



Validation of prescribing appropriateness criteria for older Australians using the RAND/UCLA Appropriateness Method

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ARTICLE SUMMARY

Article focus

- Drug-related problems (DRPs) are common in older people, resulting in under-treatment with proven medicines, and disproportionately high numbers of adverse drug events
- The aim of this study was to validate a list of prescribing appropriateness criteria for use in older people

Key messages

- The use of medication assessment criteria is one method to assist in identifying DRPs. Criteria developed elsewhere may have little or no applicability to the Australian healthcare environment
- Validation of proposed Australian prescribing appropriateness criteria for older people was accomplished using a two-round modified Delphi method, resulting in agreement for all criteria as measured by median panel ratings, and the amount of dispersion of panel ratings, based on the interpercentile range
- Use of these criteria, together with other Australian medication review processes, may assist in improving patient care by efficiently identifying DRPs to common medical conditions and commonly used medicines, and in the medication management education of health care professionals

Strengths and limitations

- A validated consensus method was used involving an expert medication management panel of varied specialization. Criteria were based on established evidence-practice gaps and degree of disease burden imposed on the health care system, and were written with the aim of conciseness and clarity
- Further developmental work is required to assess the usefulness of these criteria, which only included commonly occurring medicines and medical conditions

ABSTRACT

Objective: To update and validate proposed national prescribing appropriateness criteria to assist in identifying drug-related problems (DRPs) to commonly occurring medications and medical conditions in older (≥ 65 years old) Australians.

Design: Rand/UCLA Appropriateness Method

Participants: A panel of medication management experts were identified consisting of geriatricians, clinical pharmacists, and disease management advisors to organisations that produce Australian evidence-based therapeutic publications. This resulted in a round one panel of fifteen members, and a round two panel of twelve members

Main outcome measure: Agreement on all criteria

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3 **Results:** Forty eight prescribing criteria were rated. In the first rating round via email, there
4 was disagreement regarding 35% (17/48) of the criteria according to median panel ratings.
5 During a face-to-face second round meeting, discussion resulted in 81% (39/48) of the
6 proposed criteria being accepted, with 52% (25/48) requiring amendment or updating.
7 Twenty nine per cent (14/48) were unchanged, and 19% (9/48) deleted. Two new criteria
8 were added, resulting in a final validated list of 41 prescribing appropriateness criteria.
9 Agreement was reached for all criteria, measured by median panel ratings and the amount of
10 dispersion of panel ratings, based on the interpercentile range
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12 **Conclusions:** A set of 41 Australian prescribing appropriateness criteria were validated by an
13 expert panel. Use of these criteria, together with clinical judgement and other medication
14 review processes such as patient interview, is intended to assist in improving patient care by
15 efficiently detecting potential DRPs related to commonly occurring medicines and medical
16 conditions in older Australians. These criteria may also contribute to the medication
17 management education of health care professionals
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22 INTRODUCTION

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24 Drug-related problems (DRPs) in older people (≥ 65 years old) are common,[1-4] resulting in
25 both undertreatment with proven medicines[5-7] and disproportionately high numbers of
26 serious adverse medication events due to polypharmacy.[8-10] Methods to identify and
27 reduce DRPs include educational interventions, [11] comprehensive geriatric assessment,
28 [12] discontinuation of multiple medications, [13 ,14]electronic health record clinical
29 decision support, [15 ,16]and the use of medication assessment criteria.[11 ,17-20]
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33 However in older patients, the importance of traditional outcomes, such as discrete clinical
34 events or mortality, may be secondary to maintaining physical and cognitive function or relief
35 of symptoms.[21] Because of this, optimal care requires clinical decision support tools that
36 consider issues such as patient preferences, frailty, cost, and co-morbidities.[22] Additionally,
37 few criteria target the oldest old,[23] where evidence may be poor, and preventive
38 interventions may be encouraged in patients who have already exceeded an average
39 lifespan.[24 ,25] In Australia, issues such as these are intended to be considered when
40 patients are interviewed by an accredited pharmacist as part of the Home Medicines Review
41 program.[26] This program aims to provide the sophistication lacking in explicit (rather than
42 judgement based) criteria, and is targeted towards patients who may be (among other reasons)
43 currently taking ≥ 5 regular medicines, attending a number of different doctors, or have
44 recently been discharged from hospital.
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50 In 2008, we proposed prescribing appropriateness criteria aimed at improving detection of
51 DRPs, to be used as part of the Australian medication review process.[27] These criteria were
52 based on the most frequent medications prescribed to Australians, and the most frequent
53 medical conditions for which older Australians consult medical practitioners. Australian
54 medication and disease state resources and guidelines were used to provide content validity.
55 However, unlike our criteria, other prescribing criteria or tools have combined evidence with
56 expert opinion to provide face validity.[28 ,29]
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4 The aim of this study was to update our list of criteria, adding recommendations for co-
5 morbidity and the oldest old where possible, and to validate the criteria through expert
6 consensus. To do this, we identified a panel of medication management experts, and chose
7 the RAND/UCLA appropriateness method,[30] which has been described as the best method
8 for systematically combining recommendations from clinical guidelines, with the opinion of
9 healthcare providers.[31]
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12 13 **METHODS**

14 15 **Ethics**

16 Ethics approval was obtained from the Human Research Ethics Committee of the University
17 of Sydney.
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20 21 **Criteria development**

22 In 2008, we cross-referenced the fifty highest-volume Australian Pharmaceutical Benefits
23 Scheme (PBS) medications, with the most common reasons for older Australians to seek or
24 receive healthcare. Healthcare information was obtained using the BEACH (Bettering The
25 Evaluation and Care of Health) program, which continuously collects information about the
26 clinical activities in general practice in Australia.[32] Australian medication information
27 sources were then used to identify both optimal and inappropriate medication management of
28 these common conditions.[27] In Australia, medication availability and use is largely
29 determined by the PBS.[33] In October 2011, commonly used medications and medical
30 conditions were checked and updated using the BEACH program to ensure that criteria
31 content was current. Changes in evidence, product information, Australian consensus
32 documents, evidence-based publication recommendations or clinical practice guidelines
33 relating to our criteria were noted for evaluation by an expert medication management panel.
34 The criteria were designed to provide guidance on the process of care wherever it occurred –
35 community, hospital, hostel or nursing home. Major considerations in their development were
36 feasibility of data collection, conciseness and clarity of wording, and provision of a practical
37 number of criteria. Most were explicit to enable consistent application, with additional notes
38 provided for interpretation where necessary. They were written as a statement of the kind of
39 medication management that should or should not occur, to simplify comprehension and
40 facilitate uptake.[27]
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48 **Validation of criteria - participants**

49 To ensure comprehensive representation, we recruited three groups of medication
50 management experts to review, update and rate the criteria; geriatricians, clinical pharmacists,
51 and disease management advisors to organisations that produce Australian evidence-based
52 therapeutic publications. This resulted in a round one panel of fifteen members. The
53 geriatricians consisted of two professors of geriatric medicine; an associate professor of
54 clinical pharmacology and aged care; a research fellow in geriatric medicine; and a hospital
55 staff geriatrician. Clinical pharmacists consisted of a residential medication management
56 review pharmacist; a home medicines review pharmacist; four hospital-based pharmacists
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3 (two team leaders, one director and one education and training pharmacist), and a professor
4 of aged care (Pharmacy). Disease management advisors to Australian evidence-based
5 therapeutic organisations consisted of Therapeutic Guidelines,[34] Australian Medicines
6 Handbook,[35] and the New South Wales Therapeutic Advisory Group.[36]
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9 **RAND/UCLA Appropriateness Method round one**

10 In October 2011 candidate panel members were emailed an explanation of the project and an
11 invitation to participate. After acceptance, they were emailed a rating sheet consisting of 48
12 criteria, and asked to rate each on a nine point scale, where one meant highly inappropriate,
13 and nine represented criteria that were highly appropriate. Appropriate was defined as “the
14 expected health benefit exceeds the expected negative consequences by a sufficiently wide
15 margin that criteria are worth following, exclusive of cost”. They also received a description
16 of the way in which the criteria had been derived, and a comparison with other prescribing
17 criteria.[23 ,27] Panel members were requested to amend the wording or delete, update or
18 identify missing criteria as required. Upon return of the rating sheets, results were tabulated.
19 Agreement was based on median panel ratings and the amount of dispersion of panel ratings,
20 as per the RAND/UCLA protocol. Specifically, the median value, interpercentile range (IPR)
21 and interpercentile range adjusted for symmetry (IPRAS) was computed for each of the
22 criteria.[30]
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28 **Rand/UCLA Appropriateness Method round two**

29 In November 2011, a face-to-face meeting of the expert panel, chaired by a panel moderator
30 experienced in facilitating group discussions and criteria development, met to discuss the
31 results of round one and re-rate the criteria. One pharmacist, one staff geriatrician and a
32 disease management advisor for a therapeutics publication could not attend, resulting in a
33 twelve member panel. For this meeting, each panel member was provided with a copy of the
34 results from round one. This consisted of the frequency distribution of ratings of all panellists
35 across the 9-point scale, the overall panel median rating for each of the criteria and, for each
36 panellist, an annotation of how they had rated each of the criteria . Scores from other panel
37 members were not revealed. Depending upon panellists votes, panel agreement or
38 disagreement was also stated for each of the criteria. Agreement was reached when either
39 three or less panel members voted outside the 3-point region containing the median, or IPRS
40 was greater than IPR. Each of the criteria was then discussed, with panellists having the
41 opportunity of changing their ratings if, for example, misinterpretation had occurred because
42 of the way in which the criteria had been written, or if new evidence had become available, or
43 if criteria had been interpreted in the light of a panellists own clinical experience. Each panel
44 member consented to audio recording of the discussion. Criteria were then re-rated, and
45 values for the median, IPR and IPRAS computed.[30]
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52 **Data analysis**

53 Median values, IPR and IPRAS were computed using SPSS version 20 (SPSS, Chicago, IL,
54 USA). Audio recordings were transcribed.
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57 **RESULTS**

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4 There was agreement on the appropriateness of 65% (31/48) of the original criteria at round
5 one, according to median panel ratings, and for all of the criteria according to the amount of
6 dispersion of panel ratings. Of criteria for which there was disagreement, 21% (10/48) were
7 retained after discussion and rewording, and 15% (7/48) were deleted. Two of the criteria for
8 which there was agreement were deleted after panel discussion, as they were addressed by
9 other criteria. In total 52% (25/48) of the criteria were reworded. This included criteria for
10 which agreement was reached. Twenty nine percent (14/48) of the criteria remained
11 unchanged. Two new criteria were added, resulting in a total of 41 validated criteria.
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16 Table 1 lists the median panel ratings, the amount of dispersion of panel ratings, and whether
17 there was agreement or disagreement for the original criteria and the validated criteria. It also
18 lists the amendments made by the panel to the original criteria, and the reasons for these
19 amendments. There was 100% agreement for both median panel ratings and dispersion of
20 panel ratings for the validated criteria. Table 2 contains the final list of validated criteria,
21 arranged according to disease states. Table 3 lists usage information judged to be necessary
22 for certain criteria.
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Criteria Number	Original prescribing appropriateness criteria for older (≥ 65 years) Australians	Rating by median method[30] (median value, A= agreement, D= disagreement), n=15		Rating by IPRAS method[30] (IPR value, IPRAS value, A = agreement, D = disagreement), n=15		Validated prescribing appropriateness criteria for older (≥ 65 years) Australians	Rating by median method[30] (median value, A= agreement, D= disagreement), n=12		Rating by IPRAS method[30] (IPR value, IPRAS value, A = agreement, D = disagreement), n=12		Amendment/reason
1.	Patient taking an antihypertensive is at their target blood pressure	7	A	1.00, 6.10	A	Patient taking an antihypertensive is at the target blood pressure appropriate for them	8	A	1.10, 7.52	A	“Appropriate for them” added. Current blood pressure guidelines may not be appropriate for all older patients[37-39]. For example, in the oldest old[40]; in palliative care; and for those who are/become hypotensive and/or fall[41,42]
2.	Patient at high risk of a cardiovascular event is taking a statin	7	A	1.00, 6.10	A	Patient at high risk of a recurrent cardiovascular event is taking a statin	8	A	1.00, 6.10	A	“Recurrent” added to ensure use in secondary prevention of cardiovascular events rather than primary prevention, where evidence is less clear, especially in the oldest old[24,43-47]
3.	Patient with IHD or a history of MI is taking a beta blocker	8	A	2.00, 6.85	A	Patient with CHD or a history of MI is taking a beta blocker	7	A	1.00, 6.10	A	“CHD” replaced “IHD”. The term “coronary heart disease” is preferred over “ischemic heart disease”
4.	Patient with IHD or a history of MI is taking an antiplatelet agent unless on an oral anticoagulant	8	A	1.00, 7.60	A	Patient with CHD or a history of MI is taking an antiplatelet agent unless on an oral anticoagulant	8	A	1.00, 7.60	A	“CHD” replaced “IHD”. The term “coronary heart disease” is preferred over “ischemic heart disease”
5	Patient with heart failure is taking a beta blocker	7	A	1.00, 6.10	A	Patient with stable heart failure with left systolic ventricular dysfunction (HF-	8	A	0.10, 6.78	A	Description of heart failure amended. The use of beta blockers is contra-indicated in

						LVSD) is taking a beta blocker					unstable heart failure. The optimal treatment of heart failure with preserved ejection fraction (HFPEF) is uncertain at this time[48 ,49]
6.	Patient with heart failure is taking an ACEI or A2A	8	A	2.00 6.85	A	Patient with stable heart failure with left systolic ventricular dysfunction (HF-LVSD) is taking an ACEI or A2A	9	A	1.00, 7.60	A	Description of heart failure amended. The optimal treatment of heart failure with preserved ejection fraction (HFPEF) is uncertain at this time[48 ,49]
7.	Patient with heart failure is NOT taking medications which may exacerbate heart failure	9	A	1.00, 7.60	A	Patient with HF-LVSD or HFPEF is NOT taking medications which may exacerbate heart failure	9	A	0.10, 8.27	A	Description of heart failure amended. The types of medicines contraindicated in HF-LVSD and HFPEF may not be identical[50 ,51]
8	Patient with heart failure or hypertension is NOT taking high sodium medications	8	D	2.20, 5.50	A	Deleted	-		-	-	High sodium medicines (among others) in heart failure are addressed by indicator 7. In hypertension, they are addressed as lifestyle modifications[52 ,53]
9.	Patient with AF is taking an oral anticoagulant	7	D	2.0, 5.35	A	Patient with AF is taking an oral anticoagulant or an antiplatelet agent, depending upon stroke risk and bleeding risk	8	A	0.10, 6.93	A	An antiplatelet agent may be appropriate for patients at low risk of stroke. Bleeding risk may determine choice of antithrombotic agent[39 ,54 ,55]
10.	Patient with AF taking an anticoagulant has an INR between 2 – 3	8	A	2.20, 6.70	A	Patient taking warfarin for AF has an INR between 2-3	9	A	1.00, 7.60	A	New anticoagulants like rivaroxaban and dabigatran do not require INR monitoring
11.	Patient with a history of non-hemorrhagic stroke or TIA is taking an antiplatelet agent unless on an anticoagulant	8	A	1.00, 7.60	A	Patient with a history of non-hemorrhagic stroke or TIA is taking an antiplatelet agent unless on an anticoagulant	9	A	1.00, 7.60	A	No change
12.	Patient with risk factors for myopathy is NOT taking	7	D	3.00, 4.60	A	Patient with risk factors for statin induced myopathy is	8	A	1.10, 7.52	A	The use of all high dose high potency statins together with

	40mg or more per day of simvastatin or atorvastatin					not taking a high dose of a high potency statin					risk factors may increase the likelihood of myopathy[39 ,56 ,57]
13.	Patient with cardiovascular disease is NOT taking an NSAID	7	A	1.20, 5.95	A	Patient with cardiovascular disease is NOT taking an NSAID	8	A	1.10, 6.18	A	No change
14.	Patient with cardiovascular, respiratory disease or diabetes who smokes has been offered smoking cessation therapy	9	A	0.00, 8.35	A	Patient with cardiovascular, respiratory disease or diabetes who smokes has been offered smoking cessation options	9	A	0.00, 8.35	A	“Therapy” implies pharmacotherapy, whereas repeated counselling/psychotherapy may be preferred to avoid the risks associated with polypharmacy
15.	Patient with type 2 diabetes and hypertension and albuminuria is taking an ACEI or A2A	8	A	2.00, 6.85	A	Patient with type 2 diabetes and hypertension and albuminuria is taking an ACEI or A2A	9	A	1.00, 7.60	A	No change.
16.	Patient with diabetes at high risk of a cardiovascular event is taking an antiplatelet agent unless on an anticoagulant	7	D	2.20, 5.50	A	Patient with diabetes at high risk of a cardiovascular event is taking an antiplatelet agent unless on an anticoagulant	9	A	1.00, 7.60	A	No change
17.	Patient with diabetes is NOT taking a medication which may increase or decrease blood glucose concentrations	5	D	2.20, 3.70	A	Patient with diabetes receiving medications that may affect glycemic control is having regular monitoring of blood glucose concentrations	9	A	1.00, 7.60	A	Increased awareness and monitoring may require adjustment of hypoglycemic medication doses, depending upon the need to continue interacting medicines. For example, commencement of oral corticosteroids may worsen diabetes control[35]
18.	Patient with diabetes has had an HbA1c measurement within the previous 6 months	8	A	1.20, 7.45	A	Patient with diabetes has had an HbA1c measurement within the previous 6 months	8	A	1.00, 7.60	A	No change
19.	Patient taking metformin for diabetes has had the dose adjusted for	8	A	1.20, 7.45	A	Patient taking metformin for diabetes has had the dose adjusted for renal function	9	A	1.00, 7.60	A	Creatinine clearance may represent only one of the methods used to determine

	creatinine clearance										renal function
20.	Patient taking metformin for diabetes is NOT concurrently taking glibenclamide	6	D	2.40, 3.85	A	Deleted	-		-	-	Glibenclamide is an uncommonly used hypoglycaemic
21.	Patient with OA pain interfering with daily activities has been trialled on paracetamol 2 – 4 g per day	8	A	2.00, 6.85	A	Patient with OA pain interfering with daily activities has been trialled on regular paracetamol 2 – 4 g per day	9	A	0.40, 8.05	A	“Regular” paracetamol added to improve quality of indicator
22.	Patient taking analgesic(s) does NOT have pain that interferes with daily activities	7	D	3.2, 4.75	A	Patient taking analgesic(s) has had the dose(s) titrated in order to avoid pain that interferes with daily activities	8	A	2.00, 6.85	A	Indicator rephrased to improve clarity
23.	Patient taking an opioid is on prophylactic treatment for constipation	8	A	2.00, 6.85	A	Patient taking a regular opioid is on prophylactic treatment for constipation	9	A	1.00, 7.60	A	“Regular” use added as “when required” use may not always require prophylactic treatment
24.	Patient with risk factors for impaired renal function is NOT taking an NSAID	8	A	1.00, 7.60	A	Patient with risk factors for impaired renal function is NOT taking an NSAID	8	A	1.00, 7.60	A	No change
25.	Patient is NOT concurrently taking an ACEI or A2A, diuretic and NSAID (excluding low dose aspirin)	9	A	1.00, 7.60	A	Patient is NOT concurrently taking an ACEI or A2A, diuretic and NSAID (excluding low dose aspirin)	9	A	1.00, 7.60	A	No change
26.	Patient with sleep disturbance or anxiety has NOT been taking benzodiazepines for > 4 weeks	8	A	1.20, 7.45	A	Patient has NOT been taking benzodiazepines for > 4 weeks	9	A	1.00, 7.60	A	“Sleep disturbance or anxiety” deleted. Benzodiazepines increase the risk of oversedation, ataxia, confusion, falls, respiratory depression and short-term memory impairment, and are recommended for short term use only[35].
27.	Patient with depression is NOT taking	7	7, D	1.00, 4.60	A	Deleted	-		-	-	The issue of anticholinergic burden is addressed by

	anticholinergic type antidepressants										indicator 32
28.	Patient with a history of falls is NOT taking psychotropic medications	8	A	1.00, 6.10	A	Patient with a history of falls is NOT taking psychotropic medications	8	A	1.40, 6.40	A	No change
29.	Patient taking an SSRI is NOT concurrently taking medications known to increase the risk of GI bleeding	7	D	2.20, 5.20	A	Deleted	-		-	-	Redundant indicator. This issue would be identified by indicator 47.
30.	Patient taking an SSRI is NOT concurrently taking other medications that may contribute to serotonin toxicity	8	A	2.20, 6.70	A	Patient taking an SSRI is NOT concurrently taking other medications that may contribute to serotonin toxicity	8	A	1.40, 6.40	A	No change. Retained by panel due to its potential significance, despite the use of indicator 47
31.	Patient with dementia is NOT receiving anticholinergic medication	8	A	1.20, 7.45	A	Patient with dementia is NOT receiving anticholinergic medication	8	A	1.00, 7.60	A	No change
32.	Patient is NOT taking more than one medication with anticholinergic activity	8	A	0.2, 6.70	A	Patient is not taking medication with SIGNIFICANT anticholinergic activity	8	A	0.40, 7.15	A	Rewording focuses on the issue of anticholinergic burden
33.	Patient taking a PPI is NOT taking a medication that may cause dyspepsia	7	D	3.20, 4.45	A	Patient taking a PPI is NOT taking a medication that may cause dyspepsia unless prescribed for gastroprotection	8	A	0.40, 7.15	A	“Unless prescribed for gastroprotection” added to improve the accuracy of the indicator
34.	Patient with COPD is NOT taking benzodiazepines	7	D	3.00, 6.10	A	Patient with COPD is NOT taking benzodiazepines	8	A	1.00, 6.10	A	No change
35.	Patient with asthma using an inhaled LABA is also using an inhaled corticosteroid	9	A	0.20, 8.20	A	Patient with asthma using an inhaled LABA is also using an inhaled corticosteroid	9	A	1.00, 7.60	A	No change
36.	Patient using salbutamol or terbutaline inhaler more	9	A	1.00, 7.60	A	Patient using salbutamol or terbutaline inhaler more than	9	A	0.40, 8.05	A	“Except for exercise-induced asthma” added to improve the

	than 3 times per week for reversible airways disease has been prescribed an ICS					3 times per week for reversible airways disease has been prescribed an ICS (except for exercise-induced asthma)					accuracy of the indicator
37.	Patient with asthma is NOT taking a medication that may worsen asthma	7	A	1.20, 6.25	A	Patient with asthma is NOT taking a medication that may worsen asthma	8	A	1.00, 7.60	A	No change
38.	Female patient with recurrent UTIs has been prescribed intravaginal estrogen	5	D	2.00, 3.85	A	Deleted	-		-	-	Evidence for this indicator was judged to be poor[58]
39.	Patient with a creatinine clearance < 60 ml/min is NOT receiving nitrofurantoin for UTI	8	A	2.00, 6.85	A	Patient with a UTI is not receiving nitrofurantoin or hexamine for prophylaxis or acute treatment	8	A	1.00, 7.60	A	Hexamine and nitrofurantoin are not recommended for the prophylactic or acute treatment of UTI in older patients[35 ,39]
40.	Patient with a creatinine clearance < 50ml/min is NOT receiving hexamine for UTI prophylaxis	8	A	1.20, 6.25	A	Deleted	-	-	-	-	Hexamine and are not recommended for the prophylactic treatment of UTI in older patients[35 ,39].
41.	Patient with an URTI is NOT receiving antibiotics	7	7, D	3.00, 4.60	A	Patient with a non-specific URTI is NOT receiving antibiotics	8	A	1.00, 7.60	A	“non-specific” added to improve the accuracy of the indicator
42.	Patient with osteoporosis who is not receiving at least 600 IU Vitamin D daily from dietary sources is receiving supplementation with vitamin D	8	D	3.20, 4.75	A	Deleted	-		-	-	This indicator is covered by indicator 44 and an expanded footnote
43.	Patient with osteoporosis who is not receiving at least 1200 mg of calcium daily from dietary sources is receiving calcium	8	A	1.60, 5.95	A	Deleted	-		-	-	This indicator is covered by indicator 44 and an expanded footnote

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	supplementation										
44.	Patient with osteoporosis is receiving anti-osteoporotic medication	7	A	1.00, 6.10	A	Patient with osteoporosis is receiving appropriate anti-osteoporotic medication	8	A	0.40, 7.15	A	“Appropriate” added and an expanded footnote to include calcium and vitamin D
45.	Patient using topical corticosteroids does NOT have itch or discomfort that interferes with daily activities	6	D	2.00, 5.35	A	Patient using topical corticosteroids for contact or allergic dermatitis does not have itch or discomfort that interferes with daily activities	-		-	-	This indicator was deleted by the panel because there was no identification of the diagnosis/condition being treated. However, contact and allergic dermatitis is one of the top 40 most frequently managed problems by general practitioners in patients ≥ 65 years old in Australia,[32] so this indicator was re-worded by the authors
46.	Patient has received influenza and pneumococcal vaccination	9	A	1.00, 7.60	A	Patient has received influenza and pneumococcal vaccination	9	A	0.00, 8.35	A	No change
47.	Patient has no <i>significant</i> medication interactions (agreement between two medication interaction databases)	8	D	3.00, 6.10	A	Patient has no <i>clinically significant</i> medication interactions (agreement between two medication interaction databases)	8	A	0.40, 7.15	A	“Clinically” added to improve the accuracy of the indicator
48.	Patient has had no <i>significant</i> change in medications in the previous 90 days	5	D	1.20, 3.25	A	Deleted	-		-	-	It was preferred to transfer this information to the explanatory text of the article
New						Patient taking thyroid hormone replacement therapy has had a serum TSH measurement within the previous 12 months					Thyroid disease is a common medical condition managed by GPs in older Australians[32,59]
New						Patient with coronary heart disease is taking an ACEI or A2A					ACEIs or A2As reduce the risk of cardiovascular events[60,61]. However, a high incidence of comorbid disease

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Criteria No.	Validated criteria
1	Patient taking an antihypertensive is at the target blood pressure appropriate for them*
2	Patient at high risk of a recurrent cardiovascular event is taking a statin*
3	Patient with CHD or a history of MI is taking a beta blocker
4	Patient with CHD or a history of MI is taking an antiplatelet agent unless taking an oral anticoagulant*
5	Patient with CHD is taking an ACEI or A2A*
6	Patient with stable heart failure with HF-LVSD is taking a beta blocker
7	Patient with stable heart failure with HF-LVSD is taking an ACEI or A2A*
8	Patient with HF-LVSD or HFPEF is NOT taking medications which may exacerbate heart failure
9	Patient with AF is taking an oral anticoagulant or an antiplatelet agent, depending upon stroke risk and bleeding risk*
10	Patient taking warfarin for AF has an INR between 2-3
11	Patient with a history of non-hemorrhagic stroke or TIA is taking an antiplatelet agent unless taking an anticoagulant
12	Patient with risk factors for statin induced myopathy is not taking a high dose of a high potency statin*
13	Patient with cardiovascular disease is NOT taking an NSAID
14	Patient with cardiovascular, respiratory disease or diabetes who smokes has been offered smoking cessation options*
15	Patient with type 2 diabetes and hypertension and albuminuria is taking an ACEI or A2A
16	Patient with diabetes at high risk of a cardiovascular event is taking an antiplatelet agent unless on an anticoagulant
17	Patient with diabetes taking medications that may affect glycemic control is receiving regular monitoring of blood glucose concentrations*
18	Patient with diabetes has had an HbA1c measurement within the previous 6 months*
19	Patient taking metformin for diabetes has had the dose adjusted for renal function*
20	Patient taking thyroid hormone replacement therapy has had a serum TSH measurement within the previous 12 months
21	Patient with OA pain interfering with daily activities has been trialled on regular paracetamol 2 – 4 g per day
22	Patient taking analgesic(s) has had the dose(s) titrated in order to avoid pain that interferes with daily activities
23	Patient taking a regular opioid is on prophylactic treatment for constipation
24	Patient with risk factors for impaired renal function is NOT taking an NSAID*
25	Patient is NOT concurrently taking an ACEI or A2A, diuretic and NSAID (excluding low dose aspirin)
26	Patient has NOT been taking benzodiazepines for > 4 weeks*
27	Patient with a history of falls is NOT taking psychotropic medications*
28	Patient taking an SSRI is NOT concurrently taking other medications that may contribute to serotonin toxicity*
29	Patient with dementia is NOT receiving anticholinergic medication*
30	Patient is not taking medication with SIGNIFICANT anticholinergic activity*
31	Patient taking a PPI is NOT taking a medication that may cause dyspepsia unless prescribed for gastroprotection*
32	Patient with COPD is NOT taking benzodiazepines
33	Patient with asthma using an inhaled LABA is also using an inhaled corticosteroid
34	Patient using salbutamol or terbutaline inhaler more than 3 times per week for reversible airways disease has been prescribed an ICS (except for exercise-induced asthma)
35	Patient with asthma is NOT taking a medication that may worsen asthma*
36	Patient with a UTI is not receiving nitrofurantoin or hexamine for prophylaxis or acute treatment
37	Patient with a non-specific URTI is NOT receiving antibiotics*
38	Patient with osteoporosis is receiving appropriate anti-osteoporotic medication*

39	Patient has received influenza and pneumococcal vaccination
40	Patient using topical corticosteroids for contact or allergic dermatitis does not have itch or discomfort that interferes with daily activities
41	Patient has no <i>clinically significant</i> medication interactions (agreement between two medication interaction databases)*

a – These criteria are intended to be used by appropriately trained and qualified health professionals, as a tool to assist in making medication management decisions as part of the medication review process

b – Prior to the commencement of any medication, the contraindications and precautions for that medication should be considered

c – The intended result of using these criteria is the reasonable and appropriate medication management of individual patients, rather than the systematic application of these criteria to all patients irrespective of other considerations

A2A = angiotensin 2 receptor antagonist, ACEI = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, CHD = coronary heart disease, COPD = chronic obstructive pulmonary disease, HbA1c = glycosylated haemoglobin, HF-LVSD = Heart failure with left ventricular systolic dysfunction, HFPEF = heart failure with preserved ejection fraction, ICS = inhaled corticosteroid, INR = international normalised ratio, MI = myocardial infarct, LABA = long acting beta agonist, NSAID = non-steroidal anti-inflammatory drug, PPI = proton pump inhibitor, SSRI = selective serotonin reuptake inhibitor, TIA = transient ischemic attack, TSH = thyroid stimulating hormone, UTI = urinary tract infection.

