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ABSTRACT

Objectives One of the outcomes of a medication review service is to identify and manage medication-related problems (MRPs). The most serious MRPs may result in hospitalisation, which could be preventable if appropriate processes of care were adopted. The aim of this study was to update and adapt a previously published set of clinical indicators for use in assessing the effectiveness of a medication