence. A total of 11 cardiovascular indicators were developed, of which 5 (45.5%) were validated by the expert clinical panel; four of the five were based on level I evidence. Of the five mental health indicators developed, only one had level I evidence and none were validated by the expert panel. Six respiratory indicators were developed and five of these were validated, 80% of these were based on level I evidence. A total of seven gastrointestinal indicators, six of which were based on level I evidence were developed and five (71.4%) were validated. Of eight osteoporosis/fracture indicators, half of which were based on level I evidence and five (62.5%) were validated. Only two of the five developed renal indicators were validated, with the level of evidence being level II or less for these. Finally, six diabetes indicators were developed, four of which were based on level I evidence and all were validated by the clinical panel.

DISCUSSION

This study provides a set of face and content validated indicators of medication-related potentially preventable hospitalisations, specific for the Australian healthcare setting linking suboptimal processes of care and medication use with subsequent hospitalisation. Of a potential 48 developed indicators, 29 achieved consensus validation by the expert clinical panel and over 70% of these were based on level I evidence. An important feature of these developed indicators is that they are evidence based, systematically combining evidence-based recommendations from clinical guidelines with expert clinical opinion. In addition, these indicators focus on those chronic conditions which are included in Australia's National Health Priority Areas[20] or those that are associated with high disease burden in Australia.[21 41]

For each of the six disease clusters for which indicators were developed, the proportion validated by our expert panel ranged from only 20% (1/5) for the mental health indicators to 100% for the diabetes indicators (6/6). Interestingly, the level of evidence available for the metal health indicators around medicine use and processes of care was minimal (four of the five indicators had only level III evidence), by comparison to the diabetes indicators where the majority of evidence was level I.

The health conditions for which these indicators were developed significantly contribute to the burden of illness, social and financial costs in Australia, and prevention of hospitalisations associated with these conditions will provide significant gains in the health of Australia's population.[20] Furthermore, given the high prevalence of medication-related hospitalisations in Australia, identification of areas where medication management could be improved, particularly at the primary care level, may also lead to fewer hospitalisations. An estimated 90 000 hospital admissions annually are considered to be potentially preventable mediation-related admissions in those aged 65 years and older.[11] Based on the average cost of hospitalisation in Australia in 2010–2011 to be $A5400,[43] these unnecessary hospitalisations cost Australia's healthcare system $A480 million annually.

Analysis of the developed indicators in a population-based sample is required to establish operational validity, and this will be the focus of the next phase of this research. With the advent of computerised administrative health databases, these indicators have been developed with the potential to be analysed in such databases at the population level. Importantly, the characteristics of those patients' most vulnerable to mediation-related hospitalisations will also facilitate the identification of risk-factors associated with suboptimal medication management. Implementation of these indicators within routine monitoring of the Australian healthcare system will serve to highlight those conditions where hospitalisations could potentially be avoided through improved medication management, identify areas of current practice that may be suboptimal or evidence-practice gaps and facilitate the development of specific interventions to improve healthcare and subsequent patient outcomes.

The standard RAND appropriateness method employs two rounds; in the first round experts rate indicators independently and in the second round, experts meet face to face to discuss the indicators and rate the indicators again, based on the face-to-face discussion.[17] Our study used a modified RAND appropriateness method, with one round of independent expert panel review, and subsequent inclusion of indicators which met a priori defined criteria but no face-to-face meeting of experts. This is a potential limitation of our study, because the face-to-face meeting provides an opportunity to discuss indicators with low levels of agreement between experts, and can identify whether this is due to true clinical disagreement or simply an issue with the wording of the indicator.[44] It may be that for some indicators true consensus was not achieved if those who disagreed were strongly opposed to the indicator, and this type of issue may have been identified at a face-to-face meeting. Despite these limitations, the online survey technique used in our study eliminates any potential bias from dominant individuals who may be associated with face-to-face panel settings.[44] This allows for expert clinical panel members to express their opinions in an anonymous manner but also gives them time to consider each of the four elements of preventability together with

Table 2 Validation of Australian medication-related potentially preventable hospitalisation clinical indicator set by expert panel