Criteria No.	Description of issue	Details
1	Blood pressure targets (mm Hg)	Proteinuria >1 g/day (with or without diabetes) < 125/75. CHD, diabetes, chronic kidney disease, proteinuria (> 300mg/day), stroke or TIA < 130/80. Others <140/90[35] Current blood pressure guidelines may not be appropriate for all older patients, such as the oldest old; in palliative care; and for those who are/become hypotensive and/or fall[37 ,39-42 ,63]
2	Patients at high risk of a cardiovascular event (> 15% within the next 5 years)	Age > 75 years; history of diabetes, moderate or severe chronic kidney disease (persistent proteinuria, GFR < 60ml/min, eGFR < 45 ml/min/1.73m ²), hypercholesterolemia (familial, TC > 7.5 mmol/L), SBP ≥ 180 or DBP ≥ 110 mmHg, ISH (SBP ≥160 and DBP ≤70 mmHg), coronary heart disease, stroke, TIA, PAD, heart failure, aortic disease, LVH, family history of premature CVD.[35 ,64] The benefits of statins and risks of adverse effects are uncertain towards the end of life[65]
4	Antiplatelet agents and oral anticoagulants	Antiplatelet agents – aspirin, clopidogrel, dipyridamole, ticlopidine. Oral anticoagulants – dabigatran, phenindione, rivaroxaban, warfarin
5	Use of ACEI or A2A in CHD	A high incidence of comorbid disease in CHD (typically arthritis and/or respiratory disease) or other clinical factors (e.g. dizziness or falls, cognitive impairment, use of > 5 medicines, patient preference) may be considerations in determining medication prescribing priorities[21 ,25 ,62]
7	Medications that may exacerbate heart failure	HF-LVSD – anti-arrhythmic medicines (except for heart failure-specific beta-blockers and amiodarone), non-dihydropyridine calcium-channel blockers (e.g. verapamil or diltiazem), clozapine, corticosteroids, NSAIDs (excluding low dose aspirin), thiazolidinediones, TNF-alpha inhibitors, topical beta blockers (when added to systemic beta blockers), tricyclic antidepressants[39 ,66 ,67]. HFPEF – venodilators (e.g. isosorbide dinitrate), potent arterial

		vasodilators (e.g. hydralazine), digoxin (unless AF), excessive use of diuretics. Note: verapamil and diltiazem may improve diastolic function in HFPEF[50]
9	Stroke risk and bleeding risk	Stroke risk can be calculated using CHADS ₂ or CHA ₂ DS ₂ -VASc.[68] Risk factors for coumarin-related bleeding complications: advanced age, uncontrolled hypertension, history of MI or IHD, cerebrovascular disease, anaemia or a history of bleeding, concomitant use of aspirin/polypharmacy[69]
12	Risk factors for statin myopathy; high dose of high potency statins	Age > 70 years, presence of disease states (diabetes, hypothyroidism, renal and hepatic disease), concurrent use of cyclosporin, fibrates, CYP3A4 inhibitors (e.g. diltiazem, macrolides, protease inhibitors, verapamil [except for pravastatin and rosuvastatin], severe intercurrent illness (infection, trauma, metabolic disorder), dose ≥ 40 mg daily. High dose of high potency statins ; ≥ 40 mg atorvastatin or simvastatin; > 10mg rosuvastatin [35 ,70]
14	Smoking cessation options	Counselling (extended, brief, telephone), support services (professional, family, social, work), pharmacotherapy.
17	Medications that may affect glycemic control	Increase blood glucose: baclofen, clozapine, cyclosporin, glucocorticoids, haloperidol, olanzapine, paliperidone, phenytoin, protease inhibitors, quetiapine, risperidone, sirolimus, tacrolimus, and tricyclic antidepressants. Decrease blood glucose: excessive alcohol, disopyramide, perhexiline, quinine, trimethoprim/sulphamethoxazole[35]
18	Six monthly HbA1c measurements	Treatment intensification in response to less than optimally controlled HbA1c may be inappropriate in patients with limited life expectancy or in frail older patients[71 ,72]
19	Metformin dose	Based on creatinine clearance: 60-90 ml/min, maximum 2g daily; 30-60 ml/min, maximum 1g daily; < 30 ml/min avoid use.[35] Based on eGFR: Review dose if eGFR< 45 ml/min/1.73m ² ; avoid if eGFR<30 ml/min/1.73m ² [73]
24	Risk factors for impaired renal function	Volume depletion, age > 60 years, salt-restricted diet, concomitant use of ACEIs, A2As, cyclosporin or aspirin, GFR ≤ 60 ml/min, cirrhosis, heart failure[74]
26	Benzodiazepine use	Benzodiazepines increase the risk of oversedation, ataxia, confusion, falls, respiratory depression and short-term memory impairment, and are recommended for short term use only.[35]
27	Falls and psychotropic medications	Psychotropic medications = antidepressants (all), anxiolytics/hypnotics, antipsychotics.[75 ,76] Medications causing (postural) hypotension (e.g. cardiovascular medicines) or cognitive impairment (e.g. opioids) may also increase the risk of falls[39 ,77]
28	Medications that may contribute to serotonin syndrome	Antidepressants - desvenlafaxine, duloxetine, St John's wort, MAOIs (including moclobemide), SSRIs, TCAs, venlafaxine. Opioids - dextromethorphan, fentanyl, pethidine, tramadol. Others - selegiline, linezolid, lithium, tryptophan[35]
29 and 30	Medications with significant anticholinergic activity	amantadine, amitriptyline, atropine*, belladonna alkaloids*, benzhexol, benzotropine, biperiden, brompheniramine*, chlorpheniramine, chlorpromazine, clomipramine, clozapine, cyclizine, cyclopentolate, cyproheptadine*, darifenacin, dexchlorpheniramine*, dimenhydrinate*, diphenhydramine*, disopyramide, dothiepin, doxepin, glycopyrrolate,

		homatropine, hyoscine* (butylbromide or hydrobromide), imipramine, ipratropium (nebulised), mianserin, nortriptyline, olanzapine, orphenadrine, oxybutynin, pericyazine, pheniramine*, pimozone, pizotifen, prochlorperazine, promethazine*, propantheline, solifenacin, tiotropium, tolterodine, trimeprazine*, trimipramine, triprolidine*, tropicamide (* available over-the-counter in Australia)[35]
31	Medications that may cause dyspepsia	Drugs with anticholinergic effects, aspirin, benzodiazepines, bisphosphonates, calcium channel antagonists, oral corticosteroids, dopaminergic drugs, doxycycline, erythromycin, ferrous sulphate, nitrates, NSAIDs, potassium chloride (slow release)[34 ,35 ,39 ,78]
35	Medications that may worsen asthma	Aspirin, beta blockers (including eye drops), carbamazepine, echinacea, NSAIDs, royal jelly[35 ,79]
38	Non-specific URTI	Acute bronchitis, pharyngitis, tonsillitis, nonsuppurative otitis media and sinusitis[34]
39	Appropriate anti-osteoporotic medication	Recommended daily intake (RDI) of calcium from dietary sources and/or supplements = 1300-1500 mg daily. RDI for Vitamin D from sunlight and/or dietary sources and/or supplements = 600 iu daily. Anti-osteoporotic medication = bisphosphonates, calcitriol, denosumab, HRT, raloxifene, strontium, teriparatide.[35] Evidence for fracture risk reduction in women ≥ 75 years is either absent or lacking in NVF for alendronate, risedronate and teriparatide, and in HF for alendronate, risedronate, zoledronic acid and teriparatide. There is no data available for denosumab in VF, NVF or HF.[80] The optimal duration of bisphosphonate therapy is uncertain. Evidence supports the use of strontium for 5 years, raloxifene for 4 years, zoledronic acid and denosumab for 3 years. Exposure to teriparatide should be limited to 18 months.[81] Data are limited for non-ambulatory patients and those with significant comorbidities.[82] It should be noted that bone strength is only one of many determinants of fracture risk.[83]
42	Clinically significant medication interactions	Medication interactions that may interfere with the outcome of therapy

A2A = angiotensin 2 receptor antagonist, ACE = angiotensin converting enzyme, ACEI = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, CHADS₂ = Cardiac failure, Hypertension, Age, Diabetes, Stroke [doubled], CHA₂DS₂-VASc = Cardiac failure or dysfunction, Hypertension, Age over 75 years [doubled], Diabetes, Stroke [doubled], Vascular disease, Age 65-74 years, Sex category [female], CHD = coronary heart disease, CVD = cardiovascular disease, DBP = diastolic blood pressure, GFR = glomerular filtration rate, HF = hip fracture, HF-LVSD = Heart failure with left ventricular systolic dysfunction, HFPEF = heart failure with preserved ejection fraction, HRT = hormone replacement therapy, IHD = ischemic heart disease, ISH = isolated systolic hypertension, LVH = left ventricular hypertrophy, MAOI = monoamine oxidase inhibitor, MI = myocardial infarct, NSAID = non-steroidal anti-inflammatory drug, NVF = non-vertebral fracture, PAD = peripheral arterial disease, SBP = systolic blood pressure, SSRI = selective serotonin reuptake inhibitor, TC = total cholesterol, TCA = tricyclic antidepressant, TIA = transient ischemic attack, TNF = tumour necrosis factor, URTI = upper respiratory tract infection, VF = vertebral fracture

DISCUSSION

This study identified a panel of medication management experts to discuss and validate a set of 41 prescribing appropriateness criteria for commonly used medicines and medical conditions in older (≥ 65 years) Australians. Panel discussion resulted in retention of 81%

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3 (39/48) of the originally proposed criteria, with a little over half (25/48) being reworded.
4 These criteria do not simply represent a list of medications to avoid in the elderly, but also
5 address issues such as the need for additional therapy (e.g. criteria 23 and 34, table 2),
6 additional tests (e.g. criteria 18-20, table 2), ineffective treatment (e.g. criteria 22 and 37,
7 table 2) and medication monitoring (e.g. criteria 10 and 20, table 2). Due to its currency and
8 the nature of its development, we expect these criteria to make a significant contribution to
9 the detection of DRPs in the Australian healthcare environment.
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12 13 **Prescribing appropriateness lists in Australia**

14 Despite a desire in Australia to develop decision support tools to improve healthcare
15 quality,[84] progress has consisted of the development of a limited number of non-age
16 specific structure and process indicator lists for use in hospitals and general practice.[36 ,85
17 ,86] These lists, like many others, [23 ,87 ,88], require updating. Currently, there is no
18 Australian prescribing appropriateness criteria list to assist in improving medication
19 management in older people. The usefulness of such an approach has been acknowledged,
20 together with other approaches such as medication review.[89]
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24 25 **Co-morbidity**

26 Over 80% of older Australians have three or more chronic conditions.[90] Co-morbidity is
27 associated with poor quality of life, physical disability, high health care use, multiple
28 medicines with consequent increased risk of adverse drug events, and increased
29 mortality.[91] Yet most Australian guidelines for chronic diseases do not modify or discuss
30 the applicability of their recommendations to older patients with multiple comorbid
31 conditions. [25] This situation is not restricted to Australia. [92]Because the risk of harm in
32 older patients increases in proportion to the number of treatments prescribed, prioritization of
33 therapeutic goals is necessary. This may run counter to recommendations of disease-specific,
34 evidence-based guidelines.[25] Addition of our criteria with its associated usage information
35 to the implicit processes of the Australian medication review process, may assist in
36 addressing this problem.
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41 42 **The RAND/UCLA appropriateness method**

43 We chose the RAND/UCLA appropriateness method, a two-round modified Delphi
44 method[30] to select the most appropriate criteria. Unlike the Delphi method, which generally
45 involves multiple questionnaire-driven rounds to obtain convergence of opinion, the RAND
46 method involves an initial individual rating round, and a second face-to-face round. This
47 method has been shown to produce results that have face, construct and predictive
48 validity.[93 ,94] Systematically combining available evidence with expert opinion can create
49 quality criteria where best evidence may be lacking.[95]
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53 While most lists of prescribing criteria are based on expert consensus, this has often been
54 achieved through mail surveys rather than face-to-face meetings.[23 ,28 ,29] Although face-
55 to-face meetings restrict panel size, they allow discussion to resolve misinterpretations,
56 introduce new evidence, and improve clarity of criteria between rating rounds. We ensured
57 our panel comprised different specialities, as less disagreement has been found among same-
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3 speciality panels.[96] We addressed concern regarding potential intimidation due to dominant
4 panel personalities by choosing a moderator experienced in the development of these criteria
5 and in facilitating small group discussion. Diversity of medication and disease management
6 issues may have minimized professional, but not personal, conflict-of-interest issues. We
7 used both the median panel rating and the amount of dispersion of panel ratings to identify
8 agreement or disagreement. While it has been acknowledged that discrepancies between the
9 two methods may occur,[30] discussion and second round rating resulted in agreement for all
10 criteria for both methods.
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13 14 **The nature of decision support tools**

15 Panel members emphasized that criteria may not provide definitive answers, instead
16 indicating potential problems that might need addressing, due to a perceived unacceptable
17 variation in care.[97] While performance indicators are designed to measure the result of
18 statements made in clinical practice guidelines, these guidelines often provide
19 recommendations for care independent of other considerations such as multiple co-
20 morbidities, advanced age, frailty, patient preferences, disease burden or limited life
21 expectancy.[98-100] In such cases, less stringent goals, deprescribing or non-prescription
22 may be more appropriate.[13 ,71 ,101] For example, a frail older patient with multiple co-
23 morbidities and one or more functional impairments may have a life expectancy of
24 approximately two years or less.[65] This raises the question of whether failure to intensify
25 treatment[71] or to underuse evidence-based therapies[102] reflects appropriate clinical
26 judgement or an inappropriate care gap. The panel felt strongly that use of indicators,
27 guidelines or criteria providing clinical decision support should never replace critical thinking
28 in patient care.[103]
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37 **Strengths and weaknesses**

38 We have followed a recommended approach [84] by suggesting criteria for which high
39 quality evidence exists linking best practice with improved outcomes; where there are
40 established evidence-practice gaps[104 ,105]; and where the health conditions impose the
41 greatest burden on the healthcare system. We used a validated consensus method, an expert
42 panel of varied specialization, and criteria written with the aim of conciseness and clarity.
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45 In addition to face and content validity, these validated criteria, much like performance
46 indicators, will require further developmental work to provide evidence of their acceptability,
47 operational feasibility, reliability, and degree of predictive validity.[28 ,97] Some of this
48 work has already commenced with the original criteria.[106] Further, these criteria only
49 cover commonly occurring medicines and medical conditions. In addition, judgements made
50 by an expert panel may not be representative of all health care professionals.
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54 **Intended use**

55 These validated criteria are intended for use by health care providers to enhance the quality of
56 the Australian medication review process, for quality improvement, educational purposes and
57 internal audit. They are also intended for external quality assessment, such as use by policy
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3 makers and for public reporting. Stakeholder involvement will be critical to facilitate local
4 uptake and encourage further research into the effects on health outcomes.[89]
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7 CONCLUSION

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9 This study validated 41 prescribing appropriateness criteria to assist in identifying DRPs in
10 older (≥ 65 years) Australians. These criteria are intended to represent an addition to the
11 medication management skill set that includes consideration of limited life expectancy,
12 evidence base in the oldest old, drug burden and care coordination, patient and care-giver
13 education, empowerment for self management, and shared decision making. These skills are
14 far from a “do everything for everyone” philosophy, where aggressive treatment may
15 encourage more care, not more appropriate care.[22 ,99] Despite the presence of clinical
16 decision support tools, health care providers need to know how to think about clinical
17 problems, not just what to think.[103]
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22 **Competing interests** None declared
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25 drafted the manuscript. TFC and RJM made substantial contributions to the conception,
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3-4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3-4
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4
		(b) Describe any methods used to examine subgroups and interactions	N/A
		(c) Explain how missing data were addressed	N/A
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	4
Outcome data	15*	Report numbers of outcome events or summary measures over time	5
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	17-18
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	18-19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.



Validation of prescribing appropriateness criteria for older Australians using the RAND/UCLA Appropriateness Method

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Keywords:	drug-related problems, prescribing criteria, older patients, inappropriate drug use

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Validation of prescribing appropriateness criteria for older Australians using the RAND/UCLA Appropriateness Method

ARTICLE SUMMARY

Article focus

- Drug-related problems (DRPs) are common in older people, resulting in under-treatment with proven medicines, and disproportionately high numbers of adverse drug events
- The aim of this study was to validate a list of prescribing appropriateness criteria for use in older people

Key messages

- The use of medication assessment criteria is one method to assist in identifying DRPs. Criteria developed elsewhere may have little or no applicability to the Australian healthcare environment
- Validation of proposed Australian prescribing appropriateness criteria for older people was accomplished using a two-round modified Delphi method, resulting in agreement for all criteria as measured by median panel ratings, and the amount of dispersion of panel ratings, based on the interpercentile range
- Use of these criteria, together with other Australian medication review processes, may assist in improving patient care in a variety of settings by efficiently identifying DRPs to common medical conditions and commonly used medicines, and in. They may also contribute to the medication management education knowledge of health care professionals through education programs and by use in daily practice, and for the evaluation of the quality of pharmaceutical care in older people

Strengths and limitations

- A validated consensus method was used involving an expert medication management panel of varied specialization. Criteria were based on established evidence-practice gaps and degree of disease burden imposed on the health care system, and were written with the aim of conciseness and clarity
- Further developmental work is required to assess the usefulness of these criteria, which only included commonly occurring medicines and medical conditions

ABSTRACT

Objective: To update and validate proposed national prescribing appropriateness criteria to assist in identifying drug-related problems (DRPs) to commonly occurring medications and medical conditions in older (≥ 65 years old) Australians.

Design: Rand/UCLA Appropriateness Method

Participants: A panel of medication management experts were identified consisting of geriatricians, clinical pharmacists, and disease management advisors to organisations that

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3 produce Australian evidence-based therapeutic publications. This resulted in a round one
4 panel of fifteen members, and a round two panel of twelve members

5 **Main outcome measure:** Agreement on all criteria

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7 **Results:** Forty eight prescribing criteria were rated. In the first rating round via email, there
8 was disagreement regarding ~~35% (17/48)~~ 17 of the criteria according to median panel ratings.
9 During a face-to-face second round meeting, discussion resulted in ~~81% (39/48)~~ of the
10 proposed criteria being accepted, with ~~52% (25/48 of 48 criteria)~~ requiring amendment or
11 updating. ~~Twenty nine per cent (14/48 criteria)~~ Fourteen were unchanged, and ~~19% (9/48~~
12 ~~)criteria~~ deleted. Two new criteria were added, resulting in a final validated list of 41
13 prescribing appropriateness criteria. Agreement was reached for all 41 criteria, measured by
14 median panel ratings and the amount of dispersion of panel ratings, based on the
15 interpercentile range
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18 **Conclusions:** A set of 41 Australian prescribing appropriateness criteria were validated by an
19 expert panel. Use of these criteria, together with clinical judgement and other medication
20 review processes such as patient interview, is intended to assist in improving patient care by
21 efficiently detecting potential DRPs related to commonly occurring medicines and medical
22 conditions in older Australians. These criteria may also contribute to the medication
23 management education of health care professionals
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27 INTRODUCTION

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29 Drug-related problems (DRPs) in older people (≥ 65 years old) are common,[1-4] resulting in
30 both undertreatment with proven medicines[5-7] and disproportionately high numbers of
31 serious adverse medication events due to polypharmacy.[8-10] DRPs can occur for many
32 reasons such as inadequate monitoring of medicines, poor medicine or dose selection,
33 duplication of medicines, or factors to do with the way the patient uses the medicine.[2 ,3 ,11
34 ,12] -Methods to identify and reduce DRPs include educational interventions, [13]
35 comprehensive geriatric assessment, [14] discontinuation of multiple medications, [15
36 ,16]electronic health record clinical decision support, [17 ,18]and the use of medication
37 assessment criteria.[13 ,19-22]
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42 However in older patients, the importance of traditional outcomes, such as discrete clinical
43 events or mortality, may be secondary to maintaining physical and cognitive function or relief
44 of symptoms.[23] Because of this, optimal care requires clinical decision support tools that
45 consider issues such as patient preferences, frailty, cost, and co-morbidities.[24] Additionally,
46 few criteria target the oldest old;[25] (generally regarded as people older than 85 years),
47 where evidence may be poor, and preventive interventions may be encouraged in patients
48 who have already exceeded an average lifespan.[26 ,27] -In Australia, issues such as these are
49 intended to be considered when patients are interviewed by an accredited pharmacist as part
50 of the Home Medicines Review program.[28] This program aims to provide the
51 sophistication lacking in explicit (that is, criterion-based rather than implicit or judgement
52 based) criteria measures such as our criteria list, and is targeted towards patients who may be
53 (among other reasons) currently taking ≥ 5 regular medicines, attending a number of different
54 doctors, or have recently been discharged from hospital.
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4 In 2008, we proposed a list of 48 prescribing appropriateness criteria (45 explicit and three
5 implicit) aimed at improving detection of -DRPs, ~~to be used~~ as part of the Australian
6 medication review process.[29] When applied to a cohort of older Australians, a high
7 incidence of undertreatment and use of inappropriate medicines was detected.[30] It was also
8 intended that our criteria have application in other areas, as criteria derived outside Australia
9 have been applied in a variety of settings such as community, nursing home and hospital.[19]
10 and have been applied using a variety of study designs such as in retrospective cross-sectional
11 studies, randomized controlled trials, and in retrospective and prospective case series.[13]
12 They have been used in daily clinical practice;[31] in the evaluation of health plans[31] and in
13 the evaluation of knowledge of appropriate prescribing;[32] in the training of health care
14 professionals;[33] to evaluate nursing home adherence to medicine-related regulations;[33]
15 and to develop healthcare quality indicators.[34]

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21 The appropriateness of health care delivery in Australia for common conditions, such as atrial
22 fibrillation and osteoarthritis, has been shown to be poor.[35] ~~These~~ Our criteria were based
23 on the most frequent ~~medications~~ medicines prescribed to Australians, and the most frequent
24 medical conditions for which older Australians (≥ 65 years old) consult medical practitioners.
25 Australian medication and disease state resources and guidelines were used to provide
26 content validity.[29] However, unlike our criteria, other prescribing criteria or tools have
27 combined evidence with expert opinion to provide face validity.[36 ,37]

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31 The aim of this study was to update our list of criteria. We wished to add missing
32 recommendations; adding recommendations for co-morbidity and for the oldest old, where
33 possible, and to validate the criteria through expert consensus. To do this, we identified a
34 panel of medication management experts, and chose the RAND/UCLA appropriateness
35 method,[38] which has been described as the best method for systematically combining
36 recommendations from clinical guidelines, with the opinion of healthcare providers.[39]

37 38 39 40 **METHODS**

41 42 **Ethics**

43 Ethics approval was obtained from the Human Research Ethics Committee of the University
44 of Sydney.

45 46 47 **Criteria development**

48 In 2008, ~~we cross-referenced~~ we found the fifty 50 highest-volume Australian
49 Pharmaceutical Benefits Scheme (PBS) ~~medications~~ medicines prescribed, with and the forty
50 most common reasons for older Australians to seek or receive healthcare. Healthcare
51 information was obtained using the BEACH (Bettering The Evaluation and Care of Health)
52 program, which continuously collects information about the clinical activities in general
53 practice in Australia.[40] We then used Australian medication information sources ~~were then~~
54 used to identify both optimal and inappropriate medication management of these common
55 conditions.[29] In Australia, medication availability and use is largely determined by the
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3 PBS.[41] In October 2011, commonly used medications and medical conditions were
4 checked and updated using the BEACH program to ensure that criteria content was current.
5 Changes in evidence, product information, Australian consensus documents, evidence-based
6 publication recommendations or clinical practice guidelines relating to our criteria were noted
7 for evaluation by an expert medication management panel. The criteria were designed to
8 provide guidance on the process of care wherever it occurred – community, hospital, ~~hostel~~
9 residential home, care home or nursing home. Major considerations in their development
10 were feasibility potential accessibility of data ~~collection from the patient, their medical notes~~
11 and/or their health care professional(s), -conciseness and clarity of wording, and provision of
12 a practical number of criteria. Most were explicit to enable consistent application, with
13 additional notes provided for interpretation where necessary. They were written as a
14 statement of the kind of medication management that should or should not occur, to simplify
15 comprehension and facilitate uptake.[29]
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20 21 **Validation of criteria - participants**

22 ~~To ensure comprehensive representation, we~~ We recruited ~~three groups a multidisciplinary~~
23 group of medication management experts to review, update and rate the criteria, consisting of
24 ; geriatricians/pharmacologists, clinical pharmacists, and disease management advisors to
25 organisations that produce Australian evidence-based therapeutic publications. This resulted
26 in a round one panel of fifteen members. The geriatricians consisted of two professors of
27 geriatric medicine; an associate professor of clinical pharmacology and aged care; a research
28 fellow in geriatric medicine; and a hospital staff geriatrician. Clinical pharmacists consisted
29 of a residential medication management review pharmacist; a home medicines review
30 pharmacist; four hospital-based pharmacists (two team leaders, one director and one
31 education and training pharmacist), and a professor of aged care (Pharmacy). Disease
32 management advisors to Australian evidence-based therapeutic organisations consisted of
33 Therapeutic Guidelines,[42] Australian Medicines Handbook,[43] and the New South Wales
34 Therapeutic Advisory Group.[44]
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40 **RAND/UCLA appropriateness method**

41 The RAND/UCLA appropriateness method has been used to rate lists ranging up to over
42 3000 indications, where panellists have been asked to use the clinical literature and their best
43 clinical judgement to assess the appropriateness of performing a procedure. To do this, they
44 have rated various clinical scenarios.[45] While the number and type of our criteria may differ
45 to this, similar criteria have been developed using the RAND/UCLA method. For example, in
46 the development of indicators for patients undergoing total hip or total knee replacement, one
47 of the 68 indicators stated that for such patients, “deep venous thrombosis prophylaxis should
48 be provided for a minimum of two weeks after hospital discharge”.[46] In the development of
49 indicators for hazardous prescribing for GPs using this method, one of the 34 indicators
50 identified the hazardous use of “NSAID in a patient with heart failure”.[47] We therefore
51 followed a similar protocol.
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56 **RAND/UCLA Appropriateness Method round one**

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3 In October 2011 candidate panel members were emailed an explanation of the project and an
4 invitation to participate. After acceptance, they were emailed a rating sheet consisting of 48
5 criteria, and asked to rate each on a nine point scale, ~~where one meant highly~~ Ratings of 1-3
6 were classified as inappropriate, with a rating of one indicating the greatest degree of
7 inappropriateness. Ratings of 7-9 were classified as appropriate, with a rating of nine
8 indicating the greatest degree of appropriateness. Ratings of 4-6 were classified as neither
9 appropriate nor inappropriate. inappropriate, and nine represented criteria that were highly
10 appropriate. Appropriate was defined as “the expected health benefit exceeds the expected
11 negative consequences by a sufficiently wide margin that criteria are worth following,
12 exclusive of cost”. They also received a description of the way in which the criteria had been
13 derived, and a comparison with other prescribing criteria.[25 ,29] Panel members were
14 requested to amend the wording or delete, update or identify missing criteria as required.
15 Upon return of the rating sheets, results were tabulated. Agreement was based on four or less
16 panellists rating outside the three-point region containing the median (1-3; 4-6; 7-9), and
17 disagreement was based on five or more panellists rating in each extreme (1-3 and 7-9)
18 median panel ratings and the amount of dispersion of panel ratings, as per the RAND/UCLA
19 protocol for a fifteen member panel. Specifically, the median value, Additionally, the 30th
20 and 70th percentiles adjusted for symmetry interpercentile range (IPR) and interpercentile
21 range adjusted for symmetry (IPRAS) was were computed for each of the criteria, as it has
22 been found that when ratings were symmetric with respect to the middle (five on the 1-9
23 scale), the interpercentile range (IPR) required to label an indication as disagreement was
24 smaller than when they were asymmetric with respect to the middle (values far from five on
25 the 1-9 scale). Agreement occurred when the interpercentile range adjusted for symmetry
26 (IPRAS) was greater than the IPR .-[38]

34 35 **Rand/UCLA Appropriateness Method round two**

36 In November 2011, a face-to-face meeting of the expert panel, chaired by a panel moderator
37 experienced in facilitating group discussions and criteria development, met to discuss the
38 results of round one and re-rate each of the criteria and any potential additional criteria. - One
39 pharmacist, one staff geriatrician and a disease management advisor for a therapeutics
40 publication could not attend, resulting in a twelve member panel. For this meeting, each panel
41 member was provided with a copy of the results from round one. This consisted of the
42 frequency distribution of ratings of all panellists across the 9-point scale, the overall panel
43 median rating for each of the criteria and, for each panellist, an annotation of how they had
44 rated each of the criteria. Scores from other panel members were not revealed. Depending
45 upon panellists votes, panel agreement or disagreement was also stated for each of the round
46 one criteria.

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48 Discussion at round two occurred on the level of agreement for each of the criteria. In
49 addition, discussion was facilitated on the wording of each of the criteria to improve clarity
50 and decide whether agreement would be reached. The definitions of Agreement and
51 disagreement was were adjusted for the smaller second round twelve member panel.[38]

52 Agreement was reached when three or less panel members voted outside the 3-point region
53 containing the median, or when the IPRAS was greater than the IPR. Disagreement was
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3 determined when four or more panellists rated in each extreme (1-3 and 7-9). Each of the
4 criteria were then discussed, with panellists having the opportunity of changing their ratings
5 if, for example, misinterpretation had occurred because of the way in which the criteria had
6 been written, or if new evidence had become available, or if criteria had been interpreted in
7 the light of a panellists own clinical experience. Each panel member consented to audio
8 recording of the discussion. Values for the median, IPR and IPRAS were computed.[38]
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11 **Data analysis**

12 Median values, IPR and IPRAS were computed using SPSS version 20 (SPSS, Chicago, IL,
13 USA). Audio recordings were transcribed.
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17 **RESULTS**

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20 ~~There was agreement on the appropriateness of 65% (31/48) of the original criteria at round~~
21 ~~one, according to median panel ratings, and for all of the criteria according to the amount of~~
22 ~~dispersion of panel ratings. Of criteria for which there was disagreement, 21% (10/48) were~~
23 ~~retained after discussion and rewording, and 15% (7/48) were deleted. Two of the criteria for~~
24 ~~which there was agreement were deleted after panel discussion, as they were addressed by~~
25 ~~other criteria. In total 52% (25/48) of the criteria were reworded. This included criteria for~~
26 ~~which agreement was reached. Twenty nine percent (14/48) of the criteria remained~~
27 ~~unchanged. Two new criteria were added, resulting in a total of 41 validated criteria.~~
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31 After round one, there was agreement on the appropriateness of 31 of the 48 criteria, and
32 disagreement for 17 criteria. Discussion at round two resulted in retention of 10 criteria for
33 which there had been disagreement after round one, acceptance of 14 of the original criteria
34 with no change, deletion of nine criteria, and addition of two new criteria, resulting in 41
35 validated criteria.
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39 ~~Table 1~~An example of how the RAND/UCLA method was applied to each of our criteria is
40 described in Table 1 for indicator one. The larger the IPRAS, the less asymmetric are the
41 ratings. For example, thirteen of fifteen panellists at round one rated indicator fourteen with a
42 score of eight or nine, for which the IPRAS was 8.35.
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45 Table 2 -lists the median panel ratings, the amount of dispersion of panel ratings, and whether
46 there was agreement or disagreement for the original criteria and the validated criteria. It also
47 lists the amendments made by the panel to the original criteria, and the reasons for these
48 amendments. There was 100% agreement for both median panel ratings and dispersion of
49 panel ratings for the validated criteria. ~~Table 2~~Table 3 contains the final list of validated
50 criteria, arranged according to disease states. ~~Table 3~~Table 4 lists usage information judged to
51 be necessary for certain criteria.
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<u>Table 1 An example of the application of the RAND/UCLA appropriateness method to one criteria (indicator one) from round one</u>			
<u>Nine point scale where 1-3 = inappropriate, 4-6 = neither appropriate nor inappropriate, 7-9 = appropriate</u>	<u>Number of panellists rating this indicator (n=15)</u>	<u>Calculations, interpercentile range method[38]</u>	<u>Interpretation</u>
<u>1</u>		<u>30th percentile = 7.0</u>	<u>This indicator was accepted according to the median method because four or less panellists voted outside the 3 point region containing the median.</u>
<u>2</u>		<u>70th percentile = 8.0</u>	
<u>3</u>	<u>1</u>	<u>Interpercentile range (IPR) = 70th minus 30th percentile) = 1.0</u>	
<u>4</u>		<u>Interpercentile range central point (IPRCP) = 30th + 70th percentile divided by 2 = 7.5</u>	
<u>5</u>	<u>1</u>	<u>Asymmetry index (AI) = [5 minus IPRCP] (as an absolute value) = 2.5</u>	
<u>6</u>	<u>1</u>	<u>Interpercentile range adjusted for symmetry (IPRAS) = [2.5 plus (AI x 1.5)] = 6.1, where 2.5 is the IPR required for disagreement when perfect symmetry exists, and 1.5 is the correction factor for asymmetry</u>	
<u>7</u>	<u>5</u>		
<u>8</u>	<u>5</u>		
<u>9</u>	<u>2</u>		
	<u>median = 7.0</u>		<u>The IPRAS (6.1) was greater than the IPR (1.0) indicating no disagreement. The larger the IPRAS, the less asymmetric the ratings.</u>

Table 1 Table 2 Changes made to original criteria according to agreement, disagreement and panel discussion

Criteria Number	Original prescribing appropriateness criteria for older (≥65 years) Australians	Rating by median method[38] (median value, A= agreement, D= disagreement), n=15		Rating by IPRAS ¹ method[38] (IPR value, IPRAS value, A = agreement, D = disagreement), n=15		Validated prescribing appropriateness criteria for older (≥65 years) Australians	Rating by median method[38] (median value, A= agreement, D= disagreement), n=12		Rating by IPRAS ¹ method[38] (IPR value, IPRAS value, A = agreement, D = disagreement), n=12		Amendment/reason
1.	Patient taking an antihypertensive is at their target blood pressure	7	A	1.00, 6.10	A	Patient taking an antihypertensive is at the target blood pressure appropriate for them	8	A	1.10, 7.52	A	“Appropriate for them” added. Current blood pressure guidelines may not be appropriate for all older patients[48-50]. For example, in the oldest old[51]; in palliative care; and for those who are/become hypotensive and/or fall[52,53]
2.	Patient at high risk of a cardiovascular event is taking a statin	7	A	1.00, 6.10	A	Patient at high risk of a recurrent cardiovascular event is taking a statin	8	A	1.00, 6.10	A	“Recurrent” added to ensure use in secondary prevention of cardiovascular events rather than primary prevention, where evidence is less clear, especially in the oldest old[26,54-58]
3.	Patient with IHD or a history of MI is taking a beta blocker	8	A	2.00, 6.85	A	Patient with CHD or a history of MI is taking a beta blocker	7	A	1.00, 6.10	A	“CHD” replaced “IHD”. The term “coronary heart disease” is preferred over “ischemic heart disease”
4.	Patient with IHD or a history of MI is taking an antiplatelet agent unless on an oral anticoagulant	8	A	1.00, 7.60	A	Patient with CHD or a history of MI is taking an antiplatelet agent unless on an oral anticoagulant	8	A	1.00, 7.60	A	“CHD” replaced “IHD”. The term “coronary heart disease” is preferred over “ischemic heart disease”
5	Patient with heart failure is taking a beta blocker	7	A	1.00, 6.10	A	Patient with stable heart failure with left systolic ventricular dysfunction (HF-	8	A	0.10, 6.78	A	Description of heart failure amended. The use of beta blockers is contra-indicated in

						LVSD) is taking a beta blocker					unstable heart failure. The optimal treatment of heart failure with preserved ejection fraction (HFPEF) is uncertain at this time[59 ,60]
6.	Patient with heart failure is taking an ACEI or A2A	8	A	2.00 6.85	A	Patient with stable heart failure with left systolic ventricular dysfunction (HF-LVSD) is taking an ACEI or A2A	9	A	1.00, 7.60	A	Description of heart failure amended. The optimal treatment of heart failure with preserved ejection fraction (HFPEF) is uncertain at this time[59 ,60]
7.	Patient with heart failure is NOT taking medications which may exacerbate heart failure	9	A	1.00, 7.60	A	Patient with HF-LVSD or HFPEF is NOT taking medications which may exacerbate heart failure	9	A	0.10, 8.27	A	Description of heart failure amended. The types of medicines contraindicated in HF-LVSD and HFPEF may not be identical[61 ,62]
8	Patient with heart failure or hypertension is NOT taking high sodium medications	8	D	2.20, 5.50	A	Deleted	-		-	-	High sodium medicines (among others) in heart failure are addressed by indicator 7. In hypertension, they are addressed as lifestyle modifications[63 ,64]
9.	Patient with AF is taking an oral anticoagulant	7	D	2.0, 5.35	A	Patient with AF is taking an oral anticoagulant or an antiplatelet agent, depending upon stroke risk and bleeding risk	8	A	0.10, 6.93	A	An antiplatelet agent may be appropriate for patients at low risk of stroke. Bleeding risk may determine choice of antithrombotic agent[50 ,65 ,66]
10.	Patient with AF taking an anticoagulant has an INR between 2 – 3	8	A	2.20, 6.70	A	Patient taking warfarin for AF has an INR between 2-3	9	A	1.00, 7.60	A	New anticoagulants like rivaroxaban and dabigatran do not require INR monitoring
11.	Patient with a history of non-hemorrhagic stroke or TIA is taking an antiplatelet agent unless on an anticoagulant	8	A	1.00, 7.60	A	Patient with a history of non-hemorrhagic stroke or TIA is taking an antiplatelet agent unless on an anticoagulant	9	A	1.00, 7.60	A	No change
12.	Patient with risk factors for myopathy is NOT taking	7	D	3.00, 4.60	A	Patient with risk factors for statin induced myopathy is	8	A	1.10, 7.52	A	The use of all high dose high potency statins together with