Number	Hospitalisation outcome	Process of care (preceding hospitalisation)	Accepted	Overall score (%)	Would you expect most health professionals to*			
					Recognise the problem in the process of care? (%)	Foresee the potential for hospitalisation associated with the process of care? (%)	Know how to change the process of care to reduce the likelihood of hospitalisation? (%)	Be able to change the process of care to reduce the likelihood of hospitalisation? (%)
Cardiovascular indicators								
1	Acute coronary syndrome	1. History of MI (in 2 years prior to admission) 2. Not on aspirin, β-blocker, ACEI or ARB and statin (in 3 months prior to admission)	**Y**	**71.5**	**74**	**79**	**74**	**63**
2	Acute coronary syndrome	1. Patient has coronary artery stent (in 1 years prior to admission) 2. No use of aspirin or clopidogrel (in 12 months prior to admission)	**Y**	**75**	**78**	**72**	**72**	**78**
3	CHF	1. History of CHF (in 2 years prior to admission) 2. Not on an ACEI or ARB (in 3 months prior to admission)	**Y**	**72.5**	**80**	**70**	**70**	**70**
4	CHF	1. History of CHF (in 2 years prior to admission) 2. Not on a heart failure indicated β-blocker (in 3 months prior to admission)	N	63	68	63	63	58
5	CHF	1. History of CHF 2. Use of rosiglitazone or pioglitazone (in 6 months prior to admission)	N	38	35	29	47	41
6	CHF	1. History of CHF 2. Use of NSAID (in 3 months prior to admission)	N	54.5	56	56	50	56
7	CHF or cardiac ischaemic event	1. History of IHD (in 2 years prior to admission) 2. Use of rosiglitazone (in 6 months prior to admission)	N	36	33	28	44	39
8	CHF and/or heart block	1. History of CHF with heart block or advanced bradycardia (in 2 years prior to admission) 2. Use of digoxin (in 6 months prior to admission)	**Y**	**75**	**80**	**85**	**75**	**60**
9	CHF or MI	1. Concurrent use of insulin and rosiglitazone	N	48.5	53	41	53	47

Continued

Table 2 Continued

Number	Hospitalisation outcome	Process of care (preceding hospitalisation)	Accepted	Overall score (%)	Would you expect most health professionals to*			
					Recognise the problem in the process of care? (%)	Foresee the potential for hospitalisation associated with the process of care? (%)	Know how to change the process of care to reduce the likelihood of hospitalisation? (%)	Be able to change the process of care to reduce the likelihood of hospitalisation? (%)
10	Ischaemic stroke	1. History of chronic AF or ischaemic stroke (in 2 years prior to admission) 2. No use of warfarin or aspirin (in 3 months prior to admission)	**Y**	**94.8**	**100**	**100**	**95**	**84**
11	VTE or stroke	1. History of coronary artery disease or VTE 2. Use of raloxifene	N	54.8	56	50	63	50
Mental health indicators								
12	Bipolar disorder	1. History of bipolar disorder 2. Use of lithium 3. 3) Drug level not monitored in the previous 3 months	N	69	69	63	75	69
13	Acute confusion	1. Patient aged ≥65 years 2. Use of 2 or more agents with anticholinergic activity OR use of an agent with high anticholinergic activity	N	53.5	44	44	63	63
14	Acute confusion	1. Patient aged ≥65 years 2. Use of multiple psychotropic medications (eg, benzodiazepines, tricyclic antidepressants)	N	42.6	69	50	56	38
15	Serotonin toxicity	1. Use of duloxetine, fentanyl, tramadol, SSRIs, TCAs, or venlafaxine concurrently with MAOI or moclobemide, or within 14 days of stopping MAOI	N	53	50	50	56	56
16	Serotonin toxicity	1. Concurrent treatment with strong CYP1A2 inhibitors (eg, duloxetine) with fluvoxamine	N	59.5	63	56	63	56
Respiratory indicators								
17	Asthma or COPD	1. History of asthma or COPD 2. Use of a β-blocker eye drops for glaucoma	N	51.2	50	45	50	60
18	Asthma	1. History of asthma 2. Use of SABA more than 3 times/week or use of LABA 3. No use of inhaled corticosteroids	**Y**	**92.5**	**95**	**85**	**100**	**90**

Continued

Table 2 Continued

Number	Hospitalisation outcome	Process of care (preceding hospitalisation)	Accepted	Overall score (%)	Would you expect most health professionals to*			
					Recognise the problem in the process of care? (%)	Foresee the potential for hospitalisation associated with the process of care? (%)	Know how to change the process of care to reduce the likelihood of hospitalisation? (%)	Be able to change the process of care to reduce the likelihood of hospitalisation? (%)
19	COPD	1. Moderate-to-severe COPD with frequent exacerbation 2. Use of long-acting β-agonist or anticholinergic 3. No use of inhaled corticosteroids	**Y**	**90**	**90**	**75**	**100**	**95**
20	Asthma or COPD	1. History of asthma or COPD 2. No contraindication to influenza vaccine 3. No influenza vaccination in the previous year	**Y**	**82.5**	**80**	**75**	**90**	**85**
21	Influenza-related pneumonia	1. Patient aged ≥65 years 2. No contraindication to influenza vaccine 3. No influenza vaccine in the previous year	**Y**	**87.5**	**85**	**75**	**95**	**95**
22	Pneumococcal pneumonia or sepsis	1. Patient aged ≥65 years 2. No contraindication to pneumococcal vaccine 3. No pneumococcal vaccine in the previous 6 years	**Y**	**80**	**80**	**75**	**90**	**75**
GI indicators								
23	GI bleed, perforation or ulcer or gastritis	1. History of GI ulcer or bleeding 2. NSAID use for at least 1 month 3. 3) No use of gastroprotective agent (eg, PPI)	**Y**	**89.5**	**95**	**84**	**95**	**84**
24	Chronic constipation or impaction	1. Use of 2 or more agents with low-to-moderate anticholinergic activity; OR use of a highly anticholinergic agent	N	34.3	42	21	37	37
25	Chronic constipation or impaction	1. Regular use of a strong opioid analgesic (fentanyl, oxycodone, morphine) 2. No concurrent use of a laxative	**Y**	**91**	**95**	**79**	**95**	**95**
26	GI ulcer	1. Patient with dyspepsia 2. PPI not prescribed	**Y**	**74.8**	**89**	**58**	**84**	**68**
27	GI ulcer	1. Patient with a positive test for *Helicobacter pylori* 2. Not prescribed *H pylori* eradication therapy (PPI twice daily, clarithromycin 500 mg twice daily and amoxycillin 1 g twice daily for 7 days; OR PPI	**Y**	**86.8**	**89**	**74**	**95**	**89**

Continued

Table 2 Continued

Number	Hospitalisation outcome	Process of care (preceding hospitalisation)	Accepted	Overall score (%)	Would you expect most health professionals to*			
					Recognise the problem in the process of care? (%)	Foresee the potential for hospitalisation associated with the process of care? (%)	Know how to change the process of care to reduce the likelihood of hospitalisation? (%)	Be able to change the process of care to reduce the likelihood of hospitalisation? (%)
		twice daily, clarithromycin 500 mg twice daily and metronidazole 400 mg twice daily for 7 days; PPI twice daily, amoxycillin 500 mg three times a day and metronidazole 400 mg three times a day for 14 days)						
28	GI ulcer or bleed	1. Patient with osteoarthritis 2. Dispensed long-term NSAIDs (including COX-2) therapy	**Y**	**71**	**84**	**63**	**79**	**58**
29	Oesophagitis, oesophageal ulceration or stricture	1. History of oesophageal disorders (active oesophagitis, oesophageal ulceration, stricture or achalasia) 2. Use of alendronate	N	68.3	73	68	64	68
Osteoporosis/fracture indicators								
30a	Osteoporosis or fracture	1. Use of systemic corticosteroids for at least 3 months 2. No osteoporosis prophylaxis (women: no use of HRT, bisphosphonate, teriparatide, selective oestrogen receptor modulators or strontium; men: no use of bisphosphonate or teriparatide)	**Y**	**80.8**	**91**	**86**	**82**	**64**
31	Fracture	1. Female patient 2. History of osteoporosis or fracture 3. No use of HRT, bisphosphonate, teriparatide, selective oestrogen receptor modulators or strontium	**Y**	**81.8**	**95**	**82**	**86**	**64**
32	Fracture	1. Male patient 2. History of osteoporosis or fracture 3. No use of bisphosphonate or teriparatide	**Y**	**72.8**	**82**	**68**	**77**	**64**
33	Fracture	1. Patient aged ≥65 years 2. History of osteoporosis 3. Patient not receiving adequate levels of calcium and vitamin D	**Y**	**76**	**91**	**68**	**77**	**68**