	40mg or more per day of simvastatin or atorvastatin					not taking a high dose of a high potency statin					risk factors may increase the likelihood of myopathy[50 ,67 ,68]
13.	Patient with cardiovascular disease is NOT taking an NSAID	7	A	1.20, 5.95	A	Patient with cardiovascular disease is NOT taking an NSAID	8	A	1.10, 6.18	A	No change
14.	Patient with cardiovascular, respiratory disease or diabetes who smokes has been offered smoking cessation therapy	9	A	0.00, 8.35	A	Patient with cardiovascular, respiratory disease or diabetes who smokes has been offered smoking cessation options	9	A	0.00, 8.35	A	“Therapy” implies pharmacotherapy, whereas repeated counselling/psychotherapy may be preferred to avoid the risks associated with polypharmacy
15.	Patient with type 2 diabetes and hypertension and albuminuria is taking an ACEI or A2A	8	A	2.00, 6.85	A	Patient with type 2 diabetes and hypertension and albuminuria is taking an ACEI or A2A	9	A	1.00, 7.60	A	No change.
16.	Patient with diabetes at high risk of a cardiovascular event is taking an antiplatelet agent unless on an anticoagulant	7	D	2.20, 5.50	A	Patient with diabetes at high risk of a cardiovascular event is taking an antiplatelet agent unless on an anticoagulant	9	A	1.00, 7.60	A	No change
17.	Patient with diabetes is NOT taking a medication which may increase or decrease blood glucose concentrations	5	D	2.20, 3.70	A	Patient with diabetes receiving medications that may affect glycemic control is having regular monitoring of blood glucose concentrations	9	A	1.00, 7.60	A	Increased awareness and monitoring may require adjustment of hypoglycemic medication doses, depending upon the need to continue interacting medicines. For example, commencement of oral corticosteroids may worsen diabetes control[43]
18.	Patient with diabetes has had an HbA1c measurement within the previous 6 months	8	A	1.20, 7.45	A	Patient with diabetes has had an HbA1c measurement within the previous 6 months	8	A	1.00, 7.60	A	No change
19.	Patient taking metformin for diabetes has had the dose adjusted for	8	A	1.20, 7.45	A	Patient taking metformin for diabetes has had the dose adjusted for renal function	9	A	1.00, 7.60	A	Creatinine clearance may represent only one of the methods used to determine

	creatinine clearance										renal function
20.	Patient taking metformin for diabetes is NOT concurrently taking glibenclamide	6	D	2.40, 3.85	A	Deleted	-		-	-	Glibenclamide is an uncommonly used hypoglycaemic
21.	Patient with OA pain interfering with daily activities has been trialled on paracetamol 2 – 4 g per day	8	A	2.00, 6.85	A	Patient with OA pain interfering with daily activities has been trialled on regular paracetamol 2 – 4 g per day	9	A	0.40, 8.05	A	“Regular” paracetamol added to improve quality of indicator
22.	Patient taking analgesic(s) does NOT have pain that interferes with daily activities	7	D	3.2, 4.75	A	Patient taking analgesic(s) has had the dose(s) titrated in order to avoid pain that interferes with daily activities	8	A	2.00, 6.85	A	Indicator rephrased to improve clarity
23.	Patient taking an opioid is on prophylactic treatment for constipation	8	A	2.00, 6.85	A	Patient taking a regular opioid is on prophylactic treatment for constipation	9	A	1.00, 7.60	A	“Regular” use added as “when required” use may not always require prophylactic treatment
24.	Patient with risk factors for impaired renal function is NOT taking an NSAID	8	A	1.00, 7.60	A	Patient with risk factors for impaired renal function is NOT taking an NSAID	8	A	1.00, 7.60	A	No change
25.	Patient is NOT concurrently taking an ACEI or A2A, diuretic and NSAID (excluding low dose aspirin)	9	A	1.00, 7.60	A	Patient is NOT concurrently taking an ACEI or A2A, diuretic and NSAID (excluding low dose aspirin)	9	A	1.00, 7.60	A	No change
26.	Patient with sleep disturbance or anxiety has NOT been taking benzodiazepines for > 4 weeks	8	A	1.20, 7.45	A	Patient has NOT been taking benzodiazepines for > 4 weeks	9	A	1.00, 7.60	A	“Sleep disturbance or anxiety” deleted. Benzodiazepines increase the risk of oversedation, ataxia, confusion, falls, respiratory depression and short-term memory impairment, and are recommended for short term use only[43].
27.	Patient with depression is NOT taking	7	7, D	1.00, 4.60	A	Deleted	-		-	-	The issue of anticholinergic burden is addressed by

	anticholinergic type antidepressants										indicator 32
28.	Patient with a history of falls is NOT taking psychotropic medications	8	A	1.00, 6.10	A	Patient with a history of falls is NOT taking psychotropic medications	8	A	1.40, 6.40	A	No change
29.	Patient taking an SSRI is NOT concurrently taking medications known to increase the risk of GI bleeding	7	D	2.20, 5.20	A	Deleted	-		-	-	Redundant indicator. This issue would be identified by indicator 47.
30.	Patient taking an SSRI is NOT concurrently taking other medications that may contribute to serotonin toxicity	8	A	2.20, 6.70	A	Patient taking an SSRI is NOT concurrently taking other medications that may contribute to serotonin toxicity	8	A	1.40, 6.40	A	No change. Retained by panel due to its potential significance, despite the use of indicator 47
31.	Patient with dementia is NOT receiving anticholinergic medication	8	A	1.20, 7.45	A	Patient with dementia is NOT receiving anticholinergic medication	8	A	1.00, 7.60	A	No change
32.	Patient is NOT taking more than one medication with anticholinergic activity	8	A	0.2, 6.70	A	Patient is not taking medication with SIGNIFICANT anticholinergic activity	8	A	0.40, 7.15	A	Rewording focuses on the issue of anticholinergic burden
33.	Patient taking a PPI is NOT taking a medication that may cause dyspepsia	7	D	3.20, 4.45	A	Patient taking a PPI is NOT taking a medication that may cause dyspepsia unless prescribed for gastroprotection	8	A	0.40, 7.15	A	“Unless prescribed for gastroprotection” added to improve the accuracy of the indicator
34.	Patient with COPD is NOT taking benzodiazepines	7	D	3.00, 6.10	A	Patient with COPD is NOT taking benzodiazepines	8	A	1.00, 6.10	A	No change
35.	Patient with asthma using an inhaled LABA is also using an inhaled corticosteroid	9	A	0.20, 8.20	A	Patient with asthma using an inhaled LABA is also using an inhaled corticosteroid	9	A	1.00, 7.60	A	No change
36.	Patient using salbutamol or terbutaline inhaler more	9	A	1.00, 7.60	A	Patient using salbutamol or terbutaline inhaler more than	9	A	0.40, 8.05	A	“Except for exercise-induced asthma” added to improve the

	than 3 times per week for reversible airways disease has been prescribed an ICS					3 times per week for reversible airways disease has been prescribed an ICS (except for exercise-induced asthma)					accuracy of the indicator
37.	Patient with asthma is NOT taking a medication that may worsen asthma	7	A	1.20, 6.25	A	Patient with asthma is NOT taking a medication that may worsen asthma	8	A	1.00, 7.60	A	No change
38.	Female patient with recurrent UTIs has been prescribed intravaginal estrogen	5	D	2.00, 3.85	A	Deleted	-		-	-	Evidence for this indicator was judged to be poor[69]
39.	Patient with a creatinine clearance < 60 ml/min is NOT receiving nitrofurantoin for UTI	8	A	2.00, 6.85	A	Patient with a UTI is not receiving nitrofurantoin or hexamine for prophylaxis or acute treatment	8	A	1.00, 7.60	A	Hexamine and nitrofurantoin are not recommended for the prophylactic or acute treatment of UTI in older patients[43 ,50]
40.	Patient with a creatinine clearance < 50ml/min is NOT receiving hexamine for UTI prophylaxis	8	A	1.20, 6.25	A	Deleted	-	-	-	-	Hexamine and are not recommended for the prophylactic treatment of UTI in older patients[43 ,50].
41.	Patient with an URTI is NOT receiving antibiotics	7	7, D	3.00, 4.60	A	Patient with a non-specific URTI is NOT receiving antibiotics	8	A	1.00, 7.60	A	“non-specific” added to improve the accuracy of the indicator
42.	Patient with osteoporosis who is not receiving at least 600 IU Vitamin D daily from dietary sources is receiving supplementation with vitamin D	8	D	3.20, 4.75	A	Deleted	-		-	-	This indicator is covered by indicator 44 and an expanded footnote
43.	Patient with osteoporosis who is not receiving at least 1200 mg of calcium daily from dietary sources is receiving calcium	8	A	1.60, 5.95	A	Deleted	-		-	-	This indicator is covered by indicator 44 and an expanded footnote

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	supplementation										
44.	Patient with osteoporosis is receiving anti-osteoporotic medication	7	A	1.00, 6.10	A	Patient with osteoporosis is receiving appropriate anti-osteoporotic medication	8	A	0.40, 7.15	A	“Appropriate” added and an expanded footnote to include calcium and vitamin D
45.	Patient using topical corticosteroids does NOT have itch or discomfort that interferes with daily activities	6	D	2.00, 5.35	A	Patient using topical corticosteroids for contact or allergic dermatitis does not have itch or discomfort that interferes with daily activities	-		-	-	This indicator was deleted by the panel because there was no identification of the diagnosis/condition being treated. However, contact and allergic dermatitis is one of the top 40 most frequently managed problems by general practitioners in patients ≥ 65 years old in Australia,[40] so this indicator was re-worded by the authors
46.	Patient has received influenza and pneumococcal vaccination	9	A	1.00, 7.60	A	Patient has received influenza and pneumococcal vaccination	9	A	0.00, 8.35	A	No change
47.	Patient has no <i>significant</i> medication interactions (agreement between two medication interaction databases)	8	D	3.00, 6.10	A	Patient has no <i>clinically significant</i> medication interactions (agreement between two medication interaction databases)	8	A	0.40, 7.15	A	“Clinically” added to improve the accuracy of the indicator
48.	Patient has had no <i>significant</i> change in medications in the previous 90 days	5	D	1.20, 3.25	A	Deleted	-		-	-	It was preferred to transfer this information to the explanatory text of the article
New						Patient taking thyroid hormone replacement therapy has had a serum TSH measurement within the previous 12 months					Thyroid disease is a common medical condition managed by GPs in older Australians[40,70]
New						Patient with coronary heart disease is taking an ACEI or A2A					ACEIs or A2As reduce the risk of cardiovascular events[71,72]. However, a high incidence of comorbid disease

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												in CHD (commonly arthritis or respiratory disease) or other clinical factors (e.g. dizziness or falls, cognitive impairment, use of > 5 medicines, patient preference) may be more important in determining medication priorities[73]
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¹ **IPRAS = interpercentile range adjusted for symmetry. IPR = interpercentile range**
 ACEI = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, A2A = angiotensin 2 receptor antagonist, CHD = coronary heart disease, COPD = chronic obstructive pulmonary disease, HF-LVSD = Heart failure with left ventricular systolic dysfunction, HFPEF = Heart failure with preserved ejection fraction, HbA1c = glycosylated haemoglobin, ICS = inhaled corticosteroid, LABA = long acting beta antagonist, MI = myocardial infarct, NSAID = non-steroidal anti-inflammatory drug, OA = osteoarthritis, PPI = proton pump inhibitor, SSRI = selective serotonin reuptake inhibitor, Statin = HMG-CoA reductase inhibitor, TIA = transient ischemic attack, UTI = urinary tract infection, URTI = upper respiratory tract infection

Table 2 Table 3 Validated prescribing appropriateness criteria for older Australians (≥ 65 years) for commonly used medications and medical conditions ^{a,b,c} (*for usage information for certain criteria, see **Table 3 Table 4**)

Criteria No.	Validated criteria
1	Patient taking an antihypertensive is at the target blood pressure appropriate for them*
2	Patient at high risk of a recurrent cardiovascular event is taking a statin*
3	Patient with CHD or a history of MI is taking a beta blocker
4	Patient with CHD or a history of MI is taking an antiplatelet agent unless taking an oral anticoagulant*
5	Patient with CHD is taking an ACEI or A2A*
6	Patient with stable heart failure with HF-LVSD is taking a beta blocker
7	Patient with stable heart failure with HF-LVSD is taking an ACEI or A2A*
8	Patient with HF-LVSD or HFPEF is NOT taking medications which may exacerbate heart failure
9	Patient with AF is taking an oral anticoagulant or an antiplatelet agent, depending upon stroke risk and bleeding risk*
10	Patient taking warfarin for AF has an INR between 2-3
11	Patient with a history of non-hemorrhagic stroke or TIA is taking an antiplatelet agent unless taking an anticoagulant
12	Patient with risk factors for statin induced myopathy is not taking a high dose of a high potency statin*
13	Patient with cardiovascular disease is NOT taking an NSAID
14	Patient with cardiovascular, respiratory disease or diabetes who smokes has been offered smoking cessation options*
15	Patient with type 2 diabetes and hypertension and albuminuria is taking an ACEI or A2A
16	Patient with diabetes at high risk of a cardiovascular event is taking an antiplatelet agent unless on an anticoagulant
17	Patient with diabetes taking medications that may affect glycemic control is receiving regular monitoring of blood glucose concentrations*
18	Patient with diabetes has had an HbA1c measurement within the previous 6 months*
19	Patient taking metformin for diabetes has had the dose adjusted for renal function*
20	Patient taking thyroid hormone replacement therapy has had a serum TSH measurement within the previous 12 months
21	Patient with OA pain interfering with daily activities has been trialled on regular paracetamol 2 – 4 g per day
22	Patient taking analgesic(s) has had the dose(s) titrated in order to avoid pain that interferes with daily activities
23	Patient taking a regular opioid is on prophylactic treatment for constipation
24	Patient with risk factors for impaired renal function is NOT taking an NSAID*
25	Patient is NOT concurrently taking an ACEI or A2A, diuretic and NSAID (excluding low dose aspirin)
26	Patient has NOT been taking benzodiazepines for > 4 weeks*
27	Patient with a history of falls is NOT taking psychotropic medications*
28	Patient taking an SSRI is NOT concurrently taking other medications that may contribute to serotonin toxicity*
29	Patient with dementia is NOT receiving anticholinergic medication*
30	Patient is not taking medication with SIGNIFICANT anticholinergic activity*
31	Patient taking a PPI is NOT taking a medication that may cause dyspepsia unless prescribed for gastroprotection*
32	Patient with COPD is NOT taking benzodiazepines
33	Patient with asthma using an inhaled LABA is also using an inhaled corticosteroid
34	Patient using salbutamol or terbutaline inhaler more than 3 times per week for reversible airways disease has been prescribed an ICS (except for exercise-induced asthma)
35	Patient with asthma is NOT taking a medication that may worsen asthma*
36	Patient with a UTI is not receiving nitrofurantoin or hexamine for prophylaxis or acute treatment
37	Patient with a non-specific URTI is NOT receiving antibiotics*
38	Patient with osteoporosis is receiving appropriate anti-osteoporotic medication*

39	Patient has received influenza and pneumococcal vaccination
40	Patient using topical corticosteroids for contact or allergic dermatitis does not have itch or discomfort that interferes with daily activities
41	Patient has no <i>clinically significant</i> medication interactions (agreement between two medication interaction databases)*

a – These criteria are intended to be used by appropriately trained and qualified health professionals, as a tool to assist in making medication management decisions as part of the medication review process

b – Prior to the commencement of any medication, the contraindications and precautions for that medication should be considered

c – The intended result of using these criteria is the reasonable and appropriate medication management of individual patients, rather than the systematic application of these criteria to all patients irrespective of other considerations

A2A = angiotensin 2 receptor antagonist, ACEI = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, CHD = coronary heart disease, COPD = chronic obstructive pulmonary disease, HbA1c = glycosylated haemoglobin, HF-LVSD = Heart failure with left ventricular systolic dysfunction, HFPEF = heart failure with preserved ejection fraction, ICS = inhaled corticosteroid, INR = international normalised ratio, MI = myocardial infarct, LABA = long acting beta agonist, NSAID = non-steroidal anti-inflammatory drug, PPI = proton pump inhibitor, SSRI = selective serotonin reuptake inhibitor, TIA = transient ischemic attack, TSH = thyroid stimulating hormone, UTI = urinary tract infection.

Table 3 **Table 4** Criteria usage information

Criteria No.	Description of issue	Details
1	Blood pressure targets (mm Hg)	Proteinuria >1 g/day (with or without diabetes) < 125/75. CHD, diabetes, chronic kidney disease, proteinuria (> 300mg/day), stroke or TIA < 130/80. Others <140/90[43] Current blood pressure guidelines may not be appropriate for all older patients, such as the oldest old; in palliative care; and for those who are/become hypotensive and/or fall[48 ,50-53 ,74]
2	Patients at high risk of a cardiovascular event (> 15% within the next 5 years)	Age > 75 years; history of diabetes, moderate or severe chronic kidney disease (persistent proteinuria, GFR < 60ml/min, eGFR < 45 ml/min/1.73m ²), hypercholesterolemia (familial, TC > 7.5 mmol/L), SBP ≥ 180 or DBP ≥ 110 mmHg, ISH (SBP ≥160 and DBP ≤70 mmHg), coronary heart disease, stroke, TIA, PAD, heart failure, aortic disease, LVH, family history of premature CVD.[43 ,75] The benefits of statins and risks of adverse effects are uncertain towards the end of life[76]
4	Antiplatelet agents and oral anticoagulants	Antiplatelet agents – aspirin, clopidogrel, dipyridamole, ticlopidine. Oral anticoagulants – dabigatran, phenindione, rivaroxaban, warfarin
5	Use of ACEI or A2A in CHD	A high incidence of comorbid disease in CHD (typically arthritis and/or respiratory disease) or other clinical factors (e.g. dizziness or falls, cognitive impairment, use of > 5 medicines, patient preference) may be considerations in determining medication prescribing priorities[23 ,27 ,73]
7	Medications that may exacerbate heart failure	HF-LVSD – anti-arrhythmic medicines (except for heart failure-specific beta-blockers and amiodarone), non-dihydropyridine calcium-channel blockers (e.g. verapamil or diltiazem), clozapine, corticosteroids, NSAIDs (excluding low dose aspirin), thiazolidinediones, TNF-alpha inhibitors, topical beta blockers (when added to systemic beta blockers), tricyclic antidepressants[50 ,77 ,78]. HFPEF – venodilators (e.g. isosorbide dinitrate), potent arterial

		vasodilators (e.g. hydralazine), digoxin (unless AF), excessive use of diuretics. Note; verapamil and diltiazem may improve diastolic function in HFPEF[61]
9	Stroke risk and bleeding risk	Stroke risk can be calculated using CHADS ₂ or CHA ₂ DS ₂ -VASc.[79] Risk factors for coumarin-related bleeding complications: advanced age, uncontrolled hypertension, history of MI or IHD, cerebrovascular disease, anaemia or a history of bleeding, concomitant use of aspirin/polypharmacy[80]
12	Risk factors for statin myopathy; high dose of high potency statins	Age > 70 years, presence of disease states (diabetes, hypothyroidism, renal and hepatic disease), concurrent use of cyclosporin, fibrates, CYP3A4 inhibitors (e.g. diltiazem, macrolides, protease inhibitors, verapamil [except for pravastatin and rosuvastatin], severe intercurrent illness (infection, trauma, metabolic disorder), dose ≥ 40 mg daily. High dose of high potency statins ; ≥ 40 mg atorvastatin or simvastatin; > 10mg rosuvastatin [43 ,81]
14	Smoking cessation options	Counselling (extended, brief, telephone), support services (professional, family, social, work), pharmacotherapy.
17	Medications that may affect glycemic control	Increase blood glucose: baclofen, clozapine, cyclosporin, glucocorticoids, haloperidol, olanzapine, paliperidone, phenytoin, protease inhibitors, quetiapine, risperidone, sirolimus, tacrolimus, and tricyclic antidepressants. Decrease blood glucose: excessive alcohol, disopyramide, perhexiline, quinine, trimethoprim/sulphamethoxazole[43]
18	Six monthly HbA1c measurements	Treatment intensification in response to less than optimally controlled HbA1c may be inappropriate in patients with limited life expectancy or in frail older patients[82 ,83]
19	Metformin dose	Based on creatinine clearance: 60-90 ml/min, maximum 2g daily; 30-60 ml/min, maximum 1g daily; < 30 ml/min avoid use.[43] Based on eGFR: Review dose if eGFR< 45 ml/min/1.73m ² ; avoid if eGFR<30 ml/min/1.73m ² [84]
24	Risk factors for impaired renal function	Volume depletion, age > 60 years, salt-restricted diet, concomitant use of ACEIs, A2As, cyclosporin or aspirin, GFR ≤ 60 ml/min, cirrhosis, heart failure[85]
26	Benzodiazepine use	Benzodiazepines increase the risk of oversedation, ataxia, confusion, falls, respiratory depression and short-term memory impairment, and are recommended for short term use only.[43]
27	Falls and psychotropic medications	Psychotropic medications = antidepressants (all), anxiolytics/hypnotics, antipsychotics.[86 ,87] Medications causing (postural) hypotension (e.g. cardiovascular medicines) or cognitive impairment (e.g. opioids) may also increase the risk of falls[50 ,88]
28	Medications that may contribute to serotonin syndrome	Antidepressants - desvenlafaxine, duloxetine, St John's wort, MAOIs (including moclobemide), SSRIs, TCAs, venlafaxine. Opioids - dextromethorphan, fentanyl, pethidine, tramadol. Others - selegiline, linezolid, lithium, tryptophan[43]
29 and 30	Medications with significant anticholinergic activity	amantadine, amitriptyline, atropine*, belladonna alkaloids*, benzhexol, benzotropine, biperiden, brompheniramine*, chlorpheniramine, chlorpromazine, clomipramine, clozapine, cyclizine, cyclopentolate, cyproheptadine*, darifenacin, dexchlorpheniramine*, dimenhydrinate*, diphenhydramine*, disopyramide, dothiepin, doxepin, glycopyrrolate,

		homatropine, hyoscine* (butylbromide or hydrobromide), imipramine, ipratropium (nebulised), mianserin, nortriptyline, olanzapine, orphenadrine, oxybutynin, pericyazine, pheniramine*, pimozone, pizotifen, prochlorperazine, promethazine*, propantheline, solifenacin, tiotropium, tolterodine, trimeprazine*, trimipramine, triprolidine*, tropicamide (* available over-the-counter in Australia)[43]
31	Medications that may cause dyspepsia	Drugs with anticholinergic effects, aspirin, benzodiazepines, bisphosphonates, calcium channel antagonists, oral corticosteroids, dopaminergic drugs, doxycycline, erythromycin, ferrous sulphate, nitrates, NSAIDs, potassium chloride (slow release)[42,43,50,89]
35	Medications that may worsen asthma	Aspirin, beta blockers (including eye drops), carbamazepine, echinacea, NSAIDs, royal jelly[43,90]
38	Non-specific URTI	Acute bronchitis, pharyngitis, tonsillitis, nonsuppurative otitis media and sinusitis[42]
39	Appropriate anti-osteoporotic medication	Recommended daily intake (RDI) of calcium from dietary sources and/or supplements = 1300-1500 mg daily. RDI for Vitamin D from sunlight and/or dietary sources and/or supplements = 600 iu daily. Anti-osteoporotic medication = bisphosphonates, calcitriol, denosumab, HRT, raloxifene, strontium, teriparatide.[43] Evidence for fracture risk reduction in women ≥ 75 years is either absent or lacking in NVF for alendronate, risedronate and teriparatide, and in HF for alendronate, risedronate, zoledronic acid and teriparatide. There is no data available for denosumab in VF, NVF or HF.[91] The optimal duration of bisphosphonate therapy is uncertain. Evidence supports the use of strontium for 5 years, raloxifene for 4 years, zoledronic acid and denosumab for 3 years. Exposure to teriparatide should be limited to 18 months.[92] Data are limited for non-ambulatory patients and those with significant comorbidities.[93] It should be noted that bone strength is only one of many determinants of fracture risk.[94]
42	Clinically significant medication interactions	Medication interactions that may interfere with the outcome of therapy

A2A = angiotensin 2 receptor antagonist, ACE = angiotensin converting enzyme, ACEI = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, CHADS₂ = Cardiac failure, Hypertension, Age, Diabetes, Stroke [doubled], CHA₂DS₂-VASc = Cardiac failure or dysfunction, Hypertension, Age over 75 years [doubled], Diabetes, Stroke [doubled], Vascular disease, Age 65-74 years, Sex category [female], CHD = coronary heart disease, CVD = cardiovascular disease, DBP = diastolic blood pressure, GFR = glomerular filtration rate, HF = hip fracture, HF-LVSD = Heart failure with left ventricular systolic dysfunction, HFPEF = heart failure with preserved ejection fraction, HRT = hormone replacement therapy, IHD = ischemic heart disease, ISH = isolated systolic hypertension, LVH = left ventricular hypertrophy, MAOI = monoamine oxidase inhibitor, MI = myocardial infarct, NSAID = non-steroidal anti-inflammatory drug, NVF = non-vertebral fracture, PAD = peripheral arterial disease, SBP = systolic blood pressure, SSRI = selective serotonin reuptake inhibitor, TC = total cholesterol, TCA = tricyclic antidepressant, TIA = transient ischemic attack, TNF = tumour necrosis factor, URTI = upper respiratory tract infection, VF = vertebral fracture

DISCUSSION

This study identified a panel of medication management experts to discuss and validate a set of 41 prescribing appropriateness criteria for commonly used medicines and medical conditions in older (≥ 65 years) Australians. Panel discussion resulted in retention of **39.81%**

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3 | (~~39/48~~) of the originally proposed 48 criteria, with ~~a little over half 25 (25/48)~~ being
4 | reworded. These criteria do not simply represent a list of medications to avoid in the elderly,
5 | but also address issues such as the need for additional therapy (e.g. criteria 23 and 34, ~~table~~
6 | ~~2~~Table 3), additional tests (e.g. criteria 18-20, ~~table 2~~Table 3), ineffective treatment (e.g.
7 | criteria 22 and 37, ~~table 2~~Table 3) and medication monitoring (e.g. criteria 10 and 20, ~~table~~
8 | ~~2~~Table 3). They were designed to contribute to the Australian quality use of medicines
9 | (QUM) process.[95]- The information required to apply these criteria may be obtained from a
10 | variety of sources such as the patient or their pharmacist, or patient medical notes. [30] It may
11 | also be provided by a Home Medicines Review referral form from the patients general
12 | practitioner.[28] Due to ~~its~~ their currency and the nature of ~~its~~ their development, we expect
13 | these criteria to make a significant contribution to the detection of DRPs in the Australian
14 | healthcare environment. For example, in a review of prescribing indicators for two
15 | conditions, [36] which are common in older people in Australia – type two diabetes and
16 | cardiovascular disease [96 ,97] – disease and drug-orientated criteria such as ours have shown
17 | good content, face, concurrent and predictive validity and operational feasibility, as well as
18 | use for internal and external quality assessment in both ambulatory and hospital care.[36]
19 | Evidence-practice gaps, which formed part of the developmental process for these criteria,
20 | have identified deficiencies in the treatment of these and other areas such as vaccination,
21 | asthma and pain.[6 ,98-101]
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28 | **Prescribing appropriateness ~~lists~~ tools in Australia**

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31 | Appropriateness of prescribing has been assessed by measures that are explicit or implicit, in
32 | an effort to identify and reduce DRPs.[102] In Australia, both types of measures have been
33 | used.[103-107]However, they have been imported into the Australian healthcare
34 | environment, with consequent shortcomings related to both the intrinsic nature of the
35 | measure, as well as environment compatibility issues. For example, in a study evaluating the
36 | impact of home medicine reviews on appropriateness of prescribing, a significant number of
37 | recommendations made regarding the need for monitoring and addition of missing therapy
38 | were found to have no impact on explicitly derived scores using the Medication
39 | Appropriateness Index,[103] due to the intrinsic shortcomings of this tool. This is not a tool
40 | that gives precise guidance in relation to specific medicines.[13]
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45 | The Beers criteria,[108] perhaps the tool most widely used to assess inappropriate prescribing
46 | in older people, has been used in Australia, but with modifications to exclude medicines not
47 | listed for government subsidy.[107] This is because medicine availability and use in Australia
48 | is largely determined by the Australian Pharmaceutical Benefits Scheme[41]. Other
49 | Australian studies have found that some medicines listed as inappropriate by Beers may be
50 | appropriate for certain older people according to Australian practice:[105] many medicines
51 | listed by Beers are not available in Australia; and that some medicines considered
52 | inappropriate in Australia are not listed by Beers.[106]Disagreement between Beers and other
53 | criteria, such as the improving prescribing in the elderly tool (IPET), have been
54 | identified.[109]
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3 The Beers criteria was recently updated,[110] with approximately half the medicines listed
4 being unavailable in Australia. Further, almost three quarters of the diseases or syndromes
5 listed are not among the forty problems most frequently managed in patients over sixty five
6 years of age by Australian general practitioners.[97] Beers still contains recommendations to
7 avoid some medicines that are recommended for certain older people in Australia such as
8 amiodarone, and it has recently been shown that rhythm control in older patients with atrial
9 fibrillation may be more effective than rate control in reducing mortality over the long-
10 term.[111]. Reviews of explicit and implicit criteria have identified these and other problems
11 such as; failure to address drug-drug interactions and drug duplication, errors in
12 recommendations, underrepresentation of certain drug categories, inclusion of infrequently
13 prescribed drugs, criteria that are inapplicable for all situations, disagreement between
14 criteria, and lack of organisation of criteria.[37 ,102 ,112]

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20 This has resulted in the development by others of criteria more suited to their own particular
21 healthcare environment.[113 ,114] Nationally based criteria have been described as the most
22 desirable type of criteria, as they do not necessitate adaptation to local guidelines or national
23 formularies before they can be used with confidence.[25 ,115]We therefore sought to
24 construct and validate a set of prescribing appropriateness criteria relevant to the Australian
25 healthcare environment. Our development process differed from most other tools[22 ,108
26 ,113 ,114 ,116-119] as it did not initially involve a consensus panel, which has now been
27 addressed. This development process also resulted in criteria unavailable in other tools such
28 as monitoring, underprescribing, need for additional tests, evaluation of smoking and
29 vaccination status, and certain drug interactions[25 ,37 ,102] Because we have generally
30 named drug classes rather than specific drugs (Table 3), and targeted common medical
31 conditions found in older patients.[120 ,121] we anticipate that our work may have some
32 international usefulness.

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38 Despite a desire in Australia to develop decision support tools to improve healthcare
39 quality,[122] progress has consisted of the development of a limited number of non-age
40 specific structure and process indicator lists for use in hospitals and general practice.[44 ,123-
41 125] ~~These Many of these~~ lists ~~require updating, like many others,~~ [25 ,114 ,126], ~~require~~
42 ~~updating.~~ Currently, there is no Australian prescribing appropriateness criteria list to assist in
43 improving medication management in older people. The usefulness of such an approach has
44 been acknowledged, together with other approaches such as medication review.[127]

47 **Co-morbidity**

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49 Over 80% of older Australians have three or more chronic conditions,-[96] with Australian
50 general practitioners shown to be dealing more frequently with patients presenting with three
51 or four problems in the year 2009-10 compared with 2000-01.[128] Co-morbidity is
52 associated with poor quality of life, physical disability, high health care use, multiple
53 medicines with consequent increased risk of adverse drug events, fragmentation of care, and
54 increased mortality.[121 ,129] Yet most Australian guidelines for chronic diseases do not
55 modify or discuss the applicability of their recommendations to older patients with multiple
56 comorbid conditions. [27] This situation is not restricted to Australia.-[129 ,130]Because the
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3 risk of harm in older patients increases in proportion to the number of treatments prescribed,
4 prioritization of therapeutic goals is necessary. For example, coronary heart disease (CHD) is
5 an important co-morbidity in Australia[78 ,96] for which treatment with ACE inhibitors or
6 angiotensin 2 antagonists has been recommended to reduce the risk of cardiovascular
7 events.[71 ,72] Other criteria derived outside Australia such as STOPP/START do not
8 include this recommendation. [22] However, the presence of co-morbidity in CHD
9 (commonly arthritis or respiratory disease) or other clinical factors (such as dizziness, falls or
10 patient preference) may be more important in determining medication priorities with respect
11 to commencing these medicines (Table 4).[73] This Issues such as this may run counter to
12 recommendations of disease-specific, evidence-based guidelines,-[27] and were not contained
13 in our original set of criteria. They have been added (where possible) to increase relevance.
14 Addition of our criteria with ~~its~~ this associated usage information (Table 4) to the implicit
15 processes of ~~the~~ Australian medication review ~~process~~, may assist in addressing the~~is~~
16 problem of comorbidity.

21 22 The Oldest Old

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24 Knowledge about the state of health and function of the oldest old is limited.[131] with
25 research on their drug use being scarce, and often based on small and selected samples
26 without comparison with other age groups.[132 ,133] We know that older patients in general
27 are underrepresented in clinical trials, so that disease-specific guideline recommendations
28 based on evidence may not apply to older cohorts.[27] For example, undertreatment with
29 anti-osteoporotic medicines has been identified as a significant evidence-practice gap in
30 Australia.[98] While STOPP/START criteria recommend calcium and vitamin D
31 supplements.[22] no recommendations for more specific medicines are made. Further,
32 evidence available for fracture risk reduction has been reported to differ with age.[91](Table
33 4). Similarly, blood pressure targets appropriate for older patients may not be appropriate for
34 the oldest old.[51] with adverse effects for antihypertensives found to be among the most
35 frequent in centenarians.[134] We have attempted to achieve the advantages of using mostly
36 explicit criteria, such as ease of application, with the addition of application information
37 (Tables 2 and 4) unavailable in our previous criteria set.

38 39 Use of ~~t~~The RAND/UCLA appropriateness method

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41 We chose the RAND/UCLA appropriateness method, a two-round modified Delphi
42 method[38] to select the most appropriate criteria. Unlike the Delphi method, which generally
43 involves multiple questionnaire-driven rounds to obtain convergence of opinion, the RAND
44 method involves an initial individual rating round, and a second face-to-face round. -This
45 method has been shown to produce results that have face, construct and predictive
46 validity.[46 ,135] Systematically combining available evidence with expert opinion can
47 create quality criteria where best evidence may be lacking.[47]

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49 While most lists of prescribing criteria are based on expert consensus, this has often been
50 achieved through mail surveys rather than face-to-face meetings.[25 ,36 ,37] Although face-
51 to-face meetings restrict panel size, they allow discussion to resolve misinterpretations,
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3 introduce new evidence, and improve clarity of criteria between rating rounds. We ensured
4 our panel comprised different specialities, as less disagreement has been found among same-
5 speciality panels.[45] We addressed concern regarding potential intimidation due to dominant
6 panel personalities by choosing a moderator experienced in the development of these criteria
7 and in facilitating small group discussion. Diversity of medication and disease management
8 issues may have minimized professional, but not personal, conflict-of-interest issues. We
9 used both the median panel rating and the amount of dispersion of panel ratings to identify
10 agreement or disagreement. While it has been acknowledged that discrepancies between the
11 two methods may occur,[38] discussion and second round rating resulted in agreement for all
12 criteria for both methods.
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16 17 **The nature of decision support tools**

18 Panel members emphasized that criteria may not provide definitive answers, instead
19 indicating potential problems that might need addressing, due to a perceived unacceptable
20 variation in care.[136] While performance indicators are designed to measure the result of
21 statements made in clinical practice guidelines, these guidelines often provide
22 recommendations for care independent of other considerations such as multiple co-
23 morbidities, advanced age, frailty, patient preferences, disease burden or limited life
24 expectancy.[137-139] In such cases, less stringent goals, deprescribing or non-prescription
25 may be more appropriate.[15 ,82 ,140] For example, a frail older patient with multiple co-
26 morbidities and one or more functional impairments may have a life expectancy of
27 approximately two years or less.[76] This raises the question of whether failure to intensify
28 treatment[82] or to underuse evidence-based therapies[141] reflects appropriate clinical
29 judgement or an inappropriate care gap. The panel felt strongly that use of indicators,
30 guidelines or criteria providing clinical decision support should never replace critical thinking
31 in patient care.[142]
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39 **Strengths and weaknesses**

40 We have followed a recommended approach [122] by suggesting criteria for which high
41 quality evidence exists linking best practice with improved outcomes; where there are
42 established evidence-practice gaps[98 ,99]; and where the health conditions impose the
43 greatest burden on the healthcare system. We used a validated consensus method, an expert
44 panel of varied specialization, and criteria written with the aim of conciseness and clarity.
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48 In addition to face and content validity, these validated criteria, much like performance
49 indicators, will require further developmental work to provide evidence of their acceptability,
50 operational feasibility, reliability, and degree of predictive validity.[36 ,136] Some of this
51 work has already commenced with the original criteria.[30] Further, these criteria -only cover
52 commonly occurring medicines and medical conditions. In addition, judgements made by an
53 expert panel may not be representative of all health care professionals.
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56 **Intended use**

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3 These validated criteria are intended for use by health care providers to enhance the quality of
4 the Australian medication review process, for quality improvement, educational purposes and
5 internal audit. They are also intended for external quality assessment, such as use by policy
6 makers and for public reporting. Stakeholder involvement will be critical to facilitate local
7 uptake and encourage further research into the effects on health outcomes.[127]
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10 CONCLUSION

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13 This study validated 41 prescribing appropriateness criteria to assist in identifying DRPs in
14 older (≥ 65 years) Australians. These criteria are intended to represent an addition to the
15 medication management skill set that includes consideration of limited life expectancy,
16 evidence base in the oldest old, drug burden and care coordination, patient and care-giver
17 education, empowerment for self management, and shared decision making. These skills are
18 far from a “do everything for everyone” philosophy, where aggressive treatment may
19 encourage more care, not more appropriate care.[24 ,138] Despite the presence of clinical
20 decision support tools, health care providers need to know how to think about clinical
21 problems, not just what to think.[142]
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26 **Competing interests** None declared
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29 **Contributors** BJB designed and organised the study, analysed and interpreted the data and
30 drafted the manuscript. TFC and RJM made substantial contributions to the conception,
31 design, analysis and interpretation of the data, and to critically revising the draft. All authors
32 take responsibility for the accuracy and integrity of the study. All authors have given final
33 approval of the version to be published.
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37 commercial or not-for-profit sectors
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Validation of prescribing appropriateness criteria for older Australians using the RAND/UCLA Appropriateness Method

ARTICLE SUMMARY

Article focus

- Drug-related problems (DRPs) are common in older people, resulting in under-treatment with proven medicines, and disproportionately high numbers of adverse drug events
- The aim of this study was to validate a list of prescribing appropriateness criteria for use in older people

Key messages

- The use of medication assessment criteria is one method to assist in identifying DRPs. Criteria developed elsewhere may have little or no applicability to the Australian healthcare environment
- Validation of proposed Australian prescribing appropriateness criteria for older people was accomplished using a two-round modified Delphi method, resulting in agreement for all criteria as measured by median panel ratings, and the amount of dispersion of panel ratings, based on the interpercentile range
- Use of these criteria, together with other Australian medication review processes, may assist in improving patient care in a variety of settings by efficiently identifying DRPs to common medical conditions and commonly used medicines. They may also contribute to the medication management knowledge of health care professionals through education programs and by use in daily practice, and for the evaluation of the quality of pharmaceutical care in older people

Strengths and limitations

- A validated consensus method was used involving an expert medication management panel of varied specialization. Criteria were based on established evidence-practice gaps and degree of disease burden imposed on the health care system, and were written with the aim of conciseness and clarity
- Further developmental work is required to assess the usefulness of these criteria, which only included commonly occurring medicines and medical conditions

ABSTRACT

Objective: To update and validate proposed national prescribing appropriateness criteria to assist in identifying drug-related problems (DRPs) to commonly occurring medications and medical conditions in older (≥ 65 years old) Australians.

Design: Rand/UCLA Appropriateness Method

Participants: A panel of medication management experts were identified consisting of geriatricians, clinical pharmacists, and disease management advisors to organisations that

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3 produce Australian evidence-based therapeutic publications. This resulted in a round one
4 panel of fifteen members, and a round two panel of twelve members

5 **Main outcome measure:** Agreement on all criteria

6 **Results:** Forty eight prescribing criteria were rated. In the first rating round via email, there
7 was disagreement regarding) 17 of the criteria according to median panel ratings. During a
8 face-to-face second round meeting, discussion resulted in 39) of the proposed criteria being
9 accepted, with 25 of 48 criteria requiring amendment or updating. criteria) Fourteen were
10 unchanged, and 9 criteria deleted. Two new criteria were added, resulting in a final validated
11 list of 41 prescribing appropriateness criteria. Agreement was reached for all 41 criteria,
12 measured by median panel ratings and the amount of dispersion of panel ratings, based on the
13 interpercentile range

14 **Conclusions:** A set of 41 Australian prescribing appropriateness criteria were validated by an
15 expert panel. Use of these criteria, together with clinical judgement and other medication
16 review processes such as patient interview, is intended to assist in improving patient care by
17 efficiently detecting potential DRPs related to commonly occurring medicines and medical
18 conditions in older Australians. These criteria may also contribute to the medication
19 management education of health care professionals

20 21 22 23 24 25 26 INTRODUCTION

27
28 Drug-related problems (DRPs) in older people (≥ 65 years old) are common,[1-4] resulting in
29 both undertreatment with proven medicines[5-7] and disproportionately high numbers of
30 serious adverse medication events due to polypharmacy.[8-10] DRPs can occur for many
31 reasons such as inadequate monitoring of medicines, poor medicine or dose selection,
32 duplication of medicines, or factors to do with the way the patient uses the medicine.[2,3,11
33 ,12] Methods to identify and reduce DRPs include educational interventions, [13]
34 comprehensive geriatric assessment, [14] discontinuation of multiple medications, [15
35 ,16]electronic health record clinical decision support, [17,18]and the use of medication
36 assessment criteria.[13,19-22]

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38 However in older patients, the importance of traditional outcomes, such as discrete clinical
39 events or mortality, may be secondary to maintaining physical and cognitive function or relief
40 of symptoms.[23] Because of this, optimal care requires clinical decision support tools that
41 consider issues such as patient preferences, frailty, cost, and co-morbidities.[24] Additionally,
42 few criteria target the oldest old[25] (generally regarded as people older than 85 years),
43 where evidence may be poor, and preventive interventions may be encouraged in patients
44 who have already exceeded an average lifespan.[26,27] In Australia, issues such as these are
45 intended to be considered when patients are interviewed by an accredited pharmacist as part
46 of the Home Medicines Review program.[28] This program aims to provide the
47 sophistication lacking in explicit (that is, criterion-based rather than implicit or judgement
48 based) measures such as our criteria list, and is targeted towards patients who may be
49 (among other reasons) currently taking ≥ 5 regular medicines, attending a number of different
50 doctors, or have recently been discharged from hospital.

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3 In 2008, we proposed a list of 48 prescribing appropriateness criteria (45 explicit and three
4 implicit) aimed at improving detection of DRPs as part of the Australian medication review
5 process.[29] When applied to a cohort of older Australians, a high incidence of
6 undertreatment and use of inappropriate medicines was detected.[30] It was also intended that
7 our criteria have application in other areas, as criteria derived outside Australia have been
8 applied in a variety of settings such as community, nursing home and hospital,[19] and have
9 been applied using a variety of study designs such as in retrospective cross-sectional studies,
10 randomized controlled trials, and in retrospective and prospective case series.[13] They have
11 been used in daily clinical practice;[31] in the evaluation of health plans[31]and in the
12 evaluation of knowledge of appropriate prescribing;[32] in the training of health care
13 professionals;[33] to evaluate nursing home adherence to medicine-related regulations;[33]
14 and to develop healthcare quality indicators.[34]
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19 The appropriateness of health care delivery in Australia for common conditions, such as atrial
20 fibrillation and osteoarthritis, has been shown to be poor.[35] Our criteria were based on the
21 most frequent medicines prescribed to Australians, and the most frequent medical conditions
22 for which older Australians (≥ 65 years old) consult medical practitioners. Australian
23 medication and disease state resources and guidelines were used to provide content
24 validity.[29] However, unlike our criteria, other prescribing criteria or tools have combined
25 evidence with expert opinion to provide face validity.[36,37]
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30 The aim of this study was to update our list of criteria. We wished to add missing
31 recommendations for co-morbidity and for the oldest old where possible, and to validate the
32 criteria through expert consensus. To do this, we identified a panel of medication
33 management experts, and chose the RAND/UCLA appropriateness method,[38] which has
34 been described as the best method for systematically combining recommendations from
35 clinical guidelines, with the opinion of healthcare providers.[39]
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39 **METHODS**

40 **Ethics**

41 Ethics approval was obtained from the Human Research Ethics Committee of the University
42 of Sydney.
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46 **Criteria development**

47 In 2008, we found the 50 highest-volume Australian Pharmaceutical Benefits Scheme (PBS)
48 medicines prescribed, and the forty most common reasons for older Australians to seek or
49 receive healthcare. Healthcare information was obtained using the BEACH (Bettering The
50 Evaluation and Care of Health) program, which continuously collects information about the
51 clinical activities in general practice in Australia.[40] We then used Australian medication
52 information sources to identify both optimal and inappropriate medication management of
53 these common conditions.[29] In Australia, medication availability and use is largely
54 determined by the PBS.[41] In October 2011, commonly used medications and medical
55 conditions were checked and updated using the BEACH program to ensure that criteria
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3 content was current. Changes in evidence, product information, Australian consensus
4 documents, evidence-based publication recommendations or clinical practice guidelines
5 relating to our criteria were noted for evaluation by an expert medication management panel.
6 The criteria were designed to provide guidance on the process of care wherever it occurred –
7 community, hospital, residential home, care home or nursing home. Major considerations in
8 their development were potential accessibility of data from the patient, their medical notes
9 and/or their health care professional(s), conciseness and clarity of wording, and provision of a
10 practical number of criteria. Most were explicit to enable consistent application, with
11 additional notes provided for interpretation where necessary. They were written as a
12 statement of the kind of medication management that should or should not occur, to simplify
13 comprehension and facilitate uptake.[29]
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18 **Validation of criteria - participants**

19 We recruited a multidisciplinary group of medication management experts to review, update
20 and rate the criteria, consisting of geriatrician/pharmacologists, clinical pharmacists, and
21 disease management advisors to organisations that produce Australian evidence-based
22 therapeutic publications. This resulted in a round one panel of fifteen members. The
23 geriatricians consisted of two professors of geriatric medicine; an associate professor of
24 clinical pharmacology and aged care; a research fellow in geriatric medicine; and a hospital
25 staff geriatrician. Clinical pharmacists consisted of a residential medication management
26 review pharmacist; a home medicines review pharmacist; four hospital-based pharmacists
27 (two team leaders, one director and one education and training pharmacist), and a professor
28 of aged care (Pharmacy). Disease management advisors to Australian evidence-based
29 therapeutic organisations consisted of Therapeutic Guidelines,[42] Australian Medicines
30 Handbook,[43] and the New South Wales Therapeutic Advisory Group.[44]
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35 **RAND/UCLA appropriateness method**

36 The RAND/UCLA appropriateness method has been used to rate lists ranging up to over
37 3000 indications, where panellists have been asked to use the clinical literature and their best
38 clinical judgement to assess the appropriateness of performing a procedure. To do this, they
39 have rated various clinical scenarios.[45] While the number and type of our criteria may differ
40 to this, similar criteria have been developed using the RAND/UCLA method. For example, in
41 the development of indicators for patients undergoing total hip or total knee replacement, one
42 of the 68 indicators stated that for such patients, “deep venous thrombosis prophylaxis should
43 be provided for a minimum of two weeks after hospital discharge”.[46] In the development of
44 indicators for hazardous prescribing for GPs using this method, one of the 34 indicators
45 identified the hazardous use of “NSAID in a patient with heart failure”.[47] We therefore
46 followed a similar protocol.
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50 **RAND/UCLA Appropriateness Method round one**

51 In October 2011 candidate panel members were emailed an explanation of the project and an
52 invitation to participate. After acceptance, they were emailed a rating sheet consisting of 48
53 criteria, and asked to rate each on a nine point scale. Ratings of 1-3 were classified as
54 inappropriate, with a rating of one indicating the greatest degree of inappropriateness. Ratings
55 of 7-9 were classified as appropriate, with a rating of nine indicating the greatest degree of
56 appropriateness. Ratings of 4-6 were classified as neither appropriate nor inappropriate.
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3 Appropriate was defined as “the expected health benefit exceeds the expected negative
4 consequences by a sufficiently wide margin that criteria are worth following, exclusive of
5 cost”. They also received a description of the way in which the criteria had been derived, and
6 a comparison with other prescribing criteria.[25 ,29] Panel members were requested to amend
7 the wording or delete, update or identify missing criteria as required. Upon return of the
8 rating sheets, results were tabulated. Agreement was based on four or less panellists rating
9 outside the three-point region containing the median (1-3; 4-6; 7-9), and disagreement was
10 based on five or more panellists rating in each extreme (1-3 and 7-9) , as per the
11 RAND/UCLA protocol for a fifteen member panel Additionally, the 30th and 70th
12 percentiles adjusted for symmetry were computed for each of the criteria, as it has been
13 found that when ratings were symmetric with respect to the middle (five on the 1-9 scale), the
14 interpercentile range (IPR) required to label an indication as disagreement was smaller than
15 when they were asymmetric with respect to the middle (values far from five on the 1-9 scale).
16 Agreement occurred when the interpercentile range adjusted for symmetry (IPRAS) was
17 greater than the IPR [38]
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24 **Rand/UCLA Appropriateness Method round two**

25 In November 2011, a face-to-face meeting of the expert panel, chaired by a panel moderator
26 experienced in facilitating group discussions and criteria development, met to discuss the
27 results of round one and re-rate each of the criteria and any potential additional criteria. One
28 pharmacist, one staff geriatrician and a disease management advisor for a therapeutics
29 publication could not attend, resulting in a twelve member panel. For this meeting, each panel
30 member was provided with a copy of the results from round one. This consisted of the
31 frequency distribution of ratings of all panellists across the 9-point scale, the overall panel
32 median rating for each of the criteria and, for each panellist, an annotation of how they had
33 rated each of the criteria. Scores from other panel members were not revealed. Depending
34 upon panellists votes, panel agreement or disagreement was also stated for each of the round
35 one criterion.
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40 Discussion at round two occurred on the level of agreement for each of the criteria. In
41 addition, discussion was facilitated on the wording of each of the criteria to improve clarity
42 and decide whether agreement would be reached. The definitions of agreement and
43 disagreement were adjusted for the smaller second round twelve member panel.[38]
44 Agreement was reached when three or less panel members voted outside the 3-point region
45 containing the median, or when the IPRAS was greater than the IPR. Disagreement was
46 determined when four or more panellists rated in each extreme (1-3 and 7-9). Each of the
47 criteria were then discussed, with panellists having the opportunity of changing their ratings
48 if, for example, misinterpretation had occurred because of the way in which the criteria had
49 been written, or if new evidence had become available, or if criteria had been interpreted in
50 the light of a panellists own clinical experience. Each panel member consented to audio
51 recording of the discussion. Values for the median, IPR and IPRAS were computed.[38]
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56 **Data analysis**

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Median values, IPR and IPRAS were computed using SPSS version 20 (SPSS, Chicago, IL, USA). Audio recordings were transcribed.

RESULTS

After round one, there was agreement on the appropriateness of 31 of the 48 criteria, and disagreement for 17 criteria. Discussion at round two resulted in retention of 10 criteria for which there had been disagreement after round one, acceptance of 14 of the original criteria with no change, deletion of nine criteria, and addition of two new criteria, resulting in 41 validated criteria.

An example of how the RAND/UCLA method was applied to each of our criteria is described in Table 1 for indicator one. The larger the IPRAS, the less asymmetric are the ratings. For example, thirteen of fifteen panellists at round one rated indicator fourteen with a score of eight or nine, for which the IPRAS was 8.35.

Table 2 lists the median panel ratings, the amount of dispersion of panel ratings, and whether there was agreement or disagreement for the original criteria and the validated criteria. It also lists the amendments made by the panel to the original criteria, and the reasons for these amendments. There was 100% agreement for both median panel ratings and dispersion of panel ratings for the validated criteria. Table 3 contains the final list of validated criteria, arranged according to disease states. Table 4 lists usage information judged to be necessary for certain criteria.

Table 1 An example of the application of the RAND/UCLA appropriateness method to one criteria (indicator one) from round one			
Nine point scale where 1-3 = inappropriate, 4-6 = neither appropriate nor inappropriate, 7-9 = appropriate	Number of panellists rating this indicator (n=15)	Calculations, interpercentile range method[38]	Interpretation
1		30 th percentile = 7.0	This indicator was accepted according to the median method because four or less panellists voted outside
2		70 th percentile = 8.0	
3	1	Interpercentile range (IPR) =	
4		70 th minus 30 th percentile) =	
5	1	1.0 Interpercentile range	

6	1	central point (IPRCP) = 30 th + 70 th percentile divided by 2 = 7.5 Asymmetry index (AI) = [5 minus IPRCP] (as an absolute value) = 2.5 Interpercentile range adjusted for symmetry (IPRAS) = [2.5 plus (AI x 1.5)] = 6.1 , where 2.5 is the IPR required for disagreement when perfect symmetry exists, and 1.5 is the correction factor for asymmetry	the 3 point region containing the median. The IPRAS (6.1) was greater than the IPR (1.0) indicating no disagreement. The larger the IPRAS, the less asymmetric the ratings.
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	median = 7.0		

For peer review only

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Criteria Number	Original prescribing appropriateness criteria for older (≥ 65 years) Australians	Rating by median method[38] (median value, A= agreement, D= disagreement), n=15		Rating by IPRAS ¹ method[38] (IPR value, IPRAS value, A = agreement, D = disagreement), n=15		Validated prescribing appropriateness criteria for older (≥ 65 years) Australians	Rating by median method[38] (median value, A= agreement, D= disagreement), n=12		Rating by IPRAS ¹ method[38] (IPR value, IPRAS value, A = agreement, D = disagreement), n=12		Amendment/reason
1.	Patient taking an antihypertensive is at their target blood pressure	7	A	1.00, 6.10	A	Patient taking an antihypertensive is at the target blood pressure appropriate for them	8	A	1.10, 7.52	A	“Appropriate for them” added. Current blood pressure guidelines may not be appropriate for all older patients[48-50]. For example, in the oldest old[51]; in palliative care; and for those who are/become hypotensive and/or fall[52,53]
2.	Patient at high risk of a cardiovascular event is taking a statin	7	A	1.00, 6.10	A	Patient at high risk of a recurrent cardiovascular event is taking a statin	8	A	1.00, 6.10	A	“Recurrent” added to ensure use in secondary prevention of cardiovascular events rather than primary prevention, where evidence is less clear, especially in the oldest old[26,54-58]
3.	Patient with IHD or a history of MI is taking a beta blocker	8	A	2.00, 6.85	A	Patient with CHD or a history of MI is taking a beta blocker	7	A	1.00, 6.10	A	“CHD” replaced “IHD”. The term “coronary heart disease” is preferred over “ischemic heart disease”
4.	Patient with IHD or a history of MI is taking an antiplatelet agent unless on an oral anticoagulant	8	A	1.00, 7.60	A	Patient with CHD or a history of MI is taking an antiplatelet agent unless on an oral anticoagulant	8	A	1.00, 7.60	A	“CHD” replaced “IHD”. The term “coronary heart disease” is preferred over “ischemic heart disease”
5	Patient with heart failure is taking a beta blocker	7	A	1.00, 6.10	A	Patient with stable heart failure with left systolic ventricular dysfunction (HF-	8	A	0.10, 6.78	A	Description of heart failure amended. The use of beta blockers is contra-indicated in

						LVSD) is taking a beta blocker					unstable heart failure. The optimal treatment of heart failure with preserved ejection fraction (HFPEF) is uncertain at this time[59 ,60]
6.	Patient with heart failure is taking an ACEI or A2A	8	A	2.00 6.85	A	Patient with stable heart failure with left systolic ventricular dysfunction (HF-LVSD) is taking an ACEI or A2A	9	A	1.00, 7.60	A	Description of heart failure amended. The optimal treatment of heart failure with preserved ejection fraction (HFPEF) is uncertain at this time[59 ,60]
7.	Patient with heart failure is NOT taking medications which may exacerbate heart failure	9	A	1.00, 7.60	A	Patient with HF-LVSD or HFPEF is NOT taking medications which may exacerbate heart failure	9	A	0.10, 8.27	A	Description of heart failure amended. The types of medicines contraindicated in HF-LVSD and HFPEF may not be identical[61 ,62]
8	Patient with heart failure or hypertension is NOT taking high sodium medications	8	D	2.20, 5.50	A	Deleted	-		-	-	High sodium medicines (among others) in heart failure are addressed by indicator 7. In hypertension, they are addressed as lifestyle modifications[63 ,64]
9.	Patient with AF is taking an oral anticoagulant	7	D	2.0, 5.35	A	Patient with AF is taking an oral anticoagulant or an antiplatelet agent, depending upon stroke risk and bleeding risk	8	A	0.10, 6.93	A	An antiplatelet agent may be appropriate for patients at low risk of stroke. Bleeding risk may determine choice of antithrombotic agent[50 ,65 ,66]
10.	Patient with AF taking an anticoagulant has an INR between 2 – 3	8	A	2.20, 6.70	A	Patient taking warfarin for AF has an INR between 2-3	9	A	1.00, 7.60	A	New anticoagulants like rivaroxaban and dabigatran do not require INR monitoring
11.	Patient with a history of non-hemorrhagic stroke or TIA is taking an antiplatelet agent unless on an anticoagulant	8	A	1.00, 7.60	A	Patient with a history of non-hemorrhagic stroke or TIA is taking an antiplatelet agent unless on an anticoagulant	9	A	1.00, 7.60	A	No change
12.	Patient with risk factors for myopathy is NOT taking	7	D	3.00, 4.60	A	Patient with risk factors for statin induced myopathy is	8	A	1.10, 7.52	A	The use of all high dose high potency statins together with

	40mg or more per day of simvastatin or atorvastatin					not taking a high dose of a high potency statin					risk factors may increase the likelihood of myopathy[50 ,67 ,68]
13.	Patient with cardiovascular disease is NOT taking an NSAID	7	A	1.20, 5.95	A	Patient with cardiovascular disease is NOT taking an NSAID	8	A	1.10, 6.18	A	No change
14.	Patient with cardiovascular, respiratory disease or diabetes who smokes has been offered smoking cessation therapy	9	A	0.00, 8.35	A	Patient with cardiovascular, respiratory disease or diabetes who smokes has been offered smoking cessation options	9	A	0.00, 8.35	A	“Therapy” implies pharmacotherapy, whereas repeated counselling/psychotherapy may be preferred to avoid the risks associated with polypharmacy
15.	Patient with type 2 diabetes and hypertension and albuminuria is taking an ACEI or A2A	8	A	2.00, 6.85	A	Patient with type 2 diabetes and hypertension and albuminuria is taking an ACEI or A2A	9	A	1.00, 7.60	A	No change.
16.	Patient with diabetes at high risk of a cardiovascular event is taking an antiplatelet agent unless on an anticoagulant	7	D	2.20, 5.50	A	Patient with diabetes at high risk of a cardiovascular event is taking an antiplatelet agent unless on an anticoagulant	9	A	1.00, 7.60	A	No change
17.	Patient with diabetes is NOT taking a medication which may increase or decrease blood glucose concentrations	5	D	2.20, 3.70	A	Patient with diabetes receiving medications that may affect glycemic control is having regular monitoring of blood glucose concentrations	9	A	1.00, 7.60	A	Increased awareness and monitoring may require adjustment of hypoglycemic medication doses, depending upon the need to continue interacting medicines. For example, commencement of oral corticosteroids may worsen diabetes control[43]
18.	Patient with diabetes has had an HbA1c measurement within the previous 6 months	8	A	1.20, 7.45	A	Patient with diabetes has had an HbA1c measurement within the previous 6 months	8	A	1.00, 7.60	A	No change
19.	Patient taking metformin for diabetes has had the dose adjusted for	8	A	1.20, 7.45	A	Patient taking metformin for diabetes has had the dose adjusted for renal function	9	A	1.00, 7.60	A	Creatinine clearance may represent only one of the methods used to determine

	creatinine clearance										renal function
20.	Patient taking metformin for diabetes is NOT concurrently taking glibenclamide	6	D	2.40, 3.85	A	Deleted	-		-	-	Glibenclamide is an uncommonly used hypoglycaemic
21.	Patient with OA pain interfering with daily activities has been trialled on paracetamol 2 – 4 g per day	8	A	2.00, 6.85	A	Patient with OA pain interfering with daily activities has been trialled on regular paracetamol 2 – 4 g per day	9	A	0.40, 8.05	A	“Regular” paracetamol added to improve quality of indicator
22.	Patient taking analgesic(s) does NOT have pain that interferes with daily activities	7	D	3.2, 4.75	A	Patient taking analgesic(s) has had the dose(s) titrated in order to avoid pain that interferes with daily activities	8	A	2.00, 6.85	A	Indicator rephrased to improve clarity
23.	Patient taking an opioid is on prophylactic treatment for constipation	8	A	2.00, 6.85	A	Patient taking a regular opioid is on prophylactic treatment for constipation	9	A	1.00, 7.60	A	“Regular” use added as “when required” use may not always require prophylactic treatment
24.	Patient with risk factors for impaired renal function is NOT taking an NSAID	8	A	1.00, 7.60	A	Patient with risk factors for impaired renal function is NOT taking an NSAID	8	A	1.00, 7.60	A	No change
25.	Patient is NOT concurrently taking an ACEI or A2A, diuretic and NSAID (excluding low dose aspirin)	9	A	1.00, 7.60	A	Patient is NOT concurrently taking an ACEI or A2A, diuretic and NSAID (excluding low dose aspirin)	9	A	1.00, 7.60	A	No change
26.	Patient with sleep disturbance or anxiety has NOT been taking benzodiazepines for > 4 weeks	8	A	1.20, 7.45	A	Patient has NOT been taking benzodiazepines for > 4 weeks	9	A	1.00, 7.60	A	“Sleep disturbance or anxiety” deleted. Benzodiazepines increase the risk of oversedation, ataxia, confusion, falls, respiratory depression and short-term memory impairment, and are recommended for short term use only[43].
27.	Patient with depression is NOT taking	7	7, D	1.00, 4.60	A	Deleted	-		-	-	The issue of anticholinergic burden is addressed by

	anticholinergic type antidepressants										indicator 32
28.	Patient with a history of falls is NOT taking psychotropic medications	8	A	1.00, 6.10	A	Patient with a history of falls is NOT taking psychotropic medications	8	A	1.40, 6.40	A	No change
29.	Patient taking an SSRI is NOT concurrently taking medications known to increase the risk of GI bleeding	7	D	2.20, 5.20	A	Deleted	-		-	-	Redundant indicator. This issue would be identified by indicator 47.
30.	Patient taking an SSRI is NOT concurrently taking other medications that may contribute to serotonin toxicity	8	A	2.20, 6.70	A	Patient taking an SSRI is NOT concurrently taking other medications that may contribute to serotonin toxicity	8	A	1.40, 6.40	A	No change. Retained by panel due to its potential significance, despite the use of indicator 47
31.	Patient with dementia is NOT receiving anticholinergic medication	8	A	1.20, 7.45	A	Patient with dementia is NOT receiving anticholinergic medication	8	A	1.00, 7.60	A	No change
32.	Patient is NOT taking more than one medication with anticholinergic activity	8	A	0.2, 6.70	A	Patient is not taking medication with SIGNIFICANT anticholinergic activity	8	A	0.40, 7.15	A	Rewording focuses on the issue of anticholinergic burden
33.	Patient taking a PPI is NOT taking a medication that may cause dyspepsia	7	D	3.20, 4.45	A	Patient taking a PPI is NOT taking a medication that may cause dyspepsia unless prescribed for gastroprotection	8	A	0.40, 7.15	A	“Unless prescribed for gastroprotection” added to improve the accuracy of the indicator
34.	Patient with COPD is NOT taking benzodiazepines	7	D	3.00, 6.10	A	Patient with COPD is NOT taking benzodiazepines	8	A	1.00, 6.10	A	No change
35.	Patient with asthma using an inhaled LABA is also using an inhaled corticosteroid	9	A	0.20, 8.20	A	Patient with asthma using an inhaled LABA is also using an inhaled corticosteroid	9	A	1.00, 7.60	A	No change
36.	Patient using salbutamol or terbutaline inhaler more	9	A	1.00, 7.60	A	Patient using salbutamol or terbutaline inhaler more than	9	A	0.40, 8.05	A	“Except for exercise-induced asthma” added to improve the

	than 3 times per week for reversible airways disease has been prescribed an ICS					3 times per week for reversible airways disease has been prescribed an ICS (except for exercise-induced asthma)					accuracy of the indicator
37.	Patient with asthma is NOT taking a medication that may worsen asthma	7	A	1.20, 6.25	A	Patient with asthma is NOT taking a medication that may worsen asthma	8	A	1.00, 7.60	A	No change
38.	Female patient with recurrent UTIs has been prescribed intravaginal estrogen	5	D	2.00, 3.85	A	Deleted	-		-	-	Evidence for this indicator was judged to be poor[69]
39.	Patient with a creatinine clearance < 60 ml/min is NOT receiving nitrofurantoin for UTI	8	A	2.00, 6.85	A	Patient with a UTI is not receiving nitrofurantoin or hexamine for prophylaxis or acute treatment	8	A	1.00, 7.60	A	Hexamine and nitrofurantoin are not recommended for the prophylactic or acute treatment of UTI in older patients[43 ,50]
40.	Patient with a creatinine clearance < 50ml/min is NOT receiving hexamine for UTI prophylaxis	8	A	1.20, 6.25	A	Deleted	-	-	-	-	Hexamine and are not recommended for the prophylactic treatment of UTI in older patients[43 ,50].
41.	Patient with an URTI is NOT receiving antibiotics	7	7, D	3.00, 4.60	A	Patient with a non-specific URTI is NOT receiving antibiotics	8	A	1.00, 7.60	A	“non-specific” added to improve the accuracy of the indicator
42.	Patient with osteoporosis who is not receiving at least 600 IU Vitamin D daily from dietary sources is receiving supplementation with vitamin D	8	D	3.20, 4.75	A	Deleted	-		-	-	This indicator is covered by indicator 44 and an expanded footnote
43.	Patient with osteoporosis who is not receiving at least 1200 mg of calcium daily from dietary sources is receiving calcium	8	A	1.60, 5.95	A	Deleted	-		-	-	This indicator is covered by indicator 44 and an expanded footnote

	supplementation										
44.	Patient with osteoporosis is receiving anti-osteoporotic medication	7	A	1.00, 6.10	A	Patient with osteoporosis is receiving appropriate anti-osteoporotic medication	8	A	0.40, 7.15	A	“Appropriate” added and an expanded footnote to include calcium and vitamin D
45.	Patient using topical corticosteroids does NOT have itch or discomfort that interferes with daily activities	6	D	2.00, 5.35	A	Patient using topical corticosteroids for contact or allergic dermatitis does not have itch or discomfort that interferes with daily activities	-		-	-	This indicator was deleted by the panel because there was no identification of the diagnosis/condition being treated. However, contact and allergic dermatitis is one of the top 40 most frequently managed problems by general practitioners in patients ≥ 65 years old in Australia,[40] so this indicator was re-worded by the authors
46.	Patient has received influenza and pneumococcal vaccination	9	A	1.00, 7.60	A	Patient has received influenza and pneumococcal vaccination	9	A	0.00, 8.35	A	No change
47.	Patient has no <i>significant</i> medication interactions (agreement between two medication interaction databases)	8	D	3.00, 6.10	A	Patient has no <i>clinically significant</i> medication interactions (agreement between two medication interaction databases)	8	A	0.40, 7.15	A	“Clinically” added to improve the accuracy of the indicator
48.	Patient has had no <i>significant</i> change in medications in the previous 90 days	5	D	1.20, 3.25	A	Deleted	-		-	-	It was preferred to transfer this information to the explanatory text of the article
New						Patient taking thyroid hormone replacement therapy has had a serum TSH measurement within the previous 12 months					Thyroid disease is a common medical condition managed by GPs in older Australians[40,70]
New						Patient with coronary heart disease is taking an ACEI or A2A					ACEIs or A2As reduce the risk of cardiovascular events[71,72]. However, a high incidence of comorbid disease

Table 3 Validated prescribing appropriateness criteria for older Australians (≥ 65 years) for commonly used medications and medical conditions^{a,b,c} (*for usage information for certain criteria, see Table 4)

Criteria No.	Validated criteria
1	Patient taking an antihypertensive is at the target blood pressure appropriate for them*
2	Patient at high risk of a recurrent cardiovascular event is taking a statin*
3	Patient with CHD or a history of MI is taking a beta blocker
4	Patient with CHD or a history of MI is taking an antiplatelet agent unless taking an oral anticoagulant*
5	Patient with CHD is taking an ACEI or A2A*
6	Patient with stable heart failure with HF-LVSD is taking a beta blocker
7	Patient with stable heart failure with HF-LVSD is taking an ACEI or A2A*
8	Patient with HF-LVSD or HFPEF is NOT taking medications which may exacerbate heart failure
9	Patient with AF is taking an oral anticoagulant or an antiplatelet agent, depending upon stroke risk and bleeding risk*
10	Patient taking warfarin for AF has an INR between 2-3
11	Patient with a history of non-hemorrhagic stroke or TIA is taking an antiplatelet agent unless taking an anticoagulant
12	Patient with risk factors for statin induced myopathy is not taking a high dose of a high potency statin*
13	Patient with cardiovascular disease is NOT taking an NSAID
14	Patient with cardiovascular, respiratory disease or diabetes who smokes has been offered smoking cessation options*
15	Patient with type 2 diabetes and hypertension and albuminuria is taking an ACEI or A2A
16	Patient with diabetes at high risk of a cardiovascular event is taking an antiplatelet agent unless on an anticoagulant
17	Patient with diabetes taking medications that may affect glycemic control is receiving regular monitoring of blood glucose concentrations*
18	Patient with diabetes has had an HbA1c measurement within the previous 6 months*
19	Patient taking metformin for diabetes has had the dose adjusted for renal function*
20	Patient taking thyroid hormone replacement therapy has had a serum TSH measurement within the previous 12 months
21	Patient with OA pain interfering with daily activities has been trialled on regular paracetamol 2 – 4 g per day
22	Patient taking analgesic(s) has had the dose(s) titrated in order to avoid pain that interferes with daily activities
23	Patient taking a regular opioid is on prophylactic treatment for constipation
24	Patient with risk factors for impaired renal function is NOT taking an NSAID*
25	Patient is NOT concurrently taking an ACEI or A2A, diuretic and NSAID (excluding low dose aspirin)
26	Patient has NOT been taking benzodiazepines for > 4 weeks*
27	Patient with a history of falls is NOT taking psychotropic medications*
28	Patient taking an SSRI is NOT concurrently taking other medications that may contribute to serotonin toxicity*
29	Patient with dementia is NOT receiving anticholinergic medication*
30	Patient is not taking medication with SIGNIFICANT anticholinergic activity*
31	Patient taking a PPI is NOT taking a medication that may cause dyspepsia unless prescribed for gastroprotection*
32	Patient with COPD is NOT taking benzodiazepines
33	Patient with asthma using an inhaled LABA is also using an inhaled corticosteroid
34	Patient using salbutamol or terbutaline inhaler more than 3 times per week for reversible airways disease has been prescribed an ICS (except for exercise-induced asthma)
35	Patient with asthma is NOT taking a medication that may worsen asthma*
36	Patient with a UTI is not receiving nitrofurantoin or hexamine for prophylaxis or acute treatment
37	Patient with a non-specific URTI is NOT receiving antibiotics*
38	Patient with osteoporosis is receiving appropriate anti-osteoporotic medication*

39	Patient has received influenza and pneumococcal vaccination
40	Patient using topical corticosteroids for contact or allergic dermatitis does not have itch or discomfort that interferes with daily activities
41	Patient has no <i>clinically significant</i> medication interactions (agreement between two medication interaction databases)*

a – These criteria are intended to be used by appropriately trained and qualified health professionals, as a tool to assist in making medication management decisions as part of the medication review process

b – Prior to the commencement of any medication, the contraindications and precautions for that medication should be considered

c – The intended result of using these criteria is the reasonable and appropriate medication management of individual patients, rather than the systematic application of these criteria to all patients irrespective of other considerations

A2A = angiotensin 2 receptor antagonist, ACEI = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, CHD = coronary heart disease, COPD = chronic obstructive pulmonary disease, HbA1c = glycosylated haemoglobin, HF-LVSD = Heart failure with left ventricular systolic dysfunction, HFPEF = heart failure with preserved ejection fraction, ICS = inhaled corticosteroid, INR = international normalised ratio, MI = myocardial infarct, LABA = long acting beta agonist, NSAID = non-steroidal anti-inflammatory drug, PPI = proton pump inhibitor, SSRI = selective serotonin reuptake inhibitor, TIA = transient ischemic attack, TSH = thyroid stimulating hormone, UTI = urinary tract infection.