Continued

Table 2 Continued

Number	Hospitalisation outcome	Process of care (preceding hospitalisation)	Accepted	Overall score (%)	Would you expect most health professionals to*			
					Recognise the problem in the process of care? (%)	Foresee the potential for hospitalisation associated with the process of care? (%)	Know how to change the process of care to reduce the likelihood of hospitalisation? (%)	Be able to change the process of care to reduce the likelihood of hospitalisation? (%)
34	Fracture	1. Patient on high dose inhaled corticosteroid (≥400 µg fluticasone daily or equivalent) for more than 1 year 2. Bone mineral density not measured in the previous 24 months	N	40.8	45	32	45	41
35	Fracture	1. Patient aged ≥65 years 2. Use of a falls-risk medicine (eg, long-acting hypnotic or anxiolytic, tricyclic antidepressant)	**Y**	**71.5**	**82**	**77**	**68**	**59%**
36	Arrhythmia	1. Concurrent use of calcitriol with digoxin 2. Calcium concentration not monitored in the previous 3 months	N	31.5	18	18	45	45
37	Hypercalcaemia	1. Use of calcitriol 2. Plasma calcium concentration not monitored in the previous 3 months	N	62.8	73	55	64	59
Renal indicators								
38	Renal failure or nephropathy	1. History of diabetes 2. Microalbuminuria and plasma creatinine not monitored in the previous 12 months 3. Patient not on ACEI or ARB	**Y**	**79.3**	**88**	**65**	**82**	**82**
39	Renal failure	1. NSAID use for >3 months 2. Serum creatinine not monitored in the previous 12 months	**Y**	**79**	**76**	**76**	**88**	**76**
40	Renal failure	1. Use of lithium 2. Serum creatinine not monitored in the previous 3 months	N	66.5	65	65	65	71
41	Urinary retention	1. History of BPH 2. Use of an anticholinergic agent	N	59	59	65	59	53
42	Urinary retention	1. Use of 2 or more agents with anticholinergic activity OR use of a highly anticholinergic agent	N	39.5	35	41	41	41
Diabetes indicators								
43	Hyperglycaemia/ hypoglycaemia	1. Use of an oral hypoglycaemic agent 2. HbA1c level not monitored in the previous 6 months	**Y**	**85**	**95**	**77**	**95**	**73**

Continued

Table 2 Continued

Number	Hospitalisation outcome	Process of care (preceding hospitalisation)	Accepted	Overall score (%)	Would you expect most health professionals to*			
					Recognise the problem in the process of care? (%)	Foresee the potential for hospitalisation associated with the process of care? (%)	Know how to change the process of care to reduce the likelihood of hospitalisation? (%)	Be able to change the process of care to reduce the likelihood of hospitalisation? (%)
44	Hypoglycaemia	1. Use of a long-acting oral hypoglycaemic agent (glibenclamide or glimepiride) 2. HbA1c level not monitored in the previous 6 months	**Y**	**95**	**100**	**90**	**95**	**95**
45	Hyperglycaemia or hypoglycaemia	1. Use of insulin 2. HbA1c level not monitored in the previous 6 months	**Y**	**91.5**	**100**	**95**	**90**	**81**
46	Hyperglycaemia or hypoglycaemia	1. Use of insulin or oral hypoglycaemic medicines 2. Use of medicines that may increase or decrease blood glucose concentration 3. HbA1c level not monitored in the previous 6 months	**Y**	**76.8**	**88**	**75**	**75**	**69**
47	Hypoglycaemia	1. Use of glibenclamide or glimepiride 2. Renal function not monitored in the previous year	**Y**	**81.5**	**75**	**75**	**88**	**88**
48	Cardiovascular disease	1. History of diabetes 2. Not on lipid lowering drug	**Y**	**81.8**	**88**	**88**	**88**	**63**