Criteria No.	Description of issue	Details
1	Blood pressure targets (mm Hg)	Proteinuria >1 g/day (with or without diabetes) < 125/75. CHD, diabetes, chronic kidney disease, proteinuria (> 300mg/day), stroke or TIA < 130/80. Others <140/90[43] Current blood pressure guidelines may not be appropriate for all older patients, such as the oldest old; in palliative care; and for those who are/become hypotensive and/or fall[48 ,50-53 ,74]
2	Patients at high risk of a cardiovascular event (> 15% within the next 5 years)	Age > 75 years; history of diabetes, moderate or severe chronic kidney disease (persistent proteinuria, GFR < 60ml/min, eGFR < 45 ml/min/1.73m ²), hypercholesterolemia (familial, TC > 7.5 mmol/L), SBP ≥ 180 or DBP ≥ 110 mmHg, ISH (SBP ≥160 and DBP ≤70 mmHg), coronary heart disease, stroke, TIA, PAD, heart failure, aortic disease, LVH, family history of premature CVD.[43 ,75] The benefits of statins and risks of adverse effects are uncertain towards the end of life[76]
4	Antiplatelet agents and oral anticoagulants	Antiplatelet agents – aspirin, clopidogrel, dipyridamole, ticlopidine. Oral anticoagulants – dabigatran, phenindione, rivaroxaban, warfarin
5	Use of ACEI or A2A in CHD	A high incidence of comorbid disease in CHD (typically arthritis and/or respiratory disease) or other clinical factors (e.g. dizziness or falls, cognitive impairment, use of > 5 medicines, patient preference) may be considerations in determining medication prescribing priorities[23 ,27 ,73]
7	Medications that may exacerbate heart failure	HF-LVSD – anti-arrhythmic medicines (except for heart failure-specific beta-blockers and amiodarone), non-dihydropyridine calcium-channel blockers (e.g. verapamil or diltiazem), clozapine, corticosteroids, NSAIDs (excluding low dose aspirin), thiazolidinediones, TNF-alpha inhibitors, topical beta blockers (when added to systemic beta blockers), tricyclic antidepressants[50 ,77 ,78]. HFPEF – venodilators (e.g. isosorbide dinitrate), potent arterial

		vasodilators (e.g. hydralazine), digoxin (unless AF), excessive use of diuretics. Note; verapamil and diltiazem may improve diastolic function in HFPEF[61]
9	Stroke risk and bleeding risk	Stroke risk can be calculated using CHADS ₂ or CHA ₂ DS ₂ -VASc.[79] Risk factors for coumarin-related bleeding complications: advanced age, uncontrolled hypertension, history of MI or IHD, cerebrovascular disease, anaemia or a history of bleeding, concomitant use of aspirin/polypharmacy[80]
12	Risk factors for statin myopathy; high dose of high potency statins	Age > 70 years, presence of disease states (diabetes, hypothyroidism, renal and hepatic disease), concurrent use of cyclosporin, fibrates, CYP3A4 inhibitors (e.g. diltiazem, macrolides, protease inhibitors, verapamil [except for pravastatin and rosuvastatin], severe intercurrent illness (infection, trauma, metabolic disorder), dose ≥ 40 mg daily. High dose of high potency statins ; ≥ 40 mg atorvastatin or simvastatin; > 10mg rosuvastatin [43 ,81]
14	Smoking cessation options	Counselling (extended, brief, telephone), support services (professional, family, social, work), pharmacotherapy.
17	Medications that may affect glycemic control	Increase blood glucose: baclofen, clozapine, cyclosporin, glucocorticoids, haloperidol, olanzapine, paliperidone, phenytoin, protease inhibitors, quetiapine, risperidone, sirolimus, tacrolimus, and tricyclic antidepressants. Decrease blood glucose: excessive alcohol, disopyramide, perhexiline, quinine, trimethoprim/sulphamethoxazole[43]
18	Six monthly HbA1c measurements	Treatment intensification in response to less than optimally controlled HbA1c may be inappropriate in patients with limited life expectancy or in frail older patients[82 ,83]
19	Metformin dose	Based on creatinine clearance: 60-90 ml/min, maximum 2g daily; 30-60 ml/min, maximum 1g daily; < 30 ml/min avoid use.[43] Based on eGFR: Review dose if eGFR< 45 ml/min/1.73m ² ; avoid if eGFR<30 ml/min/1.73m ² [84]
24	Risk factors for impaired renal function	Volume depletion, age > 60 years, salt-restricted diet, concomitant use of ACEIs, A2As, cyclosporin or aspirin, GFR ≤ 60 ml/min, cirrhosis, heart failure[85]
26	Benzodiazepine use	Benzodiazepines increase the risk of oversedation, ataxia, confusion, falls, respiratory depression and short-term memory impairment, and are recommended for short term use only.[43]
27	Falls and psychotropic medications	Psychotropic medications = antidepressants (all), anxiolytics/hypnotics, antipsychotics.[86 ,87] Medications causing (postural) hypotension (e.g. cardiovascular medicines) or cognitive impairment (e.g. opioids) may also increase the risk of falls[50 ,88]
28	Medications that may contribute to serotonin syndrome	Antidepressants - desvenlafaxine, duloxetine, St John's wort, MAOIs (including moclobemide), SSRIs, TCAs, venlafaxine. Opioids - dextromethorphan, fentanyl, pethidine, tramadol. Others - selegiline, linezolid, lithium, tryptophan[43]
29 and 30	Medications with significant anticholinergic activity	amantadine, amitriptyline, atropine*, belladonna alkaloids*, benzhexol, benzotropine, biperiden, brompheniramine*, chlorpheniramine, chlorpromazine, clomipramine, clozapine, cyclizine, cyclopentolate, cyproheptadine*, darifenacin, dexchlorpheniramine*, dimenhydrinate*, diphenhydramine*, disopyramide, dothiepin, doxepin, glycopyrrolate,

		homatropine, hyoscine* (butylbromide or hydrobromide), imipramine, ipratropium (nebulised), mianserin, nortriptyline, olanzapine, orphenadrine, oxybutynin, pericyazine, pheniramine*, pimozone, pizotifen, prochlorperazine, promethazine*, propantheline, solifenacin, tiotropium, tolterodine, trimeprazine*, trimipramine, triprolidine*, tropicamide (* available over-the-counter in Australia)[43]
31	Medications that may cause dyspepsia	Drugs with anticholinergic effects, aspirin, benzodiazepines, bisphosphonates, calcium channel antagonists, oral corticosteroids, dopaminergic drugs, doxycycline, erythromycin, ferrous sulphate, nitrates, NSAIDs, potassium chloride (slow release)[42,43,50,89]
35	Medications that may worsen asthma	Aspirin, beta blockers (including eye drops), carbamazepine, echinacea, NSAIDs, royal jelly[43,90]
38	Non-specific URTI	Acute bronchitis, pharyngitis, tonsillitis, nonsuppurative otitis media and sinusitis[42]
39	Appropriate anti-osteoporotic medication	Recommended daily intake (RDI) of calcium from dietary sources and/or supplements = 1300-1500 mg daily. RDI for Vitamin D from sunlight and/or dietary sources and/or supplements = 600 iu daily. Anti-osteoporotic medication = bisphosphonates, calcitriol, denosumab, HRT, raloxifene, strontium, teriparatide.[43] Evidence for fracture risk reduction in women ≥ 75 years is either absent or lacking in NVF for alendronate, risedronate and teriparatide, and in HF for alendronate, risedronate, zoledronic acid and teriparatide. There is no data available for denosumab in VF, NVF or HF.[91] The optimal duration of bisphosphonate therapy is uncertain. Evidence supports the use of strontium for 5 years, raloxifene for 4 years, zoledronic acid and denosumab for 3 years. Exposure to teriparatide should be limited to 18 months.[92] Data are limited for non-ambulatory patients and those with significant comorbidities.[93] It should be noted that bone strength is only one of many determinants of fracture risk.[94]
42	Clinically significant medication interactions	Medication interactions that may interfere with the outcome of therapy

A2A = angiotensin 2 receptor antagonist, ACE = angiotensin converting enzyme, ACEI = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, CHADS₂ = Cardiac failure, Hypertension, Age, Diabetes, Stroke [doubled], CHA₂DS₂-VASc = Cardiac failure or dysfunction, Hypertension, Age over 75 years [doubled], Diabetes, Stroke [doubled], Vascular disease, Age 65-74 years, Sex category [female], CHD = coronary heart disease, CVD = cardiovascular disease, DBP = diastolic blood pressure, GFR = glomerular filtration rate, HF = hip fracture, HF-LVSD = Heart failure with left ventricular systolic dysfunction, HFPEF = heart failure with preserved ejection fraction, HRT = hormone replacement therapy, IHD = ischemic heart disease, ISH = isolated systolic hypertension, LVH = left ventricular hypertrophy, MAOI = monoamine oxidase inhibitor, MI = myocardial infarct, NSAID = non-steroidal anti-inflammatory drug, NVF = non-vertebral fracture, PAD = peripheral arterial disease, SBP = systolic blood pressure, SSRI = selective serotonin reuptake inhibitor, TC = total cholesterol, TCA = tricyclic antidepressant, TIA = transient ischemic attack, TNF = tumour necrosis factor, URTI = upper respiratory tract infection, VF = vertebral fracture

DISCUSSION

This study identified a panel of medication management experts to discuss and validate a set of 41 prescribing appropriateness criteria for commonly used medicines and medical conditions in older (≥ 65 years) Australians. Panel discussion resulted in retention of 39 of

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3 the originally proposed 48 criteria, with 25 being reworded. These criteria do not simply
4 represent a list of medications to avoid in the elderly, but also address issues such as the need
5 for additional therapy (e.g. criteria 23 and 34, Table 3), additional tests (e.g. criteria 18-20,
6 Table 3), ineffective treatment (e.g. criteria 22 and 37, Table 3) and medication monitoring
7 (e.g. criteria 10 and 20, Table 3). They were designed to contribute to the Australian quality
8 use of medicines (QUM) process.[95] The information required to apply these criteria may be
9 obtained from a variety of sources such as the patient or their pharmacist, or patient medical
10 notes. [30] It may also be provided by a Home Medicines Review referral form from the
11 patients general practitioner.[28] Due to their currency and the nature of their development,
12 we expect these criteria to make a significant contribution to the detection of DRPs in the
13 Australian healthcare environment. For example, in a review of prescribing indicators for two
14 conditions, [36] which are common in older people in Australia – type two diabetes and
15 cardiovascular disease [96,97] – disease and drug-orientated criteria such as ours have shown
16 good content, face, concurrent and predictive validity and operational feasibility, as well as
17 use for internal and external quality assessment in both ambulatory and hospital care.[36]
18 Evidence-practice gaps, which formed part of the developmental process for these criteria,
19 have identified deficiencies in the treatment of these and other areas such as vaccination,
20 asthma and pain.[6,98-101]

27 **Prescribing appropriateness tools in Australia**

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30 Appropriateness of prescribing has been assessed by measures that are explicit or implicit, in
31 an effort to identify and reduce DRPs.[102] In Australia, both types of measures have been
32 used.[103-107] However, they have been imported into the Australian healthcare
33 environment, with consequent shortcomings related to both the intrinsic nature of the
34 measure, as well as environment compatibility issues. For example, in a study evaluating the
35 impact of home medicine reviews on appropriateness of prescribing, a significant number of
36 recommendations made regarding the need for monitoring and addition of missing therapy
37 were found to have no impact on explicitly derived scores using the Medication
38 Appropriateness Index,[103] due to the intrinsic shortcomings of this tool. This is not a tool
39 that gives precise guidance in relation to specific medicines.[13]

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44 The Beers criteria,[108] perhaps the tool most widely used to assess inappropriate prescribing
45 in older people, has been used in Australia, but with modifications to exclude medicines not
46 listed for government subsidy.[107] This is because medicine availability and use in Australia
47 is largely determined by the Australian Pharmaceutical Benefits Scheme[41]. Other
48 Australian studies have found that some medicines listed as inappropriate by Beers may be
49 appropriate for certain older people according to Australian practice;[105] many medicines
50 listed by Beers are not available in Australia; and that some medicines considered
51 inappropriate in Australia are not listed by Beers.[106] Disagreement between Beers and other
52 criteria, such as the improving prescribing in the elderly tool (IPET), have been
53 identified.[109]

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3 The Beers criteria was recently updated,[110] with approximately half the medicines listed
4 being unavailable in Australia. Further, almost three quarters of the diseases or syndromes
5 listed are not among the forty problems most frequently managed in patients over sixty five
6 years of age by Australian general practitioners.[97] Beers still contains recommendations to
7 avoid some medicines that are recommended for certain older people in Australia such as
8 amiodarone, and it has recently been shown that rhythm control in older patients with atrial
9 fibrillation may be more effective than rate control in reducing mortality over the long-
10 term.[111]. Reviews of explicit and implicit criteria have identified these and other problems
11 such as; failure to address drug-drug interactions and drug duplication, errors in
12 recommendations, underrepresentation of certain drug categories, inclusion of infrequently
13 prescribed drugs, criteria that are inapplicable for all situations, disagreement between
14 criteria, and lack of organisation of criteria.[37 ,102 ,112]

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19 This has resulted in the development by others of criteria more suited to their own particular
20 healthcare environment.[113 ,114] Nationally based criteria have been described as the most
21 desirable type of criteria, as they do not necessitate adaptation to local guidelines or national
22 formularies before they can be used with confidence.[25 ,115] We therefore sought to
23 construct and validate a set of prescribing appropriateness criteria relevant to the Australian
24 healthcare environment. Our development process differed from most other tools[22 ,108
25 ,113 ,114 ,116-119] as it did not initially involve a consensus panel, which has now been
26 addressed. This development process also resulted in criteria unavailable in other tools such
27 as monitoring, underprescribing, need for additional tests, evaluation of smoking and
28 vaccination status, and certain drug interactions[25 ,37 ,102] Because we have generally
29 named drug classes rather than specific drugs (Table 3), and targeted common medical
30 conditions found in older patients,[120 ,121] we anticipate that our work may have some
31 international usefulness.

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Despite a desire in Australia to develop decision support tools to improve healthcare
quality,[122] progress has consisted of the development of a limited number of non-age
specific structure and process indicator lists for use in hospitals and general practice.[44 ,123-
125] Many of these lists require updating. [25 ,114 ,126] . Currently, there is no Australian
prescribing appropriateness criteria list to assist in improving medication management in
older people. The usefulness of such an approach has been acknowledged, together with other
approaches such as medication review.[127]

Co-morbidity

Over 80% of older Australians have three or more chronic conditions,[96] with Australian
general practitioners shown to be dealing more frequently with patients presenting with three
or four problems in the year 2009-10 compared with 2000-01.[128] Co-morbidity is
associated with poor quality of life, physical disability, high health care use, multiple
medicines with consequent increased risk of adverse drug events, fragmentation of care, and
increased mortality.[121 ,129] Yet most Australian guidelines for chronic diseases do not
modify or discuss the applicability of their recommendations to older patients with multiple
comorbid conditions. [27] This situation is not restricted to Australia.[129 ,130] Because the

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3 risk of harm in older patients increases in proportion to the number of treatments prescribed,
4 prioritization of therapeutic goals is necessary. For example, coronary heart disease (CHD) is
5 an important co-morbidity in Australia[78 ,96] for which treatment with ACE inhibitors or
6 angiotensin 2 antagonists has been recommended to reduce the risk of cardiovascular
7 events.[71 ,72] Other criteria derived outside Australia such as STOPP/START do not
8 include this recommendation. [22] However, the presence of co-morbidity in CHD
9 (commonly arthritis or respiratory disease) or other clinical factors (such as dizziness, falls or
10 patient preference) may be more important in determining medication priorities with respect
11 to commencing these medicines (Table 4).[73] Issues such as this may run counter to
12 recommendations of disease-specific, evidence-based guidelines,[27] and were not contained
13 in our original set of criteria. They have been added (where possible) to increase relevance.
14 Addition of our criteria with this associated usage information (Table 4) to the implicit
15 processes of Australian medication review may assist in addressing the problem of
16 comorbidity.
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22 The Oldest Old

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25 Knowledge about the state of health and function of the oldest old is limited,[131] with
26 research on their drug use being scarce, and often based on small and selected samples
27 without comparison with other age groups.[132 ,133] We know that older patients in general
28 are underrepresented in clinical trials, so that disease-specific guideline recommendations
29 based on evidence may not apply to older cohorts.[27] For example, undertreatment with
30 anti-osteoporotic medicines has been identified as a significant evidence-practice gap in
31 Australia.[98] While STOPP/START criteria recommend calcium and vitamin D
32 supplements,[22] no recommendations for more specific medicines are made. Further,
33 evidence available for fracture risk reduction has been reported to differ with age.[91](Table
34 4). Similarly, blood pressure targets appropriate for older patients may not be appropriate for
35 the oldest old,[51] with adverse effects for antihypertensives found to be among the most
36 frequent in centenarians.[134] We have attempted to achieve the advantages of using mostly
37 explicit criteria, such as ease of application, with the addition of application information
38 (Tables 2 and 4) unavailable in our previous criteria set.
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43 **Use of the RAND/UCLA appropriateness method**

44 We chose the RAND/UCLA appropriateness method, a two-round modified Delphi
45 method[38] to select the most appropriate criteria. Unlike the Delphi method, which generally
46 involves multiple questionnaire-driven rounds to obtain convergence of opinion, the RAND
47 method involves an initial individual rating round, and a second face-to-face round. This
48 method has been shown to produce results that have face, construct and predictive
49 validity.[46 ,135] Systematically combining available evidence with expert opinion can
50 create quality criteria where best evidence may be lacking.[47]
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54 While most lists of prescribing criteria are based on expert consensus, this has often been
55 achieved through mail surveys rather than face-to-face meetings.[25 ,36 ,37] Although face-
56 to-face meetings restrict panel size, they allow discussion to resolve misinterpretations,
57 introduce new evidence, and improve clarity of criteria between rating rounds. We ensured
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3 our panel comprised different specialities, as less disagreement has been found among same-
4 speciality panels.[45] We addressed concern regarding potential intimidation due to dominant
5 panel personalities by choosing a moderator experienced in the development of these criteria
6 and in facilitating small group discussion. Diversity of medication and disease management
7 issues may have minimized professional, but not personal, conflict-of-interest issues. We
8 used both the median panel rating and the amount of dispersion of panel ratings to identify
9 agreement or disagreement. While it has been acknowledged that discrepancies between the
10 two methods may occur,[38] discussion and second round rating resulted in agreement for all
11 criteria for both methods.
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14 15 16 **The nature of decision support tools**

17 Panel members emphasized that criteria may not provide definitive answers, instead
18 indicating potential problems that might need addressing, due to a perceived unacceptable
19 variation in care.[136] While performance indicators are designed to measure the result of
20 statements made in clinical practice guidelines, these guidelines often provide
21 recommendations for care independent of other considerations such as multiple co-
22 morbidities, advanced age, frailty, patient preferences, disease burden or limited life
23 expectancy.[137-139] In such cases, less stringent goals, deprescribing or non-prescription
24 may be more appropriate.[15 ,82 ,140] For example, a frail older patient with multiple co-
25 morbidities and one or more functional impairments may have a life expectancy of
26 approximately two years or less.[76] This raises the question of whether failure to intensify
27 treatment[82] or to underuse evidence-based therapies[141] reflects appropriate clinical
28 judgement or an inappropriate care gap. The panel felt strongly that use of indicators,
29 guidelines or criteria providing clinical decision support should never replace critical thinking
30 in patient care.[142]
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38 **Strengths and weaknesses**

39 We have followed a recommended approach [122] by suggesting criteria for which high
40 quality evidence exists linking best practice with improved outcomes; where there are
41 established evidence-practice gaps[98 ,99]; and where the health conditions impose the
42 greatest burden on the healthcare system. We used a validated consensus method, an expert
43 panel of varied specialization, and criteria written with the aim of conciseness and clarity.
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46 In addition to face and content validity, these validated criteria, much like performance
47 indicators, will require further developmental work to provide evidence of their acceptability,
48 operational feasibility, reliability, and degree of predictive validity.[36 ,136] Some of this
49 work has already commenced with the original criteria.[30] Further, these criteria only cover
50 commonly occurring medicines and medical conditions. In addition, judgements made by an
51 expert panel may not be representative of all health care professionals.
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55 **Intended use**

56 These validated criteria are intended for use by health care providers to enhance the quality of
57 the Australian medication review process, for quality improvement, educational purposes and
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3 internal audit. They are also intended for external quality assessment, such as use by policy
4 makers and for public reporting. Stakeholder involvement will be critical to facilitate local
5 uptake and encourage further research into the effects on health outcomes.[127]
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8 CONCLUSION

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10 This study validated 41 prescribing appropriateness criteria to assist in identifying DRPs in
11 older (≥ 65 years) Australians. These criteria are intended to represent an addition to the
12 medication management skill set that includes consideration of limited life expectancy,
13 evidence base in the oldest old, drug burden and care coordination, patient and care-giver
14 education, empowerment for self management, and shared decision making. These skills are
15 far from a “do everything for everyone” philosophy, where aggressive treatment may
16 encourage more care, not more appropriate care.[24 ,138] Despite the presence of clinical
17 decision support tools, health care providers need to know how to think about clinical
18 problems, not just what to think.[142]
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23 **Competing interests** None declared
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27 drafted the manuscript. TFC and RJM made substantial contributions to the conception,
28 design, analysis and interpretation of the data, and to critically revising the draft. All authors
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3-4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3-4
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4
		(b) Describe any methods used to examine subgroups and interactions	N/A
		(c) Explain how missing data were addressed	N/A
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	4
Outcome data	15*	Report numbers of outcome events or summary measures over time	5
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	17-18
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	18-19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.



Validation of prescribing appropriateness criteria for older Australians using the RAND/UCLA Appropriateness Method

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Validation of prescribing appropriateness criteria for older Australians using the RAND/UCLA Appropriateness Method

ARTICLE SUMMARY

Article focus

- Drug-related problems (DRPs) are common in older people. They may result in drug treatment goals not being achieved and/or the occurrence of adverse drug events
- The aim of this study was to further develop and validate a previously published list of prescribing appropriateness criteria for use in older people which may be used to improve the quality of the Australian medication review process, and for quality assessment and education in medicine use

Key messages

- The use of medication assessment criteria is one method to assist in identifying DRPs. Criteria developed elsewhere may have little or no applicability to the Australian healthcare environment
- Validation of proposed Australian prescribing appropriateness criteria for older people was accomplished using a two-round modified Delphi method, resulting in agreement for all criteria as measured by median panel ratings, and the amount of dispersion of panel ratings, based on the interpercentile range
- Use of these criteria, together with other Australian medication review processes, may assist in improving patient care in a variety of settings by efficiently identifying DRPs to common medical conditions and commonly used medicines. They may also contribute to the medication management knowledge of health care professionals through education programs and by use in daily practice, and for the evaluation of the quality of pharmaceutical care in older people

Strengths and limitations

- A validated consensus method was used involving an expert medication management panel of varied specialisation. Criteria were based on established evidence-practice gaps and degree of disease burden imposed on the health care system, and were written with the aim of conciseness and clarity
- Further developmental work is required to assess the usefulness of these criteria, which only included commonly occurring medicines and medical conditions

ABSTRACT

Objective: To further develop and validate previously published national prescribing appropriateness criteria to assist in identifying drug-related problems (DRPs) for commonly occurring medications and medical conditions in older (≥ 65 years old) Australians.

Design: Rand/UCLA Appropriateness Method

Participants: A panel of medication management experts were identified consisting of geriatricians/pharmacologists, clinical pharmacists, and disease management advisors to

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3 organisations that produce Australian evidence-based therapeutic publications. This resulted
4 in a round one panel of fifteen members, and a round two panel of twelve members

5 **Main outcome measure:** Agreement on all criteria

6 **Results:** Forty eight prescribing criteria were rated. In the first rating round via email, there
7 was disagreement regarding 17 of the criteria according to median panel ratings. During a
8 face-to-face second round meeting, discussion resulted in retention of 25 criteria after
9 amendments, , agreement for 14 criteria with no changes required, and deletion of 9 criteria.
10 Two new criteria were added, resulting in a final validated list of 41 prescribing
11 appropriateness criteria. Agreement after round two was reached for all 41 criteria, measured
12 by median panel ratings and the amount of dispersion of panel ratings, based on the
13 interpercentile range

14 **Conclusions:** A set of 41 Australian prescribing appropriateness criteria were validated by an
15 expert panel. Use of these criteria, together with clinical judgement and other medication
16 review processes such as patient interview, is intended to assist in improving patient care by
17 efficiently detecting potential DRPs related to commonly occurring medicines and medical
18 conditions in older Australians. These criteria may also contribute to the medication
19 management education of health care professionals

20 21 22 23 24 25 26 INTRODUCTION

27
28 Drug-related problems (DRPs) in older people (≥ 65 years old) are common.[1-4] They may
29 result in drug treatment goals not being achieved and/or disproportionately high numbers of
30 serious adverse medication events due to polypharmacy.[5-7] DRPs can occur for many
31 reasons such as undertreatment, inadequate monitoring of medicines, poor medicine or dose
32 selection, duplication of medicines, or factors to do with the way the patient uses the
33 medicine. [2 ,3 ,8-12] Methods to identify and reduce DRPs include health care professional
34 directed educational interventions, [13] comprehensive geriatric assessment,[14]
35 discontinuation of multiple medications, [15 ,16]electronic health record clinical decision
36 support targeted towards certain diseases or drugs,[17 ,18]and the use of medication
37 assessment criteria, which usually consist of explicit (that is, criterion-based rather than
38 implicit or judgement-based) lists of prescribing recommendations for various drugs and/or
39 disease states [13 ,19-22]

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47 In Australia, identification and resolution of DRPs are intended to be considered when
48 patients are interviewed by an accredited pharmacist as part of the Home Medicines Review
49 program.[23] This program aims to provide the sophistication lacking in the application of
50 explicit measures alone, as it takes into account other issues such as the patients history and
51 personal preferences, and is targeted towards patients who may be (among other reasons)
52 currently taking ≥ 5 regular medicines, attending a number of different doctors, or have
53 recently been discharged from hospital.[24]

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3 In 2008, we proposed a list of 48 prescribing appropriateness criteria (45 explicit and three
4 implicit) aimed at improving detection of DRPs as part of the Australian medication review
5 process.[25] These criteria were intended to be applied alongside the patient interview in
6 order to prompt appropriate history taking, particularly with respect to commonly occurring
7 medical conditions and medicines. Similar criteria derived outside Australia have been found
8 to have application in a variety of settings and for a variety of uses, such as in the training of
9 health care professionals and in the evaluation of the quality of health care.[19 ,26-29] Our
10 criteria were based on the most frequent medicines prescribed to Australians, and the most
11 frequent medical conditions for which older Australians (≥ 65 years old) consult medical
12 practitioners. Australian medication and disease state resources and guidelines were used to
13 provide content validity. [25]However, unlike our criteria, other prescribing criteria or tools
14 have combined evidence with expert opinion to provide face validity.
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21 The aim of this study was to further develop our list of criteria, supplementing it with
22 recommendations for co-morbidity and the oldest old where possible, and adding new criteria
23 where necessary through expert consensus. In older patients, the importance of traditional
24 outcomes, such as discrete clinical events or mortality, may be secondary to maintaining
25 physical or cognitive function or relief of symptoms.[30] Because of this, optimal care
26 requires clinical decision support tools that consider issues such as patient preferences,
27 frailty, cost and co-morbidities. [31] Additionally, few criteria target the oldest old[32]
28 (generally regarded as people older than 85 years), where evidence may be poor, and
29 preventive interventions may be encouraged in patients who have already exceeded an
30 average lifespan.[33 ,34]
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35 To further develop and validate our criteria list, we identified a panel of medication
36 management experts, and chose the RAND/UCLA appropriateness method, which has been
37 described as the best method for systematically combining recommendations from clinical
38 guidelines, with the opinion of healthcare providers.[35]
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41 **METHODS**

42 **Ethics**

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44 Ethics approval was obtained from the Human Research Ethics Committee of the University
45 of Sydney.
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49 **Criteria development**

50 In 2008, we identified the 50 highest-volume Australian Pharmaceutical Benefits Scheme
51 (PBS) medicines prescribed, and the forty most common reasons for older Australians to
52 seek or receive healthcare. Healthcare information was obtained using the BEACH (Bettering
53 The Evaluation and Care of Health) program, which continuously collects information about
54 the clinical activities in general practice in Australia.[36] We then used Australian medication
55 information sources to identify both optimal and inappropriate medication management of
56 these common conditions.[25] In Australia, medication availability and use is largely
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3 determined by the PBS.[37] In October 2011, commonly used medications and medical
4 conditions were checked and updated using the BEACH program to ensure that criteria
5 content was current. Changes in evidence, product information, Australian consensus
6 documents, evidence-based publication recommendations or clinical practice guidelines
7 relating to our criteria were noted for evaluation by an expert medication management panel.
8 The criteria were designed to provide guidance on the process of care wherever it occurred –
9 community, hospital, residential home, care home or nursing home. Major considerations in
10 their development were likely accessibility of data from the patient, their medical notes
11 and/or their health care professional(s), conciseness and clarity of wording, and provision of a
12 practical number of criteria. Most were explicit to enable consistent application, with
13 additional notes provided for interpretation where necessary. They were written as a
14 statement of the kind of medication management that should or should not occur, to simplify
15 comprehension and facilitate uptake.[25]
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20 21 **Validation of criteria - participants**

22 We recruited a multidisciplinary group of medication management experts to review, update
23 and rate the criteria, consisting of geriatrician/pharmacologists, clinical pharmacists, and
24 disease management advisors to organisations that produce Australian evidence-based
25 therapeutic publications. This resulted in a round one panel of fifteen members. The
26 geriatricians consisted of two professors of geriatric medicine; an associate professor of
27 clinical pharmacology and aged care; a research fellow in geriatric medicine; and a hospital
28 staff geriatrician. Clinical pharmacists consisted of a residential medication management
29 review pharmacist; a home medicines review pharmacist; four hospital-based pharmacists
30 (two team leaders, one director and one education and training pharmacist), and a professor
31 of aged care (Pharmacy). Disease management advisors to Australian evidence-based
32 therapeutic organisations consisted of Therapeutic Guidelines,[38] Australian Medicines
33 Handbook,[39] and the New South Wales Therapeutic Advisory Group.[40]
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39 **Choice of the RAND/UCLA appropriateness method**

40 We chose the RAND/UCLA appropriateness method, a two-round modified Delphi
41 method[41] to select the most appropriate criteria. Unlike the Delphi method, which generally
42 involves multiple questionnaire-driven rounds to obtain convergence of opinion, the RAND
43 method involves an initial individual rating round, and a second face-to-face round. This
44 method has been shown to produce results that have face, construct and predictive
45 validity.[42 ,43] Systematically combining available evidence with expert opinion can create
46 quality criteria where best evidence may be lacking.[44]
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50 While most lists of prescribing criteria are based on expert consensus, this has often been
51 achieved through mail surveys rather than face-to-face meetings.[32 ,35 ,45] Although face-
52 to-face meetings restrict panel size, they allow discussion to resolve misinterpretations,
53 introduce new evidence, and improve clarity of criteria between rating rounds. We ensured
54 our panel comprised different specialities, as less disagreement has been found among same-
55 speciality panels.[46] We addressed concern regarding potential intimidation due to dominant
56 panel personalities by choosing a moderator experienced in the development of these criteria
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3 and in facilitating small group discussion. This may also have assisted with conflict-of-
4 interest issues. We used both the median panel rating and the amount of dispersion of panel
5 ratings to identify agreement or disagreement. While it has been acknowledged that
6 discrepancies between these two methods may occur,[41]our aim was to achieve agreement
7 for all accepted criteria for both methods after second round discussion.
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10 **RAND/UCLA Appropriateness Method round one**

11 In October 2011 candidate panel members were emailed an explanation of the project and an
12 invitation to participate. After acceptance, they were emailed a rating sheet consisting of 48
13 criteria, and asked to rate each on a nine point scale. Ratings of 1-3 were classified as
14 inappropriate, with a rating of one indicating the greatest degree of inappropriateness. Ratings
15 of 7-9 were classified as appropriate, with a rating of nine indicating the greatest degree of
16 appropriateness. Ratings of 4-6 were classified as neither appropriate nor inappropriate.
17 Appropriate was defined as “the expected health benefit exceeds the expected negative
18 consequences by a sufficiently wide margin that criteria are worth following, exclusive of
19 cost”. They also received a description of the way in which the criteria had been derived, and
20 a comparison with other prescribing criteria.[25 ,32] Panel members were requested to amend
21 the wording or delete, update or identify missing criteria as required. Upon return of the
22 rating sheets, results were tabulated. Agreement was based on four or less panellists rating
23 outside the three-point region containing the median (1-3; 4-6; 7-9), and disagreement was
24 based on five or more panellists rating in each extreme (1-3 and 7-9), as per the
25 RAND/UCLA protocol for a fifteen member panel.[41]
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32 **Rand/UCLA Appropriateness Method round two**

33 In November 2011, a face-to-face meeting of the expert panel, chaired by a panel moderator
34 experienced in facilitating group discussions and criteria development, met to discuss the
35 results of round one and re-rate each of the criteria and any potential additional criteria. One
36 pharmacist, one staff geriatrician and a disease management advisor for a therapeutics
37 publication could not attend, resulting in a twelve member panel. For this meeting, each panel
38 member was provided with a copy of the results from round one. This consisted of the
39 frequency distribution of ratings of all panellists across the 9-point scale, the overall panel
40 median rating for each of the criteria and, for each panellist, an annotation of how they had
41 rated each of the criteria. Scores from other panel members were not revealed. Depending
42 upon panellists votes, panel agreement or disagreement was also stated for each of the round
43 one criteria. Additionally, the 30th and 70th percentiles adjusted for symmetry were
44 computed for each of the criteria, as it has been found that when ratings were symmetric with
45 respect to the middle (five on the 1-9 scale), the interpercentile range (IPR) required to label
46 an indication as disagreement was smaller than when they were asymmetric with respect to
47 the middle (values far from five on the 1-9 scale). Agreement after round two occurred when
48 the interpercentile range adjusted for symmetry (IPRAS) was greater than the IPR .[41]
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55 We used the median method to present data at the face-to-face meeting, as it provided a clear
56 visual interpretation of the ratings for each criterion. By the end of the meeting, our aim was
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3 to ensure that there was agreement between the median method and the interpercentile
4 method for all accepted criteria.
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7 Discussion at round two occurred on the level of agreement for each of the criteria. In
8 addition, discussion was facilitated on the wording of each of the criteria to improve clarity
9 and decide whether agreement would be reached. The definitions of agreement and
10 disagreement were adjusted for the smaller second round twelve member panel.[41]
11 Agreement was reached when three or less panel members voted outside the 3-point region
12 containing the median, or when the IPRAS was greater than the IPR. Disagreement was
13 determined when four or more panellists rated in each extreme (1-3 and 7-9). Each of the
14 criteria were then discussed irrespective of whether there was agreement or disagreement,
15 with panellists having the opportunity of changing their ratings if, for example,
16 misinterpretation had occurred because of the way in which the criteria had been written, or if
17 new evidence had become available, or if criteria had been interpreted in the light of a
18 panellists own clinical experience. Each panel member consented to audio recording of the
19 discussion. Values for the median, IPR and IPRAS [41] were computed using SPSS version
20 20 (SPSS, Chicago, IL, USA).
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25 26 **RESULTS**