Numbers in bold represent those who achieved an average score of ≥70% agreement by the expert panel.
*Percentage of respondents who answered 'Agree' or 'Yes' on the three-point Likert scale.
AF, atrial fibrillation; ARB, angiotensin receptor blocker; BPH, benign prostatic hyperplasia; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; HbA1c, glycated haemoglobin; IHD, ischemic heart disease; LABA, long-acting β agonist; MAOI, monoamine oxidase inhibitor; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; SABA, short-acting β agonist; SSRI, selective serotonin reuptake inhibitor; TCA, transluminal coronary angioplasty; VTE, venous thromboembolism.

the supporting evidence base of each developed indicator. In addition, our method for developing the indicators systematically combined the available evidence base with the opinion of clinical experts to develop indicators that are both face and content valid.[19] The modified RAND method used in our study has been used in indicator development studies previously.[18 45] A recent Australian study used this method to validate 657 indicators of healthcare appropriateness.[16]

Our study achieved a 22% response rate, which is lower than other Australian studies involving medical practitioners, which typically achieve a response rate of around 30%.[46–48] While this may limit the generalisability of our findings, our results are strengthened by having medical specialists, general practitioners and pharmacists on the expert review panel.[44] In addition, 78 expert clinicians reviewed the clinical indicators for our study; by comparison, previous studies which developed clinical indicators for preventable medication-related hospitalisation used fewer than 20 expert reviewers.

In conclusion, this study has developed a set of face and content validated indicators of medication-related potentially preventable hospitalisations specific for the Australian healthcare setting, linking medication use with suboptimal processes of care resulting in adverse outcomes of hospitalisations. As a measure of health system performance these indicators could identify areas of sub-optimal medication management, particularly at the primary care level, based on routinely collected health administrative health data but with the strong focus on patient outcomes and quality of care rather than processes or quantity.

Author affiliations
[1]Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia
[2]School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia

Acknowledgements The authors would like to thank the expert clinical panel and the project advisory group for their time and expertise.

Contributors GEC conceived and designed the study, and was involved in data acquisition, analysis and interpretation, drafted the article and approved the final approval version to be published. LMKE conceived and designed the study, and was involved in data acquisition, analysis and interpretation, critically revised the manuscript for important intellectual content and approved the final approval version to be published. TYW was involved in data acquisition, analysis and interpretation, critically revised the manuscript for important intellectual content and approved the final approval version to be published.

Funding This work was funded by The BUPA Health Foundation

Competing interests None.

Ethics approval Ethics approval for this study was obtained from the University of South Australia's Human Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