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30 After round one, there was agreement for the appropriateness of 31 of the 48 criteria, and
31 disagreement for 17 criteria. . Of the 31 criteria for which there was agreement, discussion at
32 round two resulted in 17 criteria being amended and retained, 2 criteria being deleted, and 12
33 criteria accepted with no change. Of the 17 criteria for which there was disagreement,
34 discussion at round two resulted in 8 criteria being amended and retained, 7 criteria being
35 deleted, and 2 criteria accepted with no change. Two new criteria were added, resulting in a
36 total of 41 validated criteria.
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40 An example of how the RAND/UCLA method was applied to each of our criteria is described
41 in Table 1 for criterion one. The larger the IPRAS, the less asymmetric are the ratings. For
42 example, thirteen of fifteen panellists at round one rated indicator fourteen with a score of
43 eight or nine, for which the IPRAS was 8.35.
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47 Table 2 lists the median panel ratings, the amount of dispersion of panel ratings, and whether
48 there was agreement or disagreement for the original criteria and the validated criteria. It also
49 lists the amendments made by the panel to the original criteria, and the reasons for these
50 amendments. There was 100% agreement for both median panel ratings and dispersion of
51 panel ratings for the validated criteria. Table 3 contains the final list of validated criteria,
52 arranged according to disease states. Table 4 lists usage information judged to be necessary
53 for certain criteria.
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Table 1 An example of the application of the RAND/UCLA appropriateness method to one criterion (criterion one) from round one			
Nine point scale where 1-3 = inappropriate, 4-6 = neither appropriate nor inappropriate, 7-9 = appropriate	Number of panellists rating this criterion (n=15)	Calculations, interpercentile range method[41]	Interpretation
1		30 th percentile = 7.0	This criterion was accepted according to the median method because four or less panellists voted outside the 3 point region containing the median.
2		70 th percentile = 8.0	
3	1	Interpercentile range (IPR) =	
4		70 th minus 30 th percentile) =	
5	1	1.0 Interpercentile range	
6	1	central point (IPRCP) = 30 th	
7	5	+ 70 th percentile divided by 2	
8	5	= 7.5	
9	2	Asymmetry index (AI) = [5	
	median = 7.0	minus IPRCP] (as an absolute value) = 2.5	The IPRAS (6.1) was greater than the IPR (1.0) indicating no disagreement. The larger the IPRAS, the less asymmetric the ratings.
		Interpercentile range adjusted for symmetry (IPRAS) = [2.5 plus (AI x 1.5)] = 6.1 , where 2.5 is the IPR required for disagreement when perfect symmetry exists, and 1.5 is the correction factor for asymmetry	

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Criteria Number	Original prescribing appropriateness criteria for older (≥ 65 years) Australians published in 2008[25]	Rating by median method[41] (median value, A= agreement, D= disagreement), n=15		Rating by IPRAS ¹ method[41] (IPR value, IPRAS value, A = agreement, D = disagreement), n=15		Validated prescribing appropriateness criteria for older (≥ 65 years) Australians as a result of this study	Rating by median method[41] (median value, A= agreement, D= disagreement), n=12		Rating by IPRAS ¹ method[41] (IPR value, IPRAS value, A = agreement, D = disagreement), n=12		Amendment/reason
1.	Patient taking an antihypertensive is at their target blood pressure	7	A	1.00, 6.10	A	Patient taking an antihypertensive is at the target blood pressure appropriate for them	8	A	1.10, 7.52	A	“Appropriate for them” added. Current blood pressure guidelines may not be appropriate for all older patients[47-49]. For example, in the oldest old[50]; in palliative care; and for those who are/become hypotensive and/or fall[51,52]
2.	Patient at high risk of a cardiovascular event is taking a statin	7	A	1.00, 6.10	A	Patient at high risk of a recurrent cardiovascular event is taking a statin	8	A	1.00, 6.10	A	“Recurrent” added to ensure use in secondary prevention of cardiovascular events rather than primary prevention, where evidence is less clear, especially in the oldest old[33,53-57]
3.	Patient with IHD or a history of MI is taking a beta blocker	8	A	2.00, 6.85	A	Patient with CHD or a history of MI is taking a beta blocker	7	A	1.00, 6.10	A	“CHD” replaced “IHD”. The term “coronary heart disease” is preferred over “ischemic heart disease”
4.	Patient with IHD or a history of MI is taking an antiplatelet agent unless on an oral anticoagulant	8	A	1.00, 7.60	A	Patient with CHD or a history of MI is taking an antiplatelet agent unless on an oral anticoagulant	8	A	1.00, 7.60	A	“CHD” replaced “IHD”. The term “coronary heart disease” is preferred over “ischemic heart disease”
5	Patient with heart failure is taking a beta blocker	7	A	1.00, 6.10	A	Patient with stable heart failure with left systolic ventricular dysfunction (HF-	8	A	0.10, 6.78	A	Description of heart failure amended. The use of beta blockers is contra-indicated in

						LVSD) is taking a beta blocker					unstable heart failure. The optimal treatment of heart failure with preserved ejection fraction (HFPEF) is uncertain at this time[58 ,59]
6.	Patient with heart failure is taking an ACEI or A2A	8	A	2.00 6.85	A	Patient with stable heart failure with left systolic ventricular dysfunction (HF-LVSD) is taking an ACEI or A2A	9	A	1.00, 7.60	A	Description of heart failure amended. The optimal treatment of heart failure with preserved ejection fraction (HFPEF) is uncertain at this time[58 ,59]
7.	Patient with heart failure is NOT taking medications which may exacerbate heart failure	9	A	1.00, 7.60	A	Patient with HF-LVSD or HFPEF is NOT taking medications which may exacerbate heart failure	9	A	0.10, 8.27	A	Description of heart failure amended. The types of medicines contraindicated in HF-LVSD and HFPEF may not be identical[60 ,61]
8	Patient with heart failure or hypertension is NOT taking high sodium medications	8	D	2.20, 5.50	A	Deleted	-		-	-	High sodium medicines (among others) in heart failure are addressed by indicator 7. In hypertension, they are addressed as lifestyle modifications[62 ,63]
9.	Patient with AF is taking an oral anticoagulant	7	D	2.0, 5.35	A	Patient with AF is taking an oral anticoagulant or an antiplatelet agent, depending upon stroke risk and bleeding risk	8	A	0.10, 6.93	A	An antiplatelet agent may be appropriate for patients at low risk of stroke. Bleeding risk may determine choice of antithrombotic agent[49 ,64 ,65]
10.	Patient with AF taking an anticoagulant has an INR between 2 – 3	8	A	2.20, 6.70	A	Patient taking warfarin for AF has an INR between 2-3	9	A	1.00, 7.60	A	New anticoagulants like rivaroxaban and dabigatran do not require INR monitoring
11.	Patient with a history of non-hemorrhagic stroke or TIA is taking an antiplatelet agent unless on an anticoagulant	8	A	1.00, 7.60	A	Patient with a history of non-hemorrhagic stroke or TIA is taking an antiplatelet agent unless on an anticoagulant	9	A	1.00, 7.60	A	No change
12.	Patient with risk factors for myopathy is NOT taking	7	D	3.00, 4.60	A	Patient with risk factors for statin induced myopathy is	8	A	1.10, 7.52	A	The use of all high dose high potency statins together with

	40mg or more per day of simvastatin or atorvastatin					not taking a high dose of a high potency statin					risk factors may increase the likelihood of myopathy[49 ,66 ,67]
13.	Patient with cardiovascular disease is NOT taking an NSAID	7	A	1.20, 5.95	A	Patient with cardiovascular disease is NOT taking an NSAID	8	A	1.10, 6.18	A	No change
14.	Patient with cardiovascular, respiratory disease or diabetes who smokes has been offered smoking cessation therapy	9	A	0.00, 8.35	A	Patient with cardiovascular, respiratory disease or diabetes who smokes has been offered smoking cessation options	9	A	0.00, 8.35	A	“Therapy” implies pharmacotherapy, whereas repeated counselling/psychotherapy may be preferred to avoid the risks associated with polypharmacy
15.	Patient with type 2 diabetes and hypertension and albuminuria is taking an ACEI or A2A	8	A	2.00, 6.85	A	Patient with type 2 diabetes and hypertension and albuminuria is taking an ACEI or A2A	9	A	1.00, 7.60	A	No change.
16.	Patient with diabetes at high risk of a cardiovascular event is taking an antiplatelet agent unless on an anticoagulant	7	D	2.20, 5.50	A	Patient with diabetes at high risk of a cardiovascular event is taking an antiplatelet agent unless on an anticoagulant	9	A	1.00, 7.60	A	No change
17.	Patient with diabetes is NOT taking a medication which may increase or decrease blood glucose concentrations	5	D	2.20, 3.70	A	Patient with diabetes receiving medications that may affect glycemic control is having regular monitoring of blood glucose concentrations	9	A	1.00, 7.60	A	Increased awareness and monitoring may require adjustment of hypoglycemic medication doses, depending upon the need to continue interacting medicines. For example, commencement of oral corticosteroids may worsen diabetes control[39]
18.	Patient with diabetes has had an HbA1c measurement within the previous 6 months	8	A	1.20, 7.45	A	Patient with diabetes has had an HbA1c measurement within the previous 6 months	8	A	1.00, 7.60	A	No change
19.	Patient taking metformin for diabetes has had the dose adjusted for	8	A	1.20, 7.45	A	Patient taking metformin for diabetes has had the dose adjusted for renal function	9	A	1.00, 7.60	A	Creatinine clearance may represent only one of the methods used to determine

	creatinine clearance										renal function
20.	Patient taking metformin for diabetes is NOT concurrently taking glibenclamide	6	D	2.40, 3.85	A	Deleted	-		-	-	Glibenclamide is an uncommonly used hypoglycaemic
21.	Patient with OA pain interfering with daily activities has been trialled on paracetamol 2 – 4 g per day	8	A	2.00, 6.85	A	Patient with OA pain interfering with daily activities has been trialled on regular paracetamol 2 – 4 g per day	9	A	0.40, 8.05	A	“Regular” paracetamol added to improve quality of indicator
22.	Patient taking analgesic(s) does NOT have pain that interferes with daily activities	7	D	3.2, 4.75	A	Patient taking analgesic(s) has had the dose(s) titrated in order to avoid pain that interferes with daily activities	8	A	2.00, 6.85	A	Indicator rephrased to improve clarity
23.	Patient taking an opioid is on prophylactic treatment for constipation	8	A	2.00, 6.85	A	Patient taking a regular opioid is on prophylactic treatment for constipation	9	A	1.00, 7.60	A	“Regular” use added as “when required” use may not always require prophylactic treatment
24.	Patient with risk factors for impaired renal function is NOT taking an NSAID	8	A	1.00, 7.60	A	Patient with risk factors for impaired renal function is NOT taking an NSAID	8	A	1.00, 7.60	A	No change
25.	Patient is NOT concurrently taking an ACEI or A2A, diuretic and NSAID (excluding low dose aspirin)	9	A	1.00, 7.60	A	Patient is NOT concurrently taking an ACEI or A2A, diuretic and NSAID (excluding low dose aspirin)	9	A	1.00, 7.60	A	No change
26.	Patient with sleep disturbance or anxiety has NOT been taking benzodiazepines for > 4 weeks	8	A	1.20, 7.45	A	Patient has NOT been taking benzodiazepines for > 4 weeks	9	A	1.00, 7.60	A	“Sleep disturbance or anxiety” deleted. Benzodiazepines increase the risk of oversedation, ataxia, confusion, falls, respiratory depression and short-term memory impairment, and are recommended for short term use only[39].
27.	Patient with depression is NOT taking	7	D	1.00, 4.60	A	Deleted	-		-	-	The issue of anticholinergic burden is addressed by

	anticholinergic type antidepressants										indicator 32
28.	Patient with a history of falls is NOT taking psychotropic medications	8	A	1.00, 6.10	A	Patient with a history of falls is NOT taking psychotropic medications	8	A	1.40, 6.40	A	No change
29.	Patient taking an SSRI is NOT concurrently taking medications known to increase the risk of GI bleeding	7	D	2.20, 5.20	A	Deleted	-		-	-	Redundant indicator. This issue would be identified by indicator 47.
30.	Patient taking an SSRI is NOT concurrently taking other medications that may contribute to serotonin toxicity	8	A	2.20, 6.70	A	Patient taking an SSRI is NOT concurrently taking other medications that may contribute to serotonin toxicity	8	A	1.40, 6.40	A	No change. Retained by panel due to its potential significance, despite the use of indicator 47
31.	Patient with dementia is NOT receiving anticholinergic medication	8	A	1.20, 7.45	A	Patient with dementia is NOT receiving anticholinergic medication	8	A	1.00, 7.60	A	No change
32.	Patient is NOT taking more than one medication with anticholinergic activity	8	A	0.2, 6.70	A	Patient is not taking medication with SIGNIFICANT anticholinergic activity	8	A	0.40, 7.15	A	Rewording focuses on the issue of anticholinergic burden
33.	Patient taking a PPI is NOT taking a medication that may cause dyspepsia	7	D	3.20, 4.45	A	Patient taking a PPI is NOT taking a medication that may cause dyspepsia unless prescribed for gastroprotection	8	A	0.40, 7.15	A	“Unless prescribed for gastroprotection” added to improve the accuracy of the indicator
34.	Patient with COPD is NOT taking benzodiazepines	7	D	3.00, 6.10	A	Patient with COPD is NOT taking benzodiazepines	8	A	1.00, 6.10	A	No change
35.	Patient with asthma using an inhaled LABA is also using an inhaled corticosteroid	9	A	0.20, 8.20	A	Patient with asthma using an inhaled LABA is also using an inhaled corticosteroid	9	A	1.00, 7.60	A	No change
36.	Patient using salbutamol or terbutaline inhaler more	9	A	1.00, 7.60	A	Patient using salbutamol or terbutaline inhaler more than	9	A	0.40, 8.05	A	“Except for exercise-induced asthma” added to improve the

	than 3 times per week for reversible airways disease has been prescribed an ICS					3 times per week for reversible airways disease has been prescribed an ICS (except for exercise-induced asthma)					accuracy of the indicator
37.	Patient with asthma is NOT taking a medication that may worsen asthma	7	A	1.20, 6.25	A	Patient with asthma is NOT taking a medication that may worsen asthma	8	A	1.00, 7.60	A	No change
38.	Female patient with recurrent UTIs has been prescribed intravaginal estrogen	5	D	2.00, 3.85	A	Deleted	-		-	-	Evidence for this indicator was judged to be poor[68]
39.	Patient with a creatinine clearance < 60 ml/min is NOT receiving nitrofurantoin for UTI	8	A	2.00, 6.85	A	Patient with a UTI is not receiving nitrofurantoin or hexamine for prophylaxis or acute treatment	8	A	1.00, 7.60	A	Hexamine and nitrofurantoin are not recommended for the prophylactic or acute treatment of UTI in older patients[39 ,49]
40.	Patient with a creatinine clearance < 50ml/min is NOT receiving hexamine for UTI prophylaxis	8	A	1.20, 6.25	A	Deleted	-	-	-	-	Hexamine and are not recommended for the prophylactic treatment of UTI in older patients[39 ,49].
41.	Patient with an URTI is NOT receiving antibiotics	7	D	3.00, 4.60	A	Patient with a non-specific URTI is NOT receiving antibiotics	8	A	1.00, 7.60	A	“non-specific” added to improve the accuracy of the indicator
42.	Patient with osteoporosis who is not receiving at least 600 IU Vitamin D daily from dietary sources is receiving supplementation with vitamin D	8	D	3.20, 4.75	A	Deleted	-		-	-	This indicator is covered by indicator 44 and an expanded footnote
43.	Patient with osteoporosis who is not receiving at least 1200 mg of calcium daily from dietary sources is receiving calcium	8	A	1.60, 5.95	A	Deleted	-		-	-	This indicator is covered by indicator 44 and an expanded footnote

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	supplementation										
44.	Patient with osteoporosis is receiving anti-osteoporotic medication	7	A	1.00, 6.10	A	Patient with osteoporosis is receiving appropriate anti-osteoporotic medication	8	A	0.40, 7.15	A	“Appropriate” added and an expanded footnote to include calcium and vitamin D
45.	Patient using topical corticosteroids does NOT have itch or discomfort that interferes with daily activities	6	D	2.00, 5.35	A	Patient using topical corticosteroids for contact or allergic dermatitis does not have itch or discomfort that interferes with daily activities	-		-	-	This indicator was deleted by the panel because there was no identification of the diagnosis/condition being treated. However, contact and allergic dermatitis is one of the top 40 most frequently managed problems by general practitioners in patients ≥ 65 years old in Australia,[36] so this indicator was re-worded by the authors
46.	Patient has received influenza and pneumococcal vaccination	9	A	1.00, 7.60	A	Patient has received influenza and pneumococcal vaccination	9	A	0.00, 8.35	A	No change
47.	Patient has no <i>significant</i> medication interactions (agreement between two medication interaction databases)	8	D	3.00, 6.10	A	Patient has no <i>clinically significant</i> medication interactions (agreement between two medication interaction databases)	8	A	0.40, 7.15	A	“Clinically” added to improve the accuracy of the indicator
48.	Patient has had no <i>significant</i> change in medications in the previous 90 days	5	D	1.20, 3.25	A	Deleted	-		-	-	It was preferred to transfer this information to the explanatory text of the article
New						Patient taking thyroid hormone replacement therapy has had a serum TSH measurement within the previous 12 months					Thyroid disease is a common medical condition managed by GPs in older Australians[36 ,69]
New						Patient with coronary heart disease is taking an ACEI or A2A					ACEIs or A2As reduce the risk of cardiovascular events[70 ,71]. However, a high incidence of comorbid disease

Table 3 Validated prescribing appropriateness criteria for older Australians (≥ 65 years) for commonly used medications and medical conditions^{a,b,c} (*for usage information for certain criteria, see Table 4)

Criteria No.	Validated criteria
1	Patient taking an antihypertensive is at the target blood pressure appropriate for them*
2	Patient at high risk of a recurrent cardiovascular event is taking a statin*
3	Patient with CHD or a history of MI is taking a beta blocker
4	Patient with CHD or a history of MI is taking an antiplatelet agent unless taking an oral anticoagulant*
5	Patient with CHD is taking an ACEI or A2A*
6	Patient with stable heart failure with HF-LVSD is taking a beta blocker
7	Patient with stable heart failure with HF-LVSD is taking an ACEI or A2A*
8	Patient with HF-LVSD or HFPEF is NOT taking medications which may exacerbate heart failure
9	Patient with AF is taking an oral anticoagulant or an antiplatelet agent, depending upon stroke risk and bleeding risk*
10	Patient taking warfarin for AF has an INR between 2-3
11	Patient with a history of non-hemorrhagic stroke or TIA is taking an antiplatelet agent unless taking an anticoagulant
12	Patient with risk factors for statin induced myopathy is not taking a high dose of a high potency statin*
13	Patient with cardiovascular disease is NOT taking an NSAID
14	Patient with cardiovascular, respiratory disease or diabetes who smokes has been offered smoking cessation options*
15	Patient with type 2 diabetes and hypertension and albuminuria is taking an ACEI or A2A
16	Patient with diabetes at high risk of a cardiovascular event is taking an antiplatelet agent unless on an anticoagulant
17	Patient with diabetes taking medications that may affect glycemic control is receiving regular monitoring of blood glucose concentrations*
18	Patient with diabetes has had an HbA1c measurement within the previous 6 months*
19	Patient taking metformin for diabetes has had the dose adjusted for renal function*
20	Patient taking thyroid hormone replacement therapy has had a serum TSH measurement within the previous 12 months
21	Patient with OA pain interfering with daily activities has been trialled on regular paracetamol 2 – 4 g per day
22	Patient taking analgesic(s) has had the dose(s) titrated in order to avoid pain that interferes with daily activities
23	Patient taking a regular opioid is on prophylactic treatment for constipation
24	Patient with risk factors for impaired renal function is NOT taking an NSAID*
25	Patient is NOT concurrently taking an ACEI or A2A, diuretic and NSAID (excluding low dose aspirin)
26	Patient has NOT been taking benzodiazepines for > 4 weeks*
27	Patient with a history of falls is NOT taking psychotropic medications*
28	Patient taking an SSRI is NOT concurrently taking other medications that may contribute to serotonin toxicity*
29	Patient with dementia is NOT receiving anticholinergic medication*
30	Patient is not taking medication with SIGNIFICANT anticholinergic activity*
31	Patient taking a PPI is NOT taking a medication that may cause dyspepsia unless prescribed for gastroprotection*
32	Patient with COPD is NOT taking benzodiazepines
33	Patient with asthma using an inhaled LABA is also using an inhaled corticosteroid
34	Patient using salbutamol or terbutaline inhaler more than 3 times per week for reversible airways disease has been prescribed an ICS (except for exercise-induced asthma)
35	Patient with asthma is NOT taking a medication that may worsen asthma*
36	Patient with a UTI is not receiving nitrofurantoin or hexamine for prophylaxis or acute treatment
37	Patient with a non-specific URTI is NOT receiving antibiotics*
38	Patient with osteoporosis is receiving appropriate anti-osteoporotic medication*

39	Patient has received influenza and pneumococcal vaccination
40	Patient using topical corticosteroids for contact or allergic dermatitis does not have itch or discomfort that interferes with daily activities
41	Patient has no <i>clinically significant</i> medication interactions (agreement between two medication interaction databases)*

a – These criteria are intended to be used by appropriately trained and qualified health professionals, as a tool to assist in making medication management decisions as part of the medication review process

b – Prior to the commencement of any medication, the contraindications and precautions for that medication should be considered

c – The intended result of using these criteria is the reasonable and appropriate medication management of individual patients, rather than the systematic application of these criteria to all patients irrespective of other considerations

A2A = angiotensin 2 receptor antagonist, ACEI = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, CHD = coronary heart disease, COPD = chronic obstructive pulmonary disease, HbA1c = glycosylated haemoglobin, HF-LVSD = Heart failure with left ventricular systolic dysfunction, HFPEF = heart failure with preserved ejection fraction, ICS = inhaled corticosteroid, INR = international normalised ratio, MI = myocardial infarct, LABA = long acting beta agonist, NSAID = non-steroidal anti-inflammatory drug, PPI = proton pump inhibitor, SSRI = selective serotonin reuptake inhibitor, TIA = transient ischemic attack, TSH = thyroid stimulating hormone, UTI = urinary tract infection.

Criteria No.	Description of issue	Details
1	Blood pressure targets (mm Hg)	Proteinuria >1 g/day (with or without diabetes) < 125/75. CHD, diabetes, chronic kidney disease, proteinuria (> 300mg/day), stroke or TIA < 130/80. Others <140/90[39] Current blood pressure guidelines may not be appropriate for all older patients, such as the oldest old; in palliative care; and for those who are/become hypotensive and/or fall[47 ,49-52 ,73]
2	Patients at high risk of a cardiovascular event (> 15% within the next 5 years)	Age > 75 years; history of diabetes, moderate or severe chronic kidney disease (persistent proteinuria, GFR < 60ml/min, eGFR < 45 ml/min/1.73m ²), hypercholesterolemia (familial, TC > 7.5 mmol/L), SBP ≥ 180 or DBP ≥ 110 mmHg, ISH (SBP ≥160 and DBP ≤70 mmHg), coronary heart disease, stroke, TIA, PAD, heart failure, aortic disease, LVH, family history of premature CVD.[39 ,74] The benefits of statins and risks of adverse effects are uncertain towards the end of life[75]
4	Antiplatelet agents and oral anticoagulants	Antiplatelet agents – aspirin, clopidogrel, dipyridamole, ticlopidine. Oral anticoagulants – dabigatran, phenindione, rivaroxaban, warfarin
5	Use of ACEI or A2A in CHD	A high incidence of comorbid disease in CHD (typically arthritis and/or respiratory disease) or other clinical factors (e.g. dizziness or falls, cognitive impairment, use of > 5 medicines, patient preference) may be considerations in determining medication prescribing priorities[30 ,34 ,72]
8	Medications that may exacerbate heart failure	HF-LVSD – anti-arrhythmic medicines (except for heart failure-specific beta-blockers and amiodarone), non-dihydropyridine calcium-channel blockers (e.g. verapamil or diltiazem), clozapine, corticosteroids, NSAIDs (excluding low dose aspirin), thiazolidinediones, TNF-alpha inhibitors, topical beta blockers (when added to systemic beta blockers), tricyclic antidepressants[49 ,76 ,77]. HFPEF – venodilators (e.g. isosorbide dinitrate), potent arterial

		vasodilators (e.g. hydralazine), digoxin (unless AF), excessive use of diuretics. Note; verapamil and diltiazem may improve diastolic function in HFPEF[60]
9	Stroke risk and bleeding risk	Stroke risk can be calculated using CHADS ₂ or CHA ₂ DS ₂ -VASc.[78] Risk factors for coumarin-related bleeding complications: advanced age, uncontrolled hypertension, history of MI or IHD, cerebrovascular disease, anaemia or a history of bleeding, concomitant use of aspirin/polypharmacy[79]
12	Risk factors for statin myopathy; high dose of high potency statins	Age > 70 years, presence of disease states (diabetes, hypothyroidism, renal and hepatic disease), concurrent use of cyclosporin, fibrates, CYP3A4 inhibitors (e.g. diltiazem, macrolides, protease inhibitors, verapamil [except for pravastatin and rosuvastatin], severe intercurrent illness (infection, trauma, metabolic disorder), dose ≥ 40 mg daily. High dose of high potency statins ; ≥ 40 mg atorvastatin or simvastatin; > 10mg rosuvastatin [39 ,80]
14	Smoking cessation options	Counselling (extended, brief, telephone), support services (professional, family, social, work), pharmacotherapy.
17	Medications that may affect glycemic control	Increase blood glucose: baclofen, clozapine, cyclosporin, glucocorticoids, haloperidol, olanzapine, paliperidone, phenytoin, protease inhibitors, quetiapine, risperidone, sirolimus, tacrolimus, and tricyclic antidepressants. Decrease blood glucose: excessive alcohol, disopyramide, perhexiline, quinine, trimethoprim/sulphamethoxazole[39]
18	Six monthly HbA1c measurements	Treatment intensification in response to less than optimally controlled HbA1c may be inappropriate in patients with limited life expectancy or in frail older patients[81 ,82]
19	Metformin dose	Based on creatinine clearance: 60-90 ml/min, maximum 2g daily; 30-60 ml/min, maximum 1g daily; < 30 ml/min avoid use.[39] Based on eGFR: Review dose if eGFR< 45 ml/min/1.73m ² ; avoid if eGFR<30 ml/min/1.73m ² [83]
24	Risk factors for impaired renal function	Volume depletion, age > 60 years, salt-restricted diet, concomitant use of ACEIs, A2As, cyclosporin or aspirin, GFR ≤ 60 ml/min, cirrhosis, heart failure[84]
26	Benzodiazepine use	Benzodiazepines increase the risk of oversedation, ataxia, confusion, falls, respiratory depression and short-term memory impairment, and are recommended for short term use only.[39]
27	Falls and psychotropic medications	Psychotropic medications = antidepressants (all), anxiolytics/hypnotics, antipsychotics.[85 ,86] Medications causing (postural) hypotension (e.g. cardiovascular medicines) or cognitive impairment (e.g. opioids) may also increase the risk of falls[49 ,87]
28	Medications that may contribute to serotonin syndrome	Antidepressants - desvenlafaxine, duloxetine, St John's wort, MAOIs (including moclobemide), SSRIs, TCAs, venlafaxine. Opioids - dextromethorphan, fentanyl, pethidine, tramadol. Others - selegiline, linezolid, lithium, tryptophan[39]
29 and 30	Medications with significant anticholinergic activity	amantadine, amitriptyline, atropine*, belladonna alkaloids*, benzhexol, benzotropine, biperiden, brompheniramine*, chlorpheniramine, chlorpromazine, clomipramine, clozapine, cyclizine, cyclopentolate, cyproheptadine*, darifenacin, dexchlorpheniramine*, dimenhydrinate*, diphenhydramine*, disopyramide, dothiepin, doxepin, glycopyrrolate,

		homatropine, hyoscine* (butylbromide or hydrobromide), imipramine, ipratropium (nebulised), mianserin, nortriptyline, olanzapine, orphenadrine, oxybutynin, pericyazine, pheniramine*, pimozone, pizotifen, prochlorperazine, promethazine*, propantheline, solifenacin, tiotropium, tolterodine, trimeprazine*, trimipramine, triprolidine*, tropicamide (* available over-the-counter in Australia)[39]
31	Medications that may cause dyspepsia	Drugs with anticholinergic effects, aspirin, benzodiazepines, bisphosphonates, calcium channel antagonists, oral corticosteroids, dopaminergic drugs, doxycycline, erythromycin, ferrous sulphate, nitrates, NSAIDs, potassium chloride (slow release)[38,39,49,88]
35	Medications that may worsen asthma	Aspirin, beta blockers (including eye drops), carbamazepine, echinacea, NSAIDs, royal jelly[39,89]
38	Non-specific URTI	Acute bronchitis, pharyngitis, tonsillitis, nonsuppurative otitis media and sinusitis[38]
39	Appropriate anti-osteoporotic medication	Recommended daily intake (RDI) of calcium from dietary sources and/or supplements = 1300-1500 mg daily. RDI for Vitamin D from sunlight and/or dietary sources and/or supplements = 600 iu daily. Anti-osteoporotic medication = bisphosphonates, calcitriol, denosumab, HRT, raloxifene, strontium, teriparatide.[39] Evidence for fracture risk reduction in women ≥ 75 years is either absent or lacking in NVF for alendronate, risedronate and teriparatide, and in HF for alendronate, risedronate, zoledronic acid and teriparatide. There is no data available for denosumab in VF, NVF or HF.[90] The optimal duration of bisphosphonate therapy is uncertain. Evidence supports the use of strontium for 5 years, raloxifene for 4 years, zoledronic acid and denosumab for 3 years. Exposure to teriparatide should be limited to 18 months.[91] Data are limited for non-ambulatory patients and those with significant comorbidities.[92] It should be noted that bone strength is only one of many determinants of fracture risk.[93]
42	Clinically significant medication interactions	Medication interactions that may interfere with the outcome of therapy

A2A = angiotensin 2 receptor antagonist, ACE = angiotensin converting enzyme, ACEI = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, CHADS₂ = Cardiac failure, Hypertension, Age, Diabetes, Stroke [doubled], CHA₂DS₂-VASc = Cardiac failure or dysfunction, Hypertension, Age over 75 years [doubled], Diabetes, Stroke [doubled], Vascular disease, Age 65-74 years, Sex category [female], CHD = coronary heart disease, CVD = cardiovascular disease, DBP = diastolic blood pressure, GFR = glomerular filtration rate, HF = hip fracture, HF-LVSD = Heart failure with left ventricular systolic dysfunction, HFPEF = heart failure with preserved ejection fraction, HRT = hormone replacement therapy, IHD = ischemic heart disease, ISH = isolated systolic hypertension, LVH = left ventricular hypertrophy, MAOI = monoamine oxidase inhibitor, MI = myocardial infarct, NSAID = non-steroidal anti-inflammatory drug, NVF = non-vertebral fracture, PAD = peripheral arterial disease, SBP = systolic blood pressure, SSRI = selective serotonin reuptake inhibitor, TC = total cholesterol, TCA = tricyclic antidepressant, TIA = transient ischemic attack, TNF = tumour necrosis factor, URTI = upper respiratory tract infection, VF = vertebral fracture

DISCUSSION

This study identified a panel of medication management experts to discuss and validate a set of 41 prescribing appropriateness criteria for commonly used medicines and medical conditions in older (≥ 65 years) Australians. Panel discussion resulted in retention of 39 of the

originally proposed 48 criteria, with 25 being reworded, and 14 accepted with no change. These criteria do not simply represent a list of medications to avoid in the elderly, but also address issues such as the need for additional therapy (e.g. criteria 23 and 34, Table 3), additional tests (e.g. criteria 18-20, Table 3), ineffective treatment (e.g. criteria 22 and 37, Table 3) and medication monitoring (e.g. criteria 10 and 20, Table 3). They were designed to contribute to the Australian quality use of medicines (QUM) process.[94] The information required to apply these criteria may be obtained from the patient or their carer, and patient medical notes and/or their health care professional. [95] It may also be provided by a Home Medicines Review referral form from the patients general practitioner.[23] Due to their currency and the nature of their development, we expect these criteria to make a significant contribution to the detection of DRPs in the Australian healthcare environment. For example, in a review of prescribing indicators for two conditions, [36] which are common in older people in Australia – type two diabetes and cardiovascular disease [96 ,97] – disease and drug-orientated criteria such as ours have shown good content, face, concurrent and predictive validity and operational feasibility, as well as use for internal and external quality assessment in both ambulatory and hospital care.[35] Evidence-practice gaps in Australia have been identified in other areas besides diabetes and cardiovascular disease, such as in asthma, pain and vaccination status.[9 ,98-101] The existence of these gaps formed part of the developmental process for these criteria.

Prescribing appropriateness tools in Australia

Appropriateness of prescribing has been assessed by measures that are explicit or implicit, in an effort to identify and reduce DRPs.[102] In Australia, both types of measures have been used.[103-107] However, they have been imported into the Australian healthcare environment, with consequent shortcomings related to both the intrinsic nature of the measure, as well as environment compatibility issues. For example, in a study evaluating the impact of Home Medicine Reviews on appropriateness of prescribing, a significant number of recommendations made regarding the need for monitoring and addition of missing therapy were found to have no impact on explicitly derived scores using the Medication Appropriateness Index,[103] due to the intrinsic shortcomings of this tool. This is not a tool that gives precise guidance in relation to specific medicines.[13]

The Beers criteria,[108] perhaps the tool most widely used to assess inappropriate prescribing in older people, has been used in Australia, but requires modification to exclude medicines not listed for government subsidy.[107] This is because medicine availability and use in Australia is largely determined by the Australian Pharmaceutical Benefits Scheme[37]. Other Australian studies have found that some medicines listed as inappropriate by Beers may be appropriate for certain older people according to Australian practice:[105] many medicines listed by Beers are not available in Australia; and that some medicines considered inappropriate in Australia are not listed by Beers.[106] Disagreement between Beers and other criteria, such as the improving prescribing in the elderly tool (IPET), have been identified.[109]

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3 The Beers criteria was recently updated,[22] with approximately half the medicines listed
4 being unavailable in Australia. Further, almost three quarters of the diseases or syndromes
5 listed are not among the forty problems most frequently managed in patients over sixty five
6 years of age by Australian general practitioners.[97] Beers still contains recommendations to
7 avoid some medicines that are recommended for certain older people in Australia such as
8 amiodarone, and it has recently been shown that rhythm control in older patients with atrial
9 fibrillation may be more effective than rate control in reducing mortality over the long-
10 term.[110]. Reviews of explicit and implicit criteria have identified these and other problems
11 such as; failure to address drug-drug interactions and drug duplication, errors in
12 recommendations, underrepresentation of certain drug categories, inclusion of infrequently
13 prescribed drugs, criteria that are inapplicable for all situations, disagreement between
14 criteria, and lack of organisation of criteria.[45 ,102 ,111]
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20 This has resulted in the development by others of criteria more suited to their own particular
21 healthcare environment.[112 ,113] Nationally based criteria have been described as the most
22 desirable type of criteria, as they do not necessitate adaptation to local guidelines or national
23 formularies before they can be used with confidence. [32]In 2008 we therefore sought to
24 construct and validate a set of prescribing appropriateness criteria relevant to the Australian
25 healthcare environment. Our development process differed from most other tools[21 ,108
26 ,112-117] as it did not initially involve a consensus panel, which has now been addressed.
27 This development process also resulted in criteria unavailable in other tools such as
28 monitoring, underprescribing, need for additional tests, evaluation of smoking and
29 vaccination status, and certain drug interactions[32 ,45 ,102] Because we have generally
30 named drug classes rather than specific drugs (Table 3), and targeted common medical
31 conditions found in older patients,[118 ,119] we anticipate that our work may have some
32 international usefulness.
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38 Despite a desire in Australia to develop decision support tools to improve healthcare
39 quality,[120] progress has consisted of the development of a limited number of non-age
40 specific structure and process indicator lists for use in hospitals and general practice.[40 ,121-
41 123] Many of these lists require updating. [32 ,113 ,124] Currently, there is no Australian
42 prescribing appropriateness criteria list to assist in improving medication management in
43 older people. The usefulness of such an approach has been acknowledged, together with other
44 approaches such as medication review.[125]
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48 **Co-morbidity**

49 Over 80% of older Australians have three or more chronic conditions,[96] with Australian
50 general practitioners shown to be dealing more frequently with patients presenting with three
51 or four problems in the year 2009-10 compared with 2000-01.[126] Co-morbidity is
52 associated with poor quality of life, physical disability, high health care use, multiple
53 medicines with consequent increased risk of adverse drug events, fragmentation of care, and
54 increased mortality.[119 ,127] Yet most Australian guidelines for chronic diseases do not
55 modify or discuss the applicability of their recommendations to older patients with multiple
56 comorbid conditions. [34] This situation is not restricted to Australia.[127 ,128]Because the
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3 risk of harm in older patients increases in proportion to the number of treatments prescribed,
4 prioritization of therapeutic goals is necessary. For example, coronary heart disease (CHD) is
5 an important morbidity in Australia[77 ,96] for which treatment with ACE inhibitors or
6 angiotensin 2 antagonists has been recommended to reduce the risk of cardiovascular
7 events.[70 ,71] Other criteria derived outside Australia such as STOPP/START do not
8 include this recommendation. [21] However, the presence of co-morbidity in CHD
9 (commonly arthritis or respiratory disease) or other clinical factors (such as dizziness, falls or
10 patient preference) may mean that medicines such as these are never commenced, due to
11 consideration of other factors. While we wished to identify problems such as these, the
12 ultimate decision regarding medicine use should always be made on a case by case basis
13 based on clinical experience, a discussion between the health care professional and the
14 patient, and best available evidence. [72] Issues such as these may run counter to
15 recommendations of disease-specific, evidence-based guidelines.[34] . Addition of our
16 criteria with this associated usage information (Table 4) to the implicit processes of
17 Australian medication review may assist in addressing the problem of co-morbidity.
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23 **The Oldest Old**

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26 Knowledge about the state of health and function of the oldest old is limited,[129] with
27 research on their drug use being scarce, and often based on small and selected samples
28 without comparison with other age groups.[130 ,131] We know that older patients in general
29 are underrepresented in clinical trials, so that disease-specific guideline recommendations
30 based on evidence may not apply to older cohorts.[34] For example, undertreatment with
31 anti-osteoporotic medicines has been identified as a significant evidence-practice gap in
32 Australia.[98] While STOPP/START criteria recommend calcium and vitamin D
33 supplements,[21] no recommendations for more specific medicines are made. Further,
34 evidence available for fracture risk reduction has been reported to differ with age.[90]).
35 Similarly, blood pressure targets appropriate for older patients may not be appropriate for the
36 oldest old,[50] with adverse effects for antihypertensives found to be among the most
37 frequent in centenarians.[132]Issues regarding the oldest old appear in table 4, criteria 1, 2, 9,
38 18, and 39. We have attempted to achieve the advantages of using mostly explicit criteria,
39 such as ease of application, with the addition of application information (Tables 2 and 4)
40 unavailable in our previous criteria set.
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46 **Rationale for the use of the RAND/UCLA appropriateness method**

47 The RAND/UCLA appropriateness method has been used to rate lists ranging up to over
48 3000 indications, where panellists have been asked to use the clinical literature and their best
49 clinical judgement to assess the appropriateness of performing a procedure. To do this, they
50 have rated various clinical scenarios.[46]While the number and type of our criteria may differ
51 to this, similar criteria have been developed using the RAND/UCLA method. For example, in
52 the development of indicators for patients undergoing total hip or total knee replacement, one
53 of the 68 indicators stated that for such patients, “deep venous thrombosis prophylaxis should
54 be provided for a minimum of two weeks after hospital discharge”. [43] In the development of
55 indicators for hazardous prescribing for GPs using this method, one of the 34 indicators
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3 identified the hazardous use of “NSAID in a patient with heart failure”.^[44] We therefore
4 followed a similar protocol.
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7 **The nature of decision support tools**

8 Panel members emphasized that criteria may not provide definitive answers, instead
9 indicating potential problems that might need addressing, due to a perceived unacceptable
10 variation in care.^[133] While performance indicators are designed to measure the result of
11 statements made in clinical practice guidelines, these guidelines often provide
12 recommendations for care independent of other considerations such as multiple co-
13 morbidities, advanced age, frailty, patient preferences, disease burden or limited life
14 expectancy.^[134-136] In such cases, less stringent goals, deprescribing or non-prescription
15 may be more appropriate.^[15,81,137] For example, a frail older patient with multiple co-
16 morbidities and one or more functional impairments may have a life expectancy of
17 approximately two years or less.^[75] This raises the question of whether failure to intensify
18 treatment^[81] or to underuse evidence-based therapies^[138] reflects appropriate clinical
19 judgement or an inappropriate care gap. The panel felt strongly that use of indicators,
20 guidelines or criteria providing clinical decision support should never replace critical thinking
21 in patient care.^[139]
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28 **Strengths and weaknesses**

29 We have followed a recommended approach ^[120] by suggesting criteria for which high
30 quality evidence exists linking best practice with improved outcomes; where there are
31 established evidence-practice gaps^[98,99]; and where the health conditions impose the
32 greatest burden on the healthcare system. We used a validated consensus method, an expert
33 panel of varied specialization, and criteria written with the aim of conciseness and clarity.
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37 In addition to face and content validity, these validated criteria, much like performance
38 indicators, will require further developmental work to provide evidence of their acceptability,
39 operational feasibility, reliability, and degree of predictive validity.^[35,133] Some of this
40 work has already commenced with the original criteria.^[95] Further, these criteria only cover
41 commonly occurring medicines and medical conditions. In addition, judgements made by an
42 expert panel may not be representative of all health care professionals.
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46 **Intended use**

47 These validated criteria are intended for use by health care providers to enhance the quality of
48 the Australian medication review process, for quality improvement, educational purposes and
49 internal audit. They are also intended for external quality assessment, such as use by policy
50 makers and for public reporting. Stakeholder involvement will be critical to facilitate local
51 uptake and encourage further research into the effects on health outcomes.^[125]
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55 **CONCLUSION**

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3 This study validated 41 prescribing appropriateness criteria to assist in identifying DRPs in
4 older (≥ 65 years) Australians. These criteria are intended to represent an addition to the
5 medication management skill set that includes consideration of limited life expectancy,
6 evidence base in the oldest old, drug burden and care coordination, patient and care-giver
7 education, empowerment for self management, and shared decision making. These skills are
8 far from a “do everything for everyone” philosophy, where aggressive treatment may
9 encourage more care, not more appropriate care.[31 ,135] Despite the presence of clinical
10 decision support tools, health care providers need to know how to think about clinical
11 problems, not just what to think.[139]
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16 **Competing interests** None declared
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19 drafted the manuscript. TFC and RJM made substantial contributions to the conception,
20 design, analysis and interpretation of the data, and to critically revising the draft. All authors
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Validation of prescribing appropriateness criteria for older Australians using the RAND/UCLA Appropriateness Method

ARTICLE SUMMARY

Article focus

- Drug-related problems (DRPs) are common in older people. They may result in drug treatment goals not being achieved and/or resulting in under-treatment with proven medicine, and disproportionately high numbers the occurrence of adverse drug events
- The aim of this study was to further develop and validate a previously published list of prescribing appropriateness criteria for use in older people which may be used to improve the quality of the Australian medication review process, and for quality assessment and education in medicine use

Key messages

- The use of medication assessment criteria is one method to assist in identifying DRPs. Criteria developed elsewhere may have little or no applicability to the Australian healthcare environment
- Validation of proposed Australian prescribing appropriateness criteria for older people was accomplished using a two-round modified Delphi method, resulting in agreement for all criteria as measured by median panel ratings, and the amount of dispersion of panel ratings, based on the interpercentile range
- Use of these criteria, together with other Australian medication review processes, may assist in improving patient care in a variety of settings by efficiently identifying DRPs to common medical conditions and commonly used medicines. They may also contribute to the medication management knowledge of health care professionals through education programs and by use in daily practice, and for the evaluation of the quality of pharmaceutical care in older people

Strengths and limitations

- A validated consensus method was used involving an expert medication management panel of varied specialisation. Criteria were based on established evidence-practice gaps and degree of disease burden imposed on the health care system, and were written with the aim of conciseness and clarity
- Further developmental work is required to assess the usefulness of these criteria, which only included commonly occurring medicines and medical conditions

ABSTRACT

Objective: To update further develop and validate previously published proposed national prescribing appropriateness criteria to assist in identifying drug-related problems (DRPs) ~~to~~ for commonly occurring medications and medical conditions in older (≥ 65 years old) Australians.

Design: Rand/UCLA Appropriateness Method

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3 **Participants:** A panel of medication management experts were identified consisting of
4 geriatricians/pharmacologists, clinical pharmacists, and disease management advisors to
5 organisations that produce Australian evidence-based therapeutic publications. This resulted
6 in a round one panel of fifteen members, and a round two panel of twelve members

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8 **Main outcome measure:** Agreement on all criteria

9 **Results:** Forty eight prescribing criteria were rated. In the first rating round via email, there
10 was disagreement regarding 17 of the criteria according to median panel ratings. During a
11 face-to-face second round meeting, discussion resulted in retention of 25 criteria after
12 amendments, 39 of the proposed criteria being accepted, with 25 of 48 criteria requiring
13 amendment or updating. Fourteen were unchanged, agreement for 14 criteria with no changes
14 required, and and 9 criteria deleted deletion of 9 criteria. Two new criteria were added,
15 resulting in a final validated list of 41 prescribing appropriateness criteria. Agreement after
16 round two was reached for all 41 criteria, measured by median panel ratings and the amount
17 of dispersion of panel ratings, based on the interpercentile range

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22 ~~After round one, there was agreement on the appropriateness of 31 of the 48 criteria, and~~
23 ~~disagreement for 17 criteria. Discussion at round two resulted in retention of 10 criteria for~~
24 ~~which there had been disagreement after round one, acceptance of 14 of the original criteria~~
25 ~~with no change, deletion of nine criteria, and addition of two new criteria,~~

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28 **Conclusions:** A set of 41 Australian prescribing appropriateness criteria were validated by an
29 expert panel. Use of these criteria, together with clinical judgement and other medication
30 review processes such as patient interview, is intended to assist in improving patient care by
31 efficiently detecting potential DRPs related to commonly occurring medicines and medical
32 conditions in older Australians. These criteria may also contribute to the medication
33 management education of health care professionals

34 INTRODUCTION

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38 Drug-related problems (DRPs) in older people (≥ 65 years old) are common, [1-4] They may
39 result in drug treatment goals not being achieved and/or resulting in both undertreatment with
40 proven medicines {Castelino, 2010 #183; Heeley, 2010 #137, #161} and disproportionately
41 high numbers of serious adverse medication events due to polypharmacy. [5-7] DRPs can
42 occur for many reasons such as undertreatment, {Castelino, 2010 #183; Heeley, 2010 #137, #161}
43 inadequate monitoring of medicines, poor medicine or dose selection, duplication of
44 medicines, or factors to do with the way the patient uses the medicine. [2, 3, 8-12] Methods
45 to identify and reduce DRPs include health care professional directed educational
46 interventions, [13] comprehensive geriatric assessment, [14] discontinuation of multiple
47 medications, [15, 16] electronic health record clinical decision support targeted towards
48 certain diseases or drugs, [17, 18] and the use of medication assessment criteria, which
49 usually consist of explicit (that is, criterion-based rather than implicit or judgement-based)
50 lists of prescribing recommendations for various drugs and/or disease states [13, 19-22]

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3 However in older patients, the importance of traditional outcomes, such as discrete clinical
4 events or mortality, may be secondary to maintaining physical and cognitive function or relief
5 of symptoms. {Fried, 2011 #301} Because of this, optimal care requires clinical decision
6 support tools that consider issues such as patient preferences, frailty, cost, and co-
7 morbidities. {Hayward, 2007 #302} Additionally, few criteria target the oldest old {Dimitrow,
8 2011 #242} (generally regarded as people older than 85 years), where evidence may be poor,
9 and preventive interventions may be encouraged in patients who have already exceeded an
10 average lifespan. {Mangin, 2007 #253; Scott, 2010 #305}

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14 In Australia, issues such as these identification and resolution of DRPs are intended to be
15 considered when patients are interviewed by an accredited pharmacist as part of the Home
16 Medicines Review program.[23] This program aims to provide the sophistication lacking in
17 the application of explicit (that is, criterion based rather than implicit or judgement based)
18 measures alone, as it takes into account other issues such as the patients history and personal
19 preferences, such as our criteria list, {Basger, 2008 #132} and is targeted towards patients
20 who may be (among other reasons) currently taking ≥ 5 regular medicines, attending a
21 number of different doctors, or have recently been discharged from hospital.[24]

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26 In 2008, we proposed a list of 48 prescribing appropriateness criteria (45 explicit and three
27 implicit) aimed at improving detection of DRPs as part of the Australian medication review
28 process. {Basger, 2008 #132} When applied to a cohort of older Australians, a high incidence
29 of undertreatment and use of inappropriate medicines was detected. {Basger, 2012 #296} It
30 was also intended that our criteria have application in other areas, as criteria derived outside
31 Australia have been applied in a variety of settings such as community, nursing home and
32 hospital, {Chang, 2010 #209} and have been applied using a variety of study designs such as
33 in retrospective cross-sectional studies, randomized controlled trials, and in retrospective and
34 prospective case series. {Kaur, 2009 #156} They have been used in daily clinical
35 practice; {Laroche, 2009 #151} in the evaluation of health plans {Laroche, 2009 #151} and in
36 the evaluation of knowledge of appropriate prescribing; {Maio, 2011 #362} in the training of
37 health care professionals; {Resnick, 2012 #356} to evaluate nursing home adherence to
38 medicine related regulations; {Resnick, 2012 #356} and to develop healthcare quality
39 indicators. {Chang, 2011 #364}

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45 In 2008, we proposed a list of 48 prescribing appropriateness criteria (45 explicit and three
46 implicit) aimed at improving detection of DRPs as part of the Australian medication review
47 process.[25] These criteria were intended to be applied alongside the patient interview in
48 order to prompt appropriate history taking, particularly with respect to commonly occurring
49 medical conditions and medicines. Similar criteria derived outside Australia have been found
50 to have application in a variety of settings and for a variety of uses, such as in the training of
51 health care professionals and in the evaluation of the quality of health care.[19 ,26-29] Our
52 criteria were based on the most frequent medicines prescribed to Australians, and the most
53 frequent medical conditions for which older Australians (≥ 65 years old) consult medical
54 practitioners. Australian medication and disease state resources and guidelines were used to

provide content validity. [25] However, unlike our criteria, other prescribing criteria or tools have combined evidence with expert opinion to provide face validity.

~~The appropriateness of health care delivery in Australia for common conditions, such as atrial fibrillation and osteoarthritis, has been shown to be poor. {Runciman, 2012 #359} Our criteria were based on the most frequent medicines prescribed to Australians, and the most frequent medical conditions for which older Australians (≥ 65 years old) consult medical practitioners. Australian medication and disease state resources and guidelines were used to provide content validity. {Basger, 2008 #132} However, unlike our criteria, other prescribing criteria or tools have combined evidence with expert opinion to provide face validity. {Martirosyan, 2010 #303; Levy, 2010 #304}~~

The aim of this study was to further develop our list of criteria, supplementing it with recommendations for co-morbidity and the oldest old where possible, and adding new criteria where necessary through expert consensus. In older patients, the importance of traditional outcomes, such as discrete clinical events or mortality, may be secondary to maintaining physical or cognitive function or relief of symptoms. [30] Because of this, optimal care requires clinical decision support tools that consider issues such as patient preferences, frailty, cost and co-morbidities. [31] Additionally, few criteria target the oldest old [32] (generally regarded as people older than 85 years), where evidence may be poor, and preventive interventions may be encouraged in patients who have already exceeded an average lifespan. [33, 34]

To further develop and validate our criteria list, we identified a panel of medication management experts, and chose the RAND/UCLA appropriateness method, which has been described as the best method for systematically combining recommendations from clinical guidelines, with the opinion of healthcare providers. [35]

~~{Fried, 2011 #301} {Hayward, 2007 #302} {Dimitrow, 2011 #242} {Mangin, 2007 #253; Scott, 2010 #305} {Basger, 2008 #132} {Chang, 2010 #209; Laroche, 2009 #151; Maio, 2011 #362; Resnick, 2012 #356; Chang, 2011 #364} The aim of this study was to update our list of criteria. We wished to add missing recommendations for co-morbidity and for the oldest old where possible, and to validate the criteria through expert consensus. To do this, we identified a panel of medication management experts, and chose the RAND/UCLA appropriateness method, {Fitch, #244} which has been described as the best method for systematically combining recommendations from clinical guidelines, with the opinion of healthcare providers. {Martirosyan, 2008 #300}~~

METHODS

Ethics

Ethics approval was obtained from the Human Research Ethics Committee of the University of Sydney.

Criteria development

In 2008, we ~~found~~ identified the -50 highest-volume Australian Pharmaceutical Benefits Scheme (PBS) -medicines prescribed,- and the forty most common reasons for older Australians to seek or receive healthcare. Healthcare information was obtained using the BEACH (Bettering The Evaluation and Care of Health) program, which continuously collects information about the clinical activities in general practice in Australia.[36] We then used Australian medication information sources to identify both optimal and inappropriate medication management of these common conditions.[25] In Australia, medication availability and use is largely determined by the PBS.[37] In October 2011, commonly used medications and medical conditions were checked and updated using the BEACH program to ensure that criteria content was current. Changes in evidence, product information, Australian consensus documents, evidence-based publication recommendations or clinical practice guidelines relating to our criteria were noted for evaluation by an expert medication management panel. The criteria were designed to provide guidance on the process of care wherever it occurred – community, hospital, -residential home, care home or nursing home. Major considerations in their development were ~~potential~~ likely accessibility of data- from the patient, their medical notes and/or their health care professional(s), conciseness and clarity of wording, and provision of a practical number of criteria. Most were explicit to enable consistent application, with additional notes provided for interpretation where necessary. They were written as a statement of the kind of medication management that should or should not occur, to simplify comprehension and facilitate uptake.[25]

Validation of criteria - participants

We recruited -a multidisciplinary group of medication management experts to review, update and rate the criteria, consisting of -geriatrician/pharmacologists, clinical pharmacists, and disease management advisors to organisations that produce Australian evidence-based therapeutic publications. This resulted in a round one panel of fifteen members. The geriatricians consisted of two professors of geriatric medicine; an associate professor of clinical pharmacology and aged care; a research fellow in geriatric medicine; and a hospital staff geriatrician. Clinical pharmacists consisted of a residential medication management review pharmacist; a home medicines review pharmacist; four hospital-based pharmacists (two team leaders, one director and one education and training pharmacist), and a professor of aged care (Pharmacy). Disease management advisors to Australian evidence-based therapeutic organisations consisted of Therapeutic Guidelines,[38] Australian Medicines Handbook,[39] and the New South Wales Therapeutic Advisory Group.[40]

Choice of the RAND/UCLA appropriateness method

We chose the RAND/UCLA appropriateness method, a two-round modified Delphi method[41] to select the most appropriate criteria. Unlike the Delphi method, which generally involves multiple questionnaire-driven rounds to obtain convergence of opinion, the RAND method involves an initial individual rating round, and a second face-to-face round. This method has been shown to produce results that have face, construct and predictive

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3 validity.[42 ,43] Systematically combining available evidence with expert opinion can create
4 quality criteria where best evidence may be lacking.[44]
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7 While most lists of prescribing criteria are based on expert consensus, this has often been
8 achieved through mail surveys rather than face-to-face meetings.[32 ,35 ,45] Although face-
9 to-face meetings restrict panel size, they allow discussion to resolve misinterpretations,
10 introduce new evidence, and improve clarity of criteria between rating rounds. We ensured
11 our panel comprised different specialities, as less disagreement has been found among same-
12 speciality panels.[46] We addressed concern regarding potential intimidation due to dominant
13 panel personalities by choosing a moderator experienced in the development of these criteria
14 and in facilitating small group discussion. This may also have assisted with conflict-of-
15 interest issues. We used both the median panel rating and the amount of dispersion of panel
16 ratings to identify agreement or disagreement. While it has been acknowledged that
17 discrepancies between these two methods may occur,[41]our aim was to achieve agreement
18 for all accepted criteria for both methods after second round discussion.
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23 **RAND/UCLA appropriateness method**

24 ~~The RAND/UCLA appropriateness method has been used to rate lists ranging up to over~~
25 ~~3000 indications, where panellists have been asked to use the clinical literature and their best~~
26 ~~clinical judgement to assess the appropriateness of performing a procedure. To do this, they~~
27 ~~have rated various clinical scenarios. {Shekelle, 2009 #318} While the number and type of our~~
28 ~~criteria may differ to this, similar criteria have been developed using the RAND/UCLA~~
29 ~~method. For example, in the development of indicators for patients undergoing total hip or~~
30 ~~total knee replacement, one of the 68 indicators stated that for such patients, “deep venous~~
31 ~~thrombosis prophylaxis should be provided for a minimum of two weeks after hospital~~
32 ~~discharge”. {SooHoo, 2011 #316} In the development of indicators for hazardous prescribing~~
33 ~~for GPs using this method, one of the 34 indicators identified the hazardous use of “NSAID~~
34 ~~in a patient with heart failure”. {Avery, 2011 #317} We therefore followed a similar protocol.~~
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39 **RAND/UCLA Appropriateness Method round one**

40 In October 2011 candidate panel members were emailed an explanation of the project and an
41 invitation to participate. After acceptance, they were emailed a rating sheet consisting of 48
42 criteria, and asked to rate each on a nine point scale. Ratings of 1-3 were classified as
43 inappropriate, with a rating of one indicating the greatest degree of inappropriateness. Ratings
44 of 7-9 were classified as appropriate, with a rating of nine indicating the greatest degree of
45 appropriateness. Ratings of 4-6 were classified as neither appropriate nor inappropriate.
46 Appropriate was defined as “the expected health benefit exceeds the expected negative
47 consequences by a sufficiently wide margin that criteria are worth following, exclusive of
48 cost”. They also received a description of the way in which the criteria had been derived, and
49 a comparison with other prescribing criteria.[25 ,32] Panel members were requested to amend
50 the wording or delete, update or identify missing criteria as required. Upon return of the
51 rating sheets, results were tabulated. Agreement was based on four or less panellists rating
52 outside the three-point region containing the median (1-3; 4-6; 7-9), and disagreement was
53 based on five or more panellists rating in each extreme (1-3 and 7-9), as per the
54 RAND/UCLA protocol for a fifteen member panel.[41] ~~Additionally, the 30th and 70th~~
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percentiles adjusted for symmetry were computed for each of the criteria, as it has been found that when ratings were symmetric with respect to the middle (five on the 1-9 scale), the interpercentile range (IPR) required to label an indication as disagreement was smaller than when they were asymmetric with respect to the middle (values far from five on the 1-9 scale). Agreement occurred when the interpercentile range adjusted for symmetry (IPRAS) was greater than the IPR {Fitch, #244}

Rand/UCLA Appropriateness Method round two

In November 2011, a face-to-face meeting of the expert panel, chaired by a panel moderator experienced in facilitating group discussions and criteria development, met to discuss the results of round one and re-rate each of the criteria and any potential additional criteria. One pharmacist, one staff geriatrician and a disease management advisor for a therapeutics publication could not attend, resulting in a twelve member panel. For this meeting, each panel member was provided with a copy of the results from round one. This consisted of the frequency distribution of ratings of all panellists across the 9-point scale, the overall panel median rating for each of the criteria and, for each panellist, an annotation of how they had rated each of the criteria. Scores from other panel members were not revealed. Depending upon panellists votes, panel agreement or disagreement was also stated for each of the round one criteria. Additionally, the 30th and 70th percentiles adjusted for symmetry were computed for each of the criteria, as it has been found that when ratings were symmetric with respect to the middle (five on the 1-9 scale), the interpercentile range (IPR) required to label an indication as disagreement was smaller than when they were asymmetric with respect to the middle (values far from five on the 1-9 scale). Agreement after round two occurred when the interpercentile range adjusted for symmetry (IPRAS) was greater than the IPR.[41]

We used the median method to present data at the face-to-face meeting, as it provided a clear visual interpretation of the ratings for each criterion. By the end of the meeting, our aim was to ensure that there was agreement between the median method and the interpercentile method for all accepted criteria.

Discussion at round two occurred on the level of agreement for each of the criteria. In addition, discussion was facilitated on the wording of each of the criteria to improve clarity and decide whether agreement would be reached. The definitions of agreement and disagreement were adjusted for the smaller second round twelve member panel.[41] Agreement was reached when three or less panel members voted outside the 3-point region containing the median, or when the IPRAS was greater than the IPR. Disagreement was determined when four or more panellists rated in each extreme (1-3 and 7-9). Each of the criteria were then discussed; irrespective of whether there was agreement or disagreement, with panellists having the opportunity of changing their ratings if, for example, misinterpretation had occurred because of the way in which the criteria had been written, or if new evidence had become available, or if criteria had been interpreted in the light of a panellists own clinical experience. Each panel member consented to audio recording of the discussion. Values for the median, IPR and IPRAS ~~were computed~~:[41] were computed using SPSS version 20 (SPSS, Chicago, IL, USA).

Data analysis

Median values, IPR and IPRAS were computed using SPSS version 20 (SPSS, Chicago, IL, USA). Audio recordings were transcribed.

RESULTS

After round one, there was agreement ~~on~~ for the appropriateness of 31 of the 48 criteria, and disagreement for 17 criteria. ~~Discussion at round two resulted in retention of 10 criteria for which there had been disagreement after round one, acceptance of 14 of the original criteria with no change, deletion of nine criteria, and addition of two new criteria, resulting in 41 validated criteria. Of the 31 criteria for which there was agreement, discussion at round two resulted in 17 criteria being amended and retained, 2 criteria being deleted, and 12 criteria accepted with no change. Of the 17 criteria for which there was disagreement, discussion at round two resulted in 8 criteria being amended and retained, 7 criteria being deleted, and 2 criteria accepted with no change. Two new criteria were added, resulting in a total of 41 validated criteria.~~

An example of how the RAND/UCLA method was applied to each of our criteria is described in Table 1 for ~~criteria~~ one. The larger the IPRAS, the less asymmetric are the ratings. For example, thirteen of fifteen panellists at round one rated indicator fourteen with a score of eight or nine, for which the IPRAS was 8.35.

Table 2 lists the median panel ratings, the amount of dispersion of panel ratings, and whether there was agreement or disagreement for the original criteria and the validated criteria. It also lists the amendments made by the panel to the original criteria, and the reasons for these amendments. There was 100% agreement for both median panel ratings and dispersion of panel ratings for the validated criteria. Table 3 contains the final list of validated criteria, arranged according to disease states. Table 4 lists usage information judged to be necessary for certain criteria.

Table 1 An example of the application of the RAND/UCLA appropriateness method to one ~~criteria~~ indicator criterion (one) from round one

Nine point scale where 1-3 = inappropriate, 4-6 =	Number of panellists rating this	Calculations, interpercentile range method[41]	Interpretation

neither appropriate nor inappropriate, 7-9 = appropriate	criterion (n=15)		
1		30 th percentile = 7.0	This criterion was accepted according to the median method because four or less panellists voted outside the 3 point region containing the median.
2		70 th percentile = 8.0	
3	1	Interpercentile range (IPR) =	
4		70 th minus 30 th percentile) =	
5	1	1.0 Interpercentile range	
6	1	central point (IPRCP) = 30 th	
7	5	+ 70 th percentile divided by 2	
8	5	= 7.5	
9	2	Asymmetry index (AI) = [5	
	median = 7.0	minus IPRCP] (as an absolute value) = 2.5 Interpercentile range adjusted for symmetry (IPRAS) = [2.5 plus (AI x 1.5)] = 6.1 , where 2.5 is the IPR required for disagreement when perfect symmetry exists, and 1.5 is the correction factor for asymmetry	The IPRAS (6.1) was greater than the IPR (1.0) indicating no disagreement. The larger the IPRAS, the less asymmetric the ratings.

Table 2 Changes made to original criteria according to agreement, disagreement and panel discussion

Criteria Number	Original prescribing appropriateness criteria for older (≥65 years) Australians published in 2008 [25]	Rating by median method[41] (median value, A= agreement, D= disagreement), n=15		Rating by IPRAS ¹ method[41] (IPR value, IPRAS value, A = agreement, D = disagreement), n=15		Validated prescribing appropriateness criteria for older (≥65 years) Australians as a result of this study	Rating by median method[41] (median value, A= agreement, D= disagreement), n=12		Rating by IPRAS ¹ method[41] (IPR value, IPRAS value, A = agreement, D = disagreement), n=12		Amendment/reason
1.	Patient taking an antihypertensive is at their target blood pressure	7	A	1.00, 6.10	A	Patient taking an antihypertensive is at the target blood pressure appropriate for them	8	A	1.10, 7.52	A	“Appropriate for them” added. Current blood pressure guidelines may not be appropriate for all older patients[47-49]. For example, in the oldest old[50]; in palliative care; and for those who are/become hypotensive and/or fall[51,52]
2.	Patient at high risk of a cardiovascular event is taking a statin	7	A	1.00, 6.10	A	Patient at high risk of a recurrent cardiovascular event is taking a statin	8	A	1.00, 6.10	A	“Recurrent” added to ensure use in secondary prevention of cardiovascular events rather than primary prevention, where evidence is less clear, especially in the oldest old[33,53-57]
3.	Patient with IHD or a history of MI is taking a beta blocker	8	A	2.00, 6.85	A	Patient with CHD or a history of MI is taking a beta blocker	7	A	1.00, 6.10	A	“CHD” replaced “IHD”. The term “coronary heart disease” is preferred over “ischemic heart disease”
4.	Patient with IHD or a history of MI is taking an antiplatelet agent unless on an oral anticoagulant	8	A	1.00, 7.60	A	Patient with CHD or a history of MI is taking an antiplatelet agent unless on an oral anticoagulant	8	A	1.00, 7.60	A	“CHD” replaced “IHD”. The term “coronary heart disease” is preferred over “ischemic heart disease”
5	Patient with heart failure is taking a beta blocker	7	A	1.00, 6.10	A	Patient with stable heart failure with left systolic ventricular dysfunction (HF-	8	A	0.10, 6.78	A	Description of heart failure amended. The use of beta blockers is contra-indicated in

						LVSD) is taking a beta blocker					unstable heart failure. The optimal treatment of heart failure with preserved ejection fraction (HFPEF) is uncertain at this time[58 ,59]
6.	Patient with heart failure is taking an ACEI or A2A	8	A	2.00 6.85	A	Patient with stable heart failure with left systolic ventricular dysfunction (HF-LVSD) is taking an ACEI or A2A	9	A	1.00, 7.60	A	Description of heart failure amended. The optimal treatment of heart failure with preserved ejection fraction (HFPEF) is uncertain at this time[58 ,59]
7.	Patient with heart failure is NOT taking medications which may exacerbate heart failure	9	A	1.00, 7.60	A	Patient with HF-LVSD or HFPEF is NOT taking medications which may exacerbate heart failure	9	A	0.10, 8.27	A	Description of heart failure amended. The types of medicines contraindicated in HF-LVSD and HFPEF may not be identical[60 ,61]
8	Patient with heart failure or hypertension is NOT taking high sodium medications	8	D	2.20, 5.50	A	Deleted	-		-	-	High sodium medicines (among others) in heart failure are addressed by indicator 7. In hypertension, they are addressed as lifestyle modifications[62 ,63]
9.	Patient with AF is taking an oral anticoagulant	7	D	2.0, 5.35	A	Patient with AF is taking an oral anticoagulant or an antiplatelet agent, depending upon stroke risk and bleeding risk	8	A	0.10, 6.93	A	An antiplatelet agent may be appropriate for patients at low risk of stroke. Bleeding risk may determine choice of antithrombotic agent[49 ,64 ,65]
10.	Patient with AF taking an anticoagulant has an INR between 2 – 3	8	A	2.20, 6.70	A	Patient taking warfarin for AF has an INR between 2-3	9	A	1.00, 7.60	A	New anticoagulants like rivaroxaban and dabigatran do not require INR monitoring
11.	Patient with a history of non-hemorrhagic stroke or TIA is taking an antiplatelet agent unless on an anticoagulant	8	A	1.00, 7.60	A	Patient with a history of non-hemorrhagic stroke or TIA is taking an antiplatelet agent unless on an anticoagulant	9	A	1.00, 7.60	A	No change
12.	Patient with risk factors for myopathy is NOT taking	7	D	3.00, 4.60	A	Patient with risk factors for statin induced myopathy is	8	A	1.10, 7.52	A	The use of all high dose high potency statins together with