REFERENCES

1. Mainz J. Defining and classifying clinical indicators for quality improvement. *Int J Qual Health Care* 2003;15:523–30.
2. Robertson H, MacKinnon N. Development of a list of consensus-approved clinical indicators of preventable drug-related morbidity in older adults. *Clin Ther* 2002;24:1595–613.
3. Bindman A, Grubmach K, Osmond D, *et al*. Preventable hospitalizations and access to health care. *JAMA* 1995;274:305–11.
4. Roughead E, Semple S. Medication safety in acute care in Australia: where are we now? Part 1: a review of the extent and causes of medication problems 2002–2008. *Aust N Z Health Policy* 2009;6:18.
5. Howard R, Avery A, Slavenburg S, *et al*. Which drugs cause preventable admissions to hospital? A systematic review. *Br J Clin Pharmacol* 2007;63:136–47.
6. MacKinnon N, Hepler C. Preventable drug-related morbidity in older adults. 1. Indicator development. *J Manag Care Pharm* 2002;8:365–71.
7. Sauer B, Hepler C, Cherney B, *et al*. Computerized indicators of potential drug-related emergency department and hospital admissions. *Am J Manag Care* 2007;13:29–35.
8. Morris CJ, Cantrill JA, Hepler CD, *et al*. Preventing drug-related morbidity—determining valid indicators. *Int J Qual Health Care* 2002;14:183–98.
9. Mackinnon NJ, Hepler CD. Indicators of preventable drug-related morbidity in older adults 2. Use within a managed care organization. *J Manag Care Pharm* 2003;9:134–41.
10. MacKinnon NJ, Hartnell NR, Bowles SK, *et al*. Incident-event rate of preventable drug-related morbidity in older Adultsin Nova Scotia. *Can J Geriatr* 2006;9:159–63.
11. Kalisch LM, Caughey GE, Barratt JD, *et al*. Prevalence of preventable medication-related hospitalizations in Australia: an opportunity to reduce harm. *Int J Qual Health Care* 2012;24:239–49.
12. Morris C, Cantrill J. Preventing drug-related morbidity—the development of quality indicators. *J Clin Pharm Ther* 2003;28:295–305.
13. Morris C, Cantrill J. Preventable drug-related morbidity indicators in the US and UK. *J Manag Care Pharm* 2002;8:372–7.
14. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. *J Adv Nurs* 2000;32:1008–15.
15. Keeney S, Hasson F, McKenna H. A critical review of the Delphi technique as a research methodology for nursing. *Int J Nurs Stud* 2001;38:195–200.
16. Runciman WB, Hunt TD, Hannaford NA, *et al*. CareTrack: assessing the appropriateness of health care delivery in Australia. *Med J Aust* 2012;197:100–5.
17. Avery A, Dex G, Mulvaney C, *et al*. Development of prescribing-safety indicators for GPs using the RAND appropriateness method. *Br J Gen Pract* 2011;61:e526–e36.
18. Hunt T, Ramanathan S, Hannaford N, *et al*. CareTrack Australia: assessing the appropriateness of adult healthcare: protocol for a retrospective medical record review. *BMJ Open* 2012;2:e000665.
19. Teresato AG, Lougheed MD, Gershon AS, *et al*. Evidence-based performance indicators of primary care for asthma: a modified RAND appropriateness method. *Int J Qual Health Care* 2010;22:476–85.
20. Australian Government Australian Institute of Health and Welfare (AIHW). Australian Institute of Health and Welfare: National Health Priority Areas. http://www.aihw.gov.au/national-health-priority-areas/ (accessed 17 Mar 2014).
21. Boyce PM, Talley NJ, Burke C, *et al*. Epidemiology of the functional gastrointestinal disorders diagnosed according to Rome II criteria: an Australian population-based study. *Intern Med J* 2006;36:28–36.
22. Australian Government National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines 2009. https://www.

nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf (accessed 17 Mar 2014).
23. Australian Government Department of Health and Ageing. Schedule of pharmaceutical benefits. http://www.pbs.gov.au/browse/publications (accessed 17 Mar 2014).
24. Therapeutic Guidelines Limited. Therapeutic guidelines. http://www.tg.org.au/ (accessed 25 Jul 2012).
25. Rossi S. ed *Australian medicines handbook*. Adelaide: AMH, 2011.
26. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (Chronic Heart Failure Guidelines Expert Writing Panel). Guidelines for the prevention, detection and management of chronic heart failure in Australia. Updated October 2011. http://www.heartfoundation.org.au/SiteCollectionDocuments/Chronic_Heart_Failure_Guidelines_2011.pdf (accessed 17 Mar 2014).
27. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. Reducing risk in heart disease 2007 (updated 2008): Guidelines for preventing cardiovascular events in people with coronary heart disease. http://www.heartfoundation.org.au/SiteCollectionDocuments/Reduce-risk-in-heart-disease-guideline.pdf (accessed 17 Mar 2014).
28. Acute Coronary Syndrome Guidelines Working Group. Guidelines for the management of acute coronary syndromes 2006. *Med J Aust* 2006;184(8 Suppl):S1–S32.
29. National Heart Foundation (National Blood Pressure Advisory Committee). Hypertension management guide for Doctors National Heart Foundation, 2004.
30. National Stroke Foundation. *Clinical guidelines for stroke management 2010*. Melbourne, Australia. http://strokefoundation.com.au/site/media/clinical_guidelines_stroke_managment_2010_interactive.pdf (accessed 17 Mar 2014).
31. McKenzie DK, Abramson M, Crockett AJ, *et al*. The COPD-X Plan: Australian and New Zealand Guidelines for the management of chronic obstructive pulmonary disease V2.30. 2011. http://www.copdx.org.au/home (accessed 17 Mar 2014).
32. National Asthma Council Australia. *Asthma management handbook 2006*. Melbourne, Australia: National Asthma Council Australia, 2006.
33. Diabetes Australia, Royal Australian College for General Practitioners. *Diabetes management in general practice. Guidelines for type 2 diabetes*. 16th edn. Diabetes Australia, 2010.
34. Colagiuri S, Dickinson S, Girgis S, *et al*. *National evidence based guideline for blood glucose control in type 2 diabetes*. Canberra, Australia: Diabetes Australia and the NHMRC, 2009.
35. Royal Australian College of General Practitioners. *Clinical guideline for the prevention and treatment of osteoporosis in postmenopausal women and older men*. 2010. http://www.racgp.org.au/download/documents/Guidelines/Musculoskeletal/racgp_osteo_guideline.pdf (accessed 17 Mar 2014).
36. The Royal Australian College of General Practitioners. *Guideline for the non-surgical management of hip and knee osteoarthritis*, South Melbourne, Victoria: RACGP, 2009. https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp117-hip-knee-osteoarthritis.pdf (accessed 17 Mar 2014).
37. Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression. Australian and New Zealand clinical practice guidelines for the treatment of depression. *Aus N Z J Psychiatry* 2004;38:389–407.
38. Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Bipolar Disorder. Australian and New Zealand clinical practice guidelines for the treatment of bipolar disorder. *Aust N Z J Psychiatry* 2004;38:280–305.
39. Australian Governement: National Health and Medical Research Council (NHMRC). *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines*. http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/levels_grades05.pdf (accessed 17 Mar 2014).
40. World Health Organization International Classification of Diseases. *International statistical classification of diseases and related health problems 10th revision*, 2007. http://www.who.int/classifications/apps/icd/icd10online/ (accessed 8 Aug 2009).
41. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;3:e442.
42. Hepler C, Strand L. Opportunities and responsibilities in pharmaceutical care. *Am J Hosp Pharm* 1990;47:533–43.
43. Australian Institute of Health and Welfare (AIHW). *Australian hospital statistics 2010-11. Health services series no 50. Cat. no. HSE 134*. Canberra: Australian Government AIHW, 2012. http://www.aihw.gov.au/publication-detail/?id=10737421633 (accessed 17 Mar 2014).
44. Fitch K, Bernstein S, Aguilar M, *et al*. *The RAND/UCLA appropriateness method user's manual*. Santa Monica: RAND, 2001.
45. McGlynn E, Asch S, Adams J, *et al*. The quality of health care delivered to adults in the United States. *New Engl J Med* 2003;348:2635–45.
46. Bonevski B, Magin P, Horton G, *et al*. Response rates in GP surveys. Trialling two recruitment strategies. *Aust Fam Phys* 2011;40:427–30.