	40mg or more per day of simvastatin or atorvastatin					not taking a high dose of a high potency statin					risk factors may increase the likelihood of myopathy[49 ,66 ,67]
13.	Patient with cardiovascular disease is NOT taking an NSAID	7	A	1.20, 5.95	A	Patient with cardiovascular disease is NOT taking an NSAID	8	A	1.10, 6.18	A	No change
14.	Patient with cardiovascular, respiratory disease or diabetes who smokes has been offered smoking cessation therapy	9	A	0.00, 8.35	A	Patient with cardiovascular, respiratory disease or diabetes who smokes has been offered smoking cessation options	9	A	0.00, 8.35	A	“Therapy” implies pharmacotherapy, whereas repeated counselling/psychotherapy may be preferred to avoid the risks associated with polypharmacy
15.	Patient with type 2 diabetes and hypertension and albuminuria is taking an ACEI or A2A	8	A	2.00, 6.85	A	Patient with type 2 diabetes and hypertension and albuminuria is taking an ACEI or A2A	9	A	1.00, 7.60	A	No change.
16.	Patient with diabetes at high risk of a cardiovascular event is taking an antiplatelet agent unless on an anticoagulant	7	D	2.20, 5.50	A	Patient with diabetes at high risk of a cardiovascular event is taking an antiplatelet agent unless on an anticoagulant	9	A	1.00, 7.60	A	No change
17.	Patient with diabetes is NOT taking a medication which may increase or decrease blood glucose concentrations	5	D	2.20, 3.70	A	Patient with diabetes receiving medications that may affect glycemic control is having regular monitoring of blood glucose concentrations	9	A	1.00, 7.60	A	Increased awareness and monitoring may require adjustment of hypoglycemic medication doses, depending upon the need to continue interacting medicines. For example, commencement of oral corticosteroids may worsen diabetes control[39]
18.	Patient with diabetes has had an HbA1c measurement within the previous 6 months	8	A	1.20, 7.45	A	Patient with diabetes has had an HbA1c measurement within the previous 6 months	8	A	1.00, 7.60	A	No change
19.	Patient taking metformin for diabetes has had the dose adjusted for	8	A	1.20, 7.45	A	Patient taking metformin for diabetes has had the dose adjusted for renal function	9	A	1.00, 7.60	A	Creatinine clearance may represent only one of the methods used to determine

	creatinine clearance										renal function
20.	Patient taking metformin for diabetes is NOT concurrently taking glibenclamide	6	D	2.40, 3.85	A	Deleted	-		-	-	Glibenclamide is an uncommonly used hypoglycaemic
21.	Patient with OA pain interfering with daily activities has been trialled on paracetamol 2 – 4 g per day	8	A	2.00, 6.85	A	Patient with OA pain interfering with daily activities has been trialled on regular paracetamol 2 – 4 g per day	9	A	0.40, 8.05	A	“Regular” paracetamol added to improve quality of indicator
22.	Patient taking analgesic(s) does NOT have pain that interferes with daily activities	7	D	3.2, 4.75	A	Patient taking analgesic(s) has had the dose(s) titrated in order to avoid pain that interferes with daily activities	8	A	2.00, 6.85	A	Indicator rephrased to improve clarity
23.	Patient taking an opioid is on prophylactic treatment for constipation	8	A	2.00, 6.85	A	Patient taking a regular opioid is on prophylactic treatment for constipation	9	A	1.00, 7.60	A	“Regular” use added as “when required” use may not always require prophylactic treatment
24.	Patient with risk factors for impaired renal function is NOT taking an NSAID	8	A	1.00, 7.60	A	Patient with risk factors for impaired renal function is NOT taking an NSAID	8	A	1.00, 7.60	A	No change
25.	Patient is NOT concurrently taking an ACEI or A2A, diuretic and NSAID (excluding low dose aspirin)	9	A	1.00, 7.60	A	Patient is NOT concurrently taking an ACEI or A2A, diuretic and NSAID (excluding low dose aspirin)	9	A	1.00, 7.60	A	No change
26.	Patient with sleep disturbance or anxiety has NOT been taking benzodiazepines for > 4 weeks	8	A	1.20, 7.45	A	Patient has NOT been taking benzodiazepines for > 4 weeks	9	A	1.00, 7.60	A	“Sleep disturbance or anxiety” deleted. Benzodiazepines increase the risk of oversedation, ataxia, confusion, falls, respiratory depression and short-term memory impairment, and are recommended for short term use only[39].
27.	Patient with depression is NOT taking	7	7 D	1.00, 4.60	A	Deleted	-		-	-	The issue of anticholinergic burden is addressed by

	anticholinergic type antidepressants										indicator 32
28.	Patient with a history of falls is NOT taking psychotropic medications	8	A	1.00, 6.10	A	Patient with a history of falls is NOT taking psychotropic medications	8	A	1.40, 6.40	A	No change
29.	Patient taking an SSRI is NOT concurrently taking medications known to increase the risk of GI bleeding	7	D	2.20, 5.20	A	Deleted	-		-	-	Redundant indicator. This issue would be identified by indicator 47.
30.	Patient taking an SSRI is NOT concurrently taking other medications that may contribute to serotonin toxicity	8	A	2.20, 6.70	A	Patient taking an SSRI is NOT concurrently taking other medications that may contribute to serotonin toxicity	8	A	1.40, 6.40	A	No change. Retained by panel due to its potential significance, despite the use of indicator 47
31.	Patient with dementia is NOT receiving anticholinergic medication	8	A	1.20, 7.45	A	Patient with dementia is NOT receiving anticholinergic medication	8	A	1.00, 7.60	A	No change
32.	Patient is NOT taking more than one medication with anticholinergic activity	8	A	0.2, 6.70	A	Patient is not taking medication with SIGNIFICANT anticholinergic activity	8	A	0.40, 7.15	A	Rewording focuses on the issue of anticholinergic burden
33.	Patient taking a PPI is NOT taking a medication that may cause dyspepsia	7	D	3.20, 4.45	A	Patient taking a PPI is NOT taking a medication that may cause dyspepsia unless prescribed for gastroprotection	8	A	0.40, 7.15	A	“Unless prescribed for gastroprotection” added to improve the accuracy of the indicator
34.	Patient with COPD is NOT taking benzodiazepines	7	D	3.00, 6.10	A	Patient with COPD is NOT taking benzodiazepines	8	A	1.00, 6.10	A	No change
35.	Patient with asthma using an inhaled LABA is also using an inhaled corticosteroid	9	A	0.20, 8.20	A	Patient with asthma using an inhaled LABA is also using an inhaled corticosteroid	9	A	1.00, 7.60	A	No change
36.	Patient using salbutamol or terbutaline inhaler more	9	A	1.00, 7.60	A	Patient using salbutamol or terbutaline inhaler more than	9	A	0.40, 8.05	A	“Except for exercise-induced asthma” added to improve the

	than 3 times per week for reversible airways disease has been prescribed an ICS					3 times per week for reversible airways disease has been prescribed an ICS (except for exercise-induced asthma)					accuracy of the indicator
37.	Patient with asthma is NOT taking a medication that may worsen asthma	7	A	1.20, 6.25	A	Patient with asthma is NOT taking a medication that may worsen asthma	8	A	1.00, 7.60	A	No change
38.	Female patient with recurrent UTIs has been prescribed intravaginal estrogen	5	D	2.00, 3.85	A	Deleted	-		-	-	Evidence for this indicator was judged to be poor[68]
39.	Patient with a creatinine clearance < 60 ml/min is NOT receiving nitrofurantoin for UTI	8	A	2.00, 6.85	A	Patient with a UTI is not receiving nitrofurantoin or hexamine for prophylaxis or acute treatment	8	A	1.00, 7.60	A	Hexamine and nitrofurantoin are not recommended for the prophylactic or acute treatment of UTI in older patients[39 ,49]
40.	Patient with a creatinine clearance < 50ml/min is NOT receiving hexamine for UTI prophylaxis	8	A	1.20, 6.25	A	Deleted	-	-	-	-	Hexamine and are not recommended for the prophylactic treatment of UTI in older patients[39 ,49].
41.	Patient with an URTI is NOT receiving antibiotics	7	7, D	3.00, 4.60	A	Patient with a non-specific URTI is NOT receiving antibiotics	8	A	1.00, 7.60	A	“non-specific” added to improve the accuracy of the indicator
42.	Patient with osteoporosis who is not receiving at least 600 IU Vitamin D daily from dietary sources is receiving supplementation with vitamin D	8	D	3.20, 4.75	A	Deleted	-		-	-	This indicator is covered by indicator 44 and an expanded footnote
43.	Patient with osteoporosis who is not receiving at least 1200 mg of calcium daily from dietary sources is receiving calcium	8	A	1.60, 5.95	A	Deleted	-		-	-	This indicator is covered by indicator 44 and an expanded footnote

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	supplementation										
44.	Patient with osteoporosis is receiving anti-osteoporotic medication	7	A	1.00, 6.10	A	Patient with osteoporosis is receiving appropriate anti-osteoporotic medication	8	A	0.40, 7.15	A	“Appropriate” added and an expanded footnote to include calcium and vitamin D
45.	Patient using topical corticosteroids does NOT have itch or discomfort that interferes with daily activities	6	D	2.00, 5.35	A	Patient using topical corticosteroids for contact or allergic dermatitis does not have itch or discomfort that interferes with daily activities	-		-	-	This indicator was deleted by the panel because there was no identification of the diagnosis/condition being treated. However, contact and allergic dermatitis is one of the top 40 most frequently managed problems by general practitioners in patients ≥ 65 years old in Australia,[36] so this indicator was re-worded by the authors
46.	Patient has received influenza and pneumococcal vaccination	9	A	1.00, 7.60	A	Patient has received influenza and pneumococcal vaccination	9	A	0.00, 8.35	A	No change
47.	Patient has no <i>significant</i> medication interactions (agreement between two medication interaction databases)	8	D	3.00, 6.10	A	Patient has no <i>clinically significant</i> medication interactions (agreement between two medication interaction databases)	8	A	0.40, 7.15	A	“Clinically” added to improve the accuracy of the indicator
48.	Patient has had no <i>significant</i> change in medications in the previous 90 days	5	D	1.20, 3.25	A	Deleted	-		-	-	It was preferred to transfer this information to the explanatory text of the article
New						Patient taking thyroid hormone replacement therapy has had a serum TSH measurement within the previous 12 months					Thyroid disease is a common medical condition managed by GPs in older Australians[36 ,69]
New						Patient with coronary heart disease is taking an ACEI or A2A					ACEIs or A2As reduce the risk of cardiovascular events[70 ,71]. However, a high incidence of comorbid disease

Table 3 Validated prescribing appropriateness criteria for older Australians (≥ 65 years) for commonly used medications and medical conditions^{a,b,c} (*for usage information for certain criteria, see Table 4)

Criteria No.	Validated criteria
1	Patient taking an antihypertensive is at the target blood pressure appropriate for them*
2	Patient at high risk of a recurrent cardiovascular event is taking a statin*
3	Patient with CHD or a history of MI is taking a beta blocker
4	Patient with CHD or a history of MI is taking an antiplatelet agent unless taking an oral anticoagulant*
5	Patient with CHD is taking an ACEI or A2A*
6	Patient with stable heart failure with HF-LVSD is taking a beta blocker
7	Patient with stable heart failure with HF-LVSD is taking an ACEI or A2A*
8	Patient with HF-LVSD or HFPEF is NOT taking medications which may exacerbate heart failure
9	Patient with AF is taking an oral anticoagulant or an antiplatelet agent, depending upon stroke risk and bleeding risk*
10	Patient taking warfarin for AF has an INR between 2-3
11	Patient with a history of non-hemorrhagic stroke or TIA is taking an antiplatelet agent unless taking an anticoagulant
12	Patient with risk factors for statin induced myopathy is not taking a high dose of a high potency statin*
13	Patient with cardiovascular disease is NOT taking an NSAID
14	Patient with cardiovascular, respiratory disease or diabetes who smokes has been offered smoking cessation options*
15	Patient with type 2 diabetes and hypertension and albuminuria is taking an ACEI or A2A
16	Patient with diabetes at high risk of a cardiovascular event is taking an antiplatelet agent unless on an anticoagulant
17	Patient with diabetes taking medications that may affect glycemic control is receiving regular monitoring of blood glucose concentrations*
18	Patient with diabetes has had an HbA1c measurement within the previous 6 months*
19	Patient taking metformin for diabetes has had the dose adjusted for renal function*
20	Patient taking thyroid hormone replacement therapy has had a serum TSH measurement within the previous 12 months
21	Patient with OA pain interfering with daily activities has been trialled on regular paracetamol 2 – 4 g per day
22	Patient taking analgesic(s) has had the dose(s) titrated in order to avoid pain that interferes with daily activities
23	Patient taking a regular opioid is on prophylactic treatment for constipation
24	Patient with risk factors for impaired renal function is NOT taking an NSAID*
25	Patient is NOT concurrently taking an ACEI or A2A, diuretic and NSAID (excluding low dose aspirin)
26	Patient has NOT been taking benzodiazepines for > 4 weeks*
27	Patient with a history of falls is NOT taking psychotropic medications*
28	Patient taking an SSRI is NOT concurrently taking other medications that may contribute to serotonin toxicity*
29	Patient with dementia is NOT receiving anticholinergic medication*
30	Patient is not taking medication with SIGNIFICANT anticholinergic activity*
31	Patient taking a PPI is NOT taking a medication that may cause dyspepsia unless prescribed for gastroprotection*
32	Patient with COPD is NOT taking benzodiazepines
33	Patient with asthma using an inhaled LABA is also using an inhaled corticosteroid
34	Patient using salbutamol or terbutaline inhaler more than 3 times per week for reversible airways disease has been prescribed an ICS (except for exercise-induced asthma)
35	Patient with asthma is NOT taking a medication that may worsen asthma*
36	Patient with a UTI is not receiving nitrofurantoin or hexamine for prophylaxis or acute treatment
37	Patient with a non-specific URTI is NOT receiving antibiotics*
38	Patient with osteoporosis is receiving appropriate anti-osteoporotic medication*

39	Patient has received influenza and pneumococcal vaccination
40	Patient using topical corticosteroids for contact or allergic dermatitis does not have itch or discomfort that interferes with daily activities
41	Patient has no <i>clinically significant</i> medication interactions (agreement between two medication interaction databases)*

a – These criteria are intended to be used by appropriately trained and qualified health professionals, as a tool to assist in making medication management decisions as part of the medication review process

b – Prior to the commencement of any medication, the contraindications and precautions for that medication should be considered

c – The intended result of using these criteria is the reasonable and appropriate medication management of individual patients, rather than the systematic application of these criteria to all patients irrespective of other considerations

A2A = angiotensin 2 receptor antagonist, ACEI = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, CHD = coronary heart disease, COPD = chronic obstructive pulmonary disease, HbA1c = glycosylated haemoglobin, HF-LVSD = Heart failure with left ventricular systolic dysfunction, HFPEF = heart failure with preserved ejection fraction, ICS = inhaled corticosteroid, INR = international normalised ratio, MI = myocardial infarct, LABA = long acting beta agonist, NSAID = non-steroidal anti-inflammatory drug, PPI = proton pump inhibitor, SSRI = selective serotonin reuptake inhibitor, TIA = transient ischemic attack, TSH = thyroid stimulating hormone, UTI = urinary tract infection.

Criteria No.	Description of issue	Details
1	Blood pressure targets (mm Hg)	Proteinuria >1 g/day (with or without diabetes) < 125/75. CHD, diabetes, chronic kidney disease, proteinuria (> 300mg/day), stroke or TIA < 130/80. Others <140/90[39] Current blood pressure guidelines may not be appropriate for all older patients, such as the oldest old; in palliative care; and for those who are/become hypotensive and/or fall[47 ,49-52 ,73]
2	Patients at high risk of a cardiovascular event (> 15% within the next 5 years)	Age > 75 years; history of diabetes, moderate or severe chronic kidney disease (persistent proteinuria, GFR < 60ml/min, eGFR < 45 ml/min/1.73m ²), hypercholesterolemia (familial, TC > 7.5 mmol/L), SBP ≥ 180 or DBP ≥ 110 mmHg, ISH (SBP ≥160 and DBP ≤70 mmHg), coronary heart disease, stroke, TIA, PAD, heart failure, aortic disease, LVH, family history of premature CVD.[39 ,74] The benefits of statins and risks of adverse effects are uncertain towards the end of life[75]
4	Antiplatelet agents and oral anticoagulants	Antiplatelet agents – aspirin, clopidogrel, dipyridamole, ticlopidine. Oral anticoagulants – dabigatran, phenindione, rivaroxaban, warfarin
5	Use of ACEI or A2A in CHD	A high incidence of comorbid disease in CHD (typically arthritis and/or respiratory disease) or other clinical factors (e.g. dizziness or falls, cognitive impairment, use of > 5 medicines, patient preference) may be considerations in determining medication prescribing priorities[30 ,34 ,72]
78	Medications that may exacerbate heart failure	HF-LVSD – anti-arrhythmic medicines (except for heart failure-specific beta-blockers and amiodarone), non-dihydropyridine calcium-channel blockers (e.g. verapamil or diltiazem), clozapine, corticosteroids, NSAIDs (excluding low dose aspirin), thiazolidinediones, TNF-alpha inhibitors, topical beta blockers (when added to systemic beta blockers), tricyclic antidepressants[49 ,76 ,77]. HFPEF – venodilators (e.g. isosorbide dinitrate), potent arterial

		vasodilators (e.g. hydralazine), digoxin (unless AF), excessive use of diuretics. Note; verapamil and diltiazem may improve diastolic function in HFPEF[60]
9	Stroke risk and bleeding risk	Stroke risk can be calculated using CHADS ₂ or CHA ₂ DS ₂ -VASc.[78] Risk factors for coumarin-related bleeding complications: advanced age, uncontrolled hypertension, history of MI or IHD, cerebrovascular disease, anaemia or a history of bleeding, concomitant use of aspirin/polypharmacy[79]
12	Risk factors for statin myopathy; high dose of high potency statins	Age > 70 years, presence of disease states (diabetes, hypothyroidism, renal and hepatic disease), concurrent use of cyclosporin, fibrates, CYP3A4 inhibitors (e.g. diltiazem, macrolides, protease inhibitors, verapamil [except for pravastatin and rosuvastatin], severe intercurrent illness (infection, trauma, metabolic disorder), dose ≥ 40 mg daily. High dose of high potency statins ; ≥ 40 mg atorvastatin or simvastatin; > 10mg rosuvastatin [39 ,80]
14	Smoking cessation options	Counselling (extended, brief, telephone), support services (professional, family, social, work), pharmacotherapy.
17	Medications that may affect glycemic control	Increase blood glucose: baclofen, clozapine, cyclosporin, glucocorticoids, haloperidol, olanzapine, paliperidone, phenytoin, protease inhibitors, quetiapine, risperidone, sirolimus, tacrolimus, and tricyclic antidepressants. Decrease blood glucose: excessive alcohol, disopyramide, perhexiline, quinine, trimethoprim/sulphamethoxazole[39]
18	Six monthly HbA1c measurements	Treatment intensification in response to less than optimally controlled HbA1c may be inappropriate in patients with limited life expectancy or in frail older patients[81 ,82]
19	Metformin dose	Based on creatinine clearance: 60-90 ml/min, maximum 2g daily; 30-60 ml/min, maximum 1g daily; < 30 ml/min avoid use.[39] Based on eGFR: Review dose if eGFR< 45 ml/min/1.73m ² ; avoid if eGFR<30 ml/min/1.73m ² [83]
24	Risk factors for impaired renal function	Volume depletion, age > 60 years, salt-restricted diet, concomitant use of ACEIs, A2As, cyclosporin or aspirin, GFR ≤ 60 ml/min, cirrhosis, heart failure[84]
26	Benzodiazepine use	Benzodiazepines increase the risk of oversedation, ataxia, confusion, falls, respiratory depression and short-term memory impairment, and are recommended for short term use only.[39]
27	Falls and psychotropic medications	Psychotropic medications = antidepressants (all), anxiolytics/hypnotics, antipsychotics.[85 ,86] Medications causing (postural) hypotension (e.g. cardiovascular medicines) or cognitive impairment (e.g. opioids) may also increase the risk of falls[49 ,87]
28	Medications that may contribute to serotonin syndrome	Antidepressants - desvenlafaxine, duloxetine, St John's wort, MAOIs (including moclobemide), SSRIs, TCAs, venlafaxine. Opioids - dextromethorphan, fentanyl, pethidine, tramadol. Others - selegiline, linezolid, lithium, tryptophan[39]
29 and 30	Medications with significant anticholinergic activity	amantadine, amitriptyline, atropine*, belladonna alkaloids*, benzhexol, benzotropine, biperiden, brompheniramine*, chlorpheniramine, chlorpromazine, clomipramine, clozapine, cyclizine, cyclopentolate, cyproheptadine*, darifenacin, dexchlorpheniramine*, dimenhydrinate*, diphenhydramine*, disopyramide, dothiepin, doxepin, glycopyrrolate,

		homatropine, hyoscine* (butylbromide or hydrobromide), imipramine, ipratropium (nebulised), mianserin, nortriptyline, olanzapine, orphenadrine, oxybutynin, pericyazine, pheniramine*, pimozone, pizotifen, prochlorperazine, promethazine*, propantheline, solifenacin, tiotropium, tolterodine, trimeprazine*, trimipramine, triprolidine*, tropicamide (* available over-the-counter in Australia)[39]
31	Medications that may cause dyspepsia	Drugs with anticholinergic effects, aspirin, benzodiazepines, bisphosphonates, calcium channel antagonists, oral corticosteroids, dopaminergic drugs, doxycycline, erythromycin, ferrous sulphate, nitrates, NSAIDs, potassium chloride (slow release)[38,39,49,88]
35	Medications that may worsen asthma	Aspirin, beta blockers (including eye drops), carbamazepine, echinacea, NSAIDs, royal jelly[39,89]
38	Non-specific URTI	Acute bronchitis, pharyngitis, tonsillitis, nonsuppurative otitis media and sinusitis[38]
39	Appropriate anti-osteoporotic medication	Recommended daily intake (RDI) of calcium from dietary sources and/or supplements = 1300-1500 mg daily. RDI for Vitamin D from sunlight and/or dietary sources and/or supplements = 600 iu daily. Anti-osteoporotic medication = bisphosphonates, calcitriol, denosumab, HRT, raloxifene, strontium, teriparatide.[39] Evidence for fracture risk reduction in women ≥ 75 years is either absent or lacking in NVF for alendronate, risedronate and teriparatide, and in HF for alendronate, risedronate, zoledronic acid and teriparatide. There is no data available for denosumab in VF, NVF or HF.[90] The optimal duration of bisphosphonate therapy is uncertain. Evidence supports the use of strontium for 5 years, raloxifene for 4 years, zoledronic acid and denosumab for 3 years. Exposure to teriparatide should be limited to 18 months.[91] Data are limited for non-ambulatory patients and those with significant comorbidities.[92] It should be noted that bone strength is only one of many determinants of fracture risk.[93]
42	Clinically significant medication interactions	Medication interactions that may interfere with the outcome of therapy

A2A = angiotensin 2 receptor antagonist, ACE = angiotensin converting enzyme, ACEI = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, CHADS₂ = Cardiac failure, Hypertension, Age, Diabetes, Stroke [doubled], CHA₂DS₂-VASc = Cardiac failure or dysfunction, Hypertension, Age over 75 years [doubled], Diabetes, Stroke [doubled], Vascular disease, Age 65-74 years, Sex category [female], CHD = coronary heart disease, CVD = cardiovascular disease, DBP = diastolic blood pressure, GFR = glomerular filtration rate, HF = hip fracture, HF-LVSD = Heart failure with left ventricular systolic dysfunction, HFPEF = heart failure with preserved ejection fraction, HRT = hormone replacement therapy, IHD = ischemic heart disease, ISH = isolated systolic hypertension, LVH = left ventricular hypertrophy, MAOI = monoamine oxidase inhibitor, MI = myocardial infarct, NSAID = non-steroidal anti-inflammatory drug, NVF = non-vertebral fracture, PAD = peripheral arterial disease, SBP = systolic blood pressure, SSRI = selective serotonin reuptake inhibitor, TC = total cholesterol, TCA = tricyclic antidepressant, TIA = transient ischemic attack, TNF = tumour necrosis factor, URTI = upper respiratory tract infection, VF = vertebral fracture

DISCUSSION

This study identified a panel of medication management experts to discuss and validate a set of 41 prescribing appropriateness criteria for commonly used medicines and medical conditions in older (≥ 65 years) Australians. Panel discussion resulted in retention of 39 of the

originally proposed 48 criteria, with 25 being reworded, and 14 accepted with no change. These criteria do not simply represent a list of medications to avoid in the elderly, but also address issues such as the need for additional therapy (e.g. criteria 23 and 34, Table 3), additional tests (e.g. criteria 18-20, Table 3), ineffective treatment (e.g. criteria 22 and 37, Table 3) and medication monitoring (e.g. criteria 10 and 20, Table 3). They were designed to contribute to the Australian quality use of medicines (QUM) process.[94] The information required to apply these criteria may be obtained from a variety of sources such as the patient or their carer, and pharmacist, or patient medical notes and/or their health care professional. [95] It may also be provided by a Home Medicines Review referral form from the patients general practitioner.[23] Due to their currency and the nature of their development, we expect these criteria to make a significant contribution to the detection of DRPs in the Australian healthcare environment. For example, in a review of prescribing indicators for two conditions, [36] which are common in older people in Australia – type two diabetes and cardiovascular disease [96, 97] – disease and drug-orientated criteria such as ours have shown good content, face, concurrent and predictive validity and operational feasibility, as well as use for internal and external quality assessment in both ambulatory and hospital care.[35] Evidence practice gaps, which formed part of the developmental process for these criteria, have identified deficiencies in the treatment of these and other areas such as vaccination, asthma and pain. (, #46, #45, #360; Bajorek, 2012 #361; Heeley, 2010 #137) Evidence-practice gaps in Australia have been identified in other areas besides diabetes and cardiovascular disease, such as in asthma, pain and vaccination status.[9, 98-101] The existence of these gaps formed part of the developmental process for these criteria.

Prescribing appropriateness- tools in Australia

Appropriateness of prescribing has been assessed by measures that are explicit or implicit, in an effort to identify and reduce DRPs.[102] In Australia, both types of measures have been used.[103-107] However, they have been imported into the Australian healthcare environment, with consequent shortcomings related to both the intrinsic nature of the measure, as well as environment compatibility issues. For example, in a study evaluating the impact of Home Medicine Reviews on appropriateness of prescribing, a significant number of recommendations made regarding the need for monitoring and addition of missing therapy were found to have no impact on explicitly derived scores using the Medication Appropriateness Index,[103] due to the intrinsic shortcomings of this tool. This is not a tool that gives precise guidance in relation to specific medicines.[13]

The Beers criteria,[108] perhaps the tool most widely used to assess inappropriate prescribing in older people, has been used in Australia, but with requires modifications to exclude medicines not listed for government subsidy.[107] This is because medicine availability and use in Australia is largely determined by the Australian Pharmaceutical Benefits Scheme[37]. Other Australian studies have found that some medicines listed as inappropriate by Beers may be appropriate for certain older people according to Australian practice;[105] many medicines listed by Beers are not available in Australia; and that some medicines considered

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3 inappropriate in Australia are not listed by Beers.[106]Disagreement between Beers and other
4 criteria, such as the improving prescribing in the elderly tool (IPET), have been
5 identified.[109]
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8 The Beers criteria was recently updated,[22] with approximately half the medicines listed
9 being unavailable in Australia. Further, almost three quarters of the diseases or syndromes
10 listed are not among the forty problems most frequently managed in patients over sixty five
11 years of age by Australian general practitioners.[97] Beers still contains recommendations to
12 avoid some medicines that are recommended for certain older people in Australia such as
13 amiodarone, and it has recently been shown that rhythm control in older patients with atrial
14 fibrillation may be more effective than rate control in reducing mortality over the long-
15 term.[110]. Reviews of explicit and implicit criteria have identified these and other problems
16 such as; failure to address drug-drug interactions and drug duplication, errors in
17 recommendations, underrepresentation of certain drug categories, inclusion of infrequently
18 prescribed drugs, criteria that are inapplicable for all situations, disagreement between
19 criteria, and lack of organisation of criteria.[45 ,102 ,111]
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25 This has resulted in the development by others of criteria more suited to their own particular
26 healthcare environment.[112 ,113] Nationally based criteria have been described as the most
27 desirable type of criteria, as they do not necessitate adaptation to local guidelines or national
28 formularies before they can be used with confidence. ~~{Castelino, 2009 #182;Dimitrow, 2011~~
29 ~~#242}~~[32] In 2008 wWe therefore sought to construct and validate a set of prescribing
30 appropriateness criteria relevant to the Australian healthcare environment. Our development
31 process differed from most other tools[21 ,108 ,112-117] as it did not initially involve a
32 consensus panel, which has now been addressed. This development process also resulted in
33 criteria unavailable in other tools such as monitoring, underprescribing, need for additional
34 tests, evaluation of smoking and vaccination status, and certain drug interactions[32 ,45 ,102]
35 Because we have generally named drug classes rather than specific drugs (Table 3), and
36 targeted common medical conditions found in older patients,[118 ,119] we anticipate that our
37 work may have some international usefulness.
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43 Despite a desire in Australia to develop decision support tools to improve healthcare
44 quality,[120] progress has consisted of the development of a limited number of non-age
45 specific structure and process indicator lists for use in hospitals and general practice.[40 ,121-
46 123] Many of these lists require updating. [32 ,113 ,124] – Currently, there is no Australian
47 prescribing appropriateness criteria list to assist in improving medication management in
48 older people. The usefulness of such an approach has been acknowledged, together with other
49 approaches such as medication review.[125]
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52 53 **Co-morbidity**

54 Over 80% of older Australians have three or more chronic conditions,[96] with Australian
55 general practitioners shown to be dealing more frequently with patients presenting with three
56 or four problems in the year 2009-10 compared with 2000-01.[126] Co-morbidity is
57 associated with poor quality of life, physical disability, high health care use, multiple
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3 medicines with consequent increased risk of adverse drug events, fragmentation of care, and
4 increased mortality.[119 ,127] Yet most Australian guidelines for chronic diseases do not
5 modify or discuss the applicability of their recommendations to older patients with multiple
6 comorbid conditions. [34] This situation is not restricted to Australia.[127 ,128]Because the
7 risk of harm in older patients increases in proportion to the number of treatments prescribed,
8 prioritization of therapeutic goals is necessary. For example, coronary heart disease (CHD) is
9 an important ~~co~~-morbidity in Australia[77 ,96] for which treatment with ACE inhibitors or
10 angiotensin 2 antagonists has been recommended to reduce the risk of cardiovascular
11 events.[70 ,71] Other criteria derived outside Australia such as STOPP/START do not
12 include this recommendation. [21] However, ~~the~~ presence of co-morbidity in CHD
13 (commonly arthritis or respiratory disease) or other clinical factors (such as dizziness, falls or
14 patient preference) may mean that medicines such as these are never commenced, due to
15 consideration of other factors. While we wished to identify problems such as these, the
16 ultimate decision regarding medicine use should always be made on a case by case basis
17 based on clinical experience, a discussion between the health care professional and the
18 patient, and best available evidence. be more important in determining medication priorities
19 with respect to commencing these medicines (Table 4).[72] -Issues such as ~~this these~~ may
20 run counter to recommendations of disease-specific, evidence-based guidelines,~~[34] and~~
21 ~~were not contained in our original set of criteria. They have been added (where possible) to~~
22 ~~increase relevance.~~ Addition of our criteria with this associated usage information (Table 4)
23 to the implicit processes of Australian medication review may assist in addressing the
24 problem of co-morbidity.
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32 **The Oldest Old**

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35 Knowledge about the state of health and function of the oldest old is limited,[129] with
36 research on their drug use being scarce, and often based on small and selected samples
37 without comparison with other age groups.[130 ,131] We know that older patients in general
38 are underrepresented in clinical trials, so that disease-specific guideline recommendations
39 based on evidence may not apply to older cohorts.[34] For example, undertreatment with
40 anti-osteoporotic medicines has been identified as a significant evidence-practice gap in
41 Australia.[98] While STOPP/START criteria recommend calcium and vitamin D
42 supplements,[21] no recommendations for more specific medicines are made. Further,
43 evidence available for fracture risk reduction has been reported to differ with age.[90](~~Table~~
44 ~~4~~). Similarly, blood pressure targets appropriate for older patients may not be appropriate for
45 the oldest old,[50] with adverse effects for antihypertensives found to be among the most
46 frequent in centenarians.[132]Issues regarding the oldest old appear in table 4, criteria 1, 2, 9,
47 18, and 39. We have attempted to achieve the advantages of using mostly explicit criteria,
48 such as ease of application, with the addition of application information (Tables 2 and 4)
49 unavailable in our previous criteria set.
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55 **Rationale for the use of the RAND/UCLA appropriateness method**

56 The RAND/UCLA appropriateness method has been used to rate lists ranging up to over
57 3000 indications, where panellists have been asked to use the clinical literature and their best
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3 clinical judgement to assess the appropriateness of performing a procedure. To do this, they
4 have rated various clinical scenarios.[46]While the number and type of our criteria may differ
5 to this, similar criteria have been developed using the RAND/UCLA method. For example, in
6 the development of indicators for patients undergoing total hip or total knee replacement, one
7 of the 68 indicators stated that for such patients, “deep venous thrombosis prophylaxis should
8 be provided for a minimum of two weeks after hospital discharge”.[43] In the development of
9 indicators for hazardous prescribing for GPs using this method, one of the 34 indicators
10 identified the hazardous use of “NSAID in a patient with heart failure”.[44] We therefore
11 followed a similar protocol.

14 **Use of the RAND/UCLA appropriateness method**

15 We chose the RAND/UCLA appropriateness method, a two-round modified Delphi
16 method[37] to select the most appropriate criteria. Unlike the Delphi method, which generally
17 involves multiple questionnaire-driven rounds to obtain convergence of opinion, the RAND
18 method involves an initial individual rating round, and a second face-to-face round. This
19 method has been shown to produce results that have face, construct and predictive
20 validity.[44,45] Systematically combining available evidence with expert opinion can create
21 quality criteria where best evidence may be lacking.[46]

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26 While most lists of prescribing criteria are based on expert consensus, this has often been
27 achieved through mail surveys rather than face-to-face meetings. {Levy, 2010
28 #304;Dimitrow, 2011 #242;Martirosyan, 2010 #303} Although face-to-face meetings restrict
29 panel size, they allow discussion to resolve misinterpretations, introduce new evidence, and
30 improve clarity of criteria between rating rounds. We ensured our panel comprised different
31 specialities, as less disagreement has been found among same-speciality panels. {Shekelle,
32 2009 #318} We addressed concern regarding potential intimidation due to dominant panel
33 personalities by choosing a moderator experienced in the development of these criteria and in
34 facilitating small group discussion. Diversity of medication and disease management issues
35 may have minimized professional, but not personal, conflict of interest issues. We used both
36 the median panel rating and the amount of dispersion of panel ratings to identify agreement
37 or disagreement. While it has been acknowledged that discrepancies between the two
38 methods may occur, {Fitch, #244} discussion and second round rating resulted in agreement
39 for all criteria for both methods.

45 **The nature of decision support tools**

46 Panel members emphasized that criteria may not provide definitive answers, instead
47 indicating potential problems that might need addressing, due to a perceived unacceptable
48 variation in care.[133] While performance indicators are designed to measure the result of
49 statements made in clinical practice guidelines, these guidelines often provide
50 recommendations for care independent of other considerations such as multiple co-
51 morbidities, advanced age, frailty, patient preferences, disease burden or limited life
52 expectancy.[134-136] In such cases, less stringent goals, deprescribing or non-prescription
53 may be more appropriate.[15,81,137] For example, a frail older patient with multiple co-
54 morbidities and one or more functional impairments may have a life expectancy of
55 approximately two years or less.[75] This raises the question of whether failure to intensify
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3 treatment[81] or to underuse evidence-based therapies[138] reflects appropriate clinical
4 judgement or an inappropriate care gap. The panel felt strongly that use of indicators,
5 guidelines or criteria providing clinical decision support should never replace critical thinking
6 in patient care.[139]
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10 11 **Strengths and weaknesses**

12 We have followed a recommended approach [120] by suggesting criteria for which high
13 quality evidence exists linking best practice with improved outcomes; where there are
14 established evidence-practice gaps[98 ,99]; and where the health conditions impose the
15 greatest burden on the healthcare system. We used a validated consensus method, an expert
16 panel of varied specialization, and criteria written with the aim of conciseness and clarity.
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19 In addition to face and content validity, these validated criteria, much like performance
20 indicators, will require further developmental work to provide evidence of their acceptability,
21 operational feasibility, reliability, and degree of predictive validity.[35 ,133] Some of this
22 work has already commenced with the original criteria.[95] Further, these criteria only cover
23 commonly occurring medicines and medical conditions. In addition, judgements made by an
24 expert panel may not be representative of all health care professionals.
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28 29 **Intended use**

30 These validated criteria are intended for use by health care providers to enhance the quality of
31 the Australian medication review process, for quality improvement, educational purposes and
32 internal audit. They are also intended for external quality assessment, such as use by policy
33 makers and for public reporting. Stakeholder involvement will be critical to facilitate local
34 uptake and encourage further research into the effects on health outcomes.[125]
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37 38 **CONCLUSION**

39 This study validated 41 prescribing appropriateness criteria to assist in identifying DRPs in
40 older (≥ 65 years) Australians. These criteria are intended to represent an addition to the
41 medication management skill set that includes consideration of limited life expectancy,
42 evidence base in the oldest old, drug burden and care coordination, patient and care-giver
43 education, empowerment for self management, and shared decision making. These skills are
44 far from a “do everything for everyone” philosophy, where aggressive treatment may
45 encourage more care, not more appropriate care.[31 ,135] Despite the presence of clinical
46 decision support tools, health care providers need to know how to think about clinical
47 problems, not just what to think.[139]
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53 **Competing interests** None declared
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55 **Contributors** BJB designed and organised the study, analysed and interpreted the data and
56 drafted the manuscript. TFC and RJM made substantial contributions to the conception,
57 design, analysis and interpretation of the data, and to critically revising the draft. All authors
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3 take responsibility for the accuracy and integrity of the study. All authors have given final
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3-4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3-4
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4
		(b) Describe any methods used to examine subgroups and interactions	N/A
		(c) Explain how missing data were addressed	N/A
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	4
Outcome data	15*	Report numbers of outcome events or summary measures over time	5
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(b) Report category boundaries when continuous variables were categorized	N/A
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	5-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	17-18
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	18-19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.