47. Britt H, Miller G, Charles J, *et al*. *General practice activity in Australia 2008-09. BEACH: bettering the evaluation and care of health. General Practice Series No. 25. Cat No. GEP 25*. Canberra: AIHW, 2009.
48. Johnson C, Lizama N, Garg N, *et al*. Australian general practitioners' preferences for managing the care of people diagnosed with cancer. *Asia Pac J Clin Oncol* 2012; doi: 10.1111/ajco.12047
49. Scott PA, Kingsley GH, Scott DL. Non-steroidal anti-inflammatory drugs and cardiac failure: meta-analyses of observational studies and randomised controlled trials. *Eur J Heart Fail* 2008;10:1102–7.
50. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356:2457–71.
51. Hunt SA, Abraham WT, Chin MH, *et al*. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005;112:e154–235.
52. Mosca L, Grady D, Barrett-Connor E, *et al*. Effect of raloxifene on stroke and venous thromboembolism according to subgroups in postmenopausal women at increased risk of coronary heart disease. *Stroke* 2009;40:147–55.
53. Han L, McCusker J, Cole M, *et al*. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. *Arch Intern Med* 2001;161:1099–105.
54. Edwards JG, Anderson I. Systematic review and guide to selection of selective serotonin reuptake inhibitors. *Drugs* 1999;57:507–33.
55. Centre for Allied Health Evidence; NHMRC, Department of Health and Ageing. *Systematic literature review on the detection, diagnosis, management and prevention of glaucoma*. Canberra, Australia: Australian Government, National Health and Medical Research Council, 2009.
56. Gross PA, Hermogenes AW, Sacks HS, *et al*. The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. *Ann Intern Med* 1995;123:518–27.
57. Australian Government. Department of Health and Ageing. NHMRC. *The Australian immunisation handbook*. 9th edn. Canberra, Australia: Commonwealth of Australia, 2009.
58. Griffin MR, Zhu Y, Moore MR, *et al*. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. *New Engl J Med* 2013;369:155–63.
59. Macintyre PE, Scott DA, Visser EJ, *et al*. *Working group of the Australian and, New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute pain management: scientific evidence*. 3rd edn. Melbourne: ANZCA & FPM, 2010.
60. Herbison P, Hay-Smith J, Ellis G, *et al*. Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: systematic review. *BMJ* 2003;326:841.
61. McNicol E, Horowicz-Mehler N, Fisk RA, *et al*. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. *J Pain* 2003;4:231–56.
62. Wang WH, Huang JQ, Zheng GF, *et al*. Effects of proton-pump inhibitors on functional dyspepsia: a meta-analysis of randomized placebo-controlled trials. *Clin Gastroenterol Hepatol* 2007;5:178–85.
63. Moayyedi P, Deeks J, Talley NJ, *et al*. An update of the Cochrane systematic review of Helicobacter pylori eradication therapy in nonulcer dyspepsia: resolving the discrepancy between systematic reviews. *Am J Gastroenterol* 2003;98:2621–6.
64. Laine L, Smith R, Min K, *et al*. Systematic review: the lower gastrointestinal adverse effects of non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther* 2006;24:751–67.
65. Lloyd Jones M, Wilkinson A. *Adverse effects and persistence with therapy in patients taking oral alendronate, etidronate or risedronate: a systematic review*. The National Institute for Clinical Excellence, 2006.
66. Kanis JA, Johansson H, Oden A, *et al*. A Meta-analysis of prior corticosteroid use and fracture risk. *J Bone Mineral Res* 2004;19:893–9.
67. Hartikainen S, Lönnroos E, Louhivuori K. Medication as a risk factor for falls: critical systematic review. *J Gerontol Series A Biol Sci Med Sci* 2007;62:1172–81.

68. Gheorghiade M, van Veldhuisen DJ, *et al*. Contemporary use of digoxin in the management of cardiovascular disorders. *Circulation* 2006;113:2556–64.
69. Kallas M, Green F, Hewison M, *et al*. Rare causes of calcitriol-mediated hypercalcemia: a case report and literature review. *J Clin Endocrinol Metabol* 2010;95:3111–17.
70. Chadban S HM, Twigg S, Thomas M, *et al*. *National evidence based guideline for diagnosis, prevention and management of chronic kidney disease in type 2 diabetes*. Canberra, Australia. http://diabetesaustralia.com.au/PageFiles/763/Chronic%20Kidney%20Disease%20Guideline%20August%202009.pdf (accessed 17 Mar 2014).
71. Diabetes Australia Guideline Development Consortium; Australian Centre for Diabetes Strategies. *National evidence based guidelines for the management of type 2 diabetes mellitus. Part 7 lipid control in type 2 diabetes*. Australian Centre for Diabetes Strategies. http://www.nhmrc.gov.au/publications/synopses/di7todi13syn.htm (accessed 17 Mar 2014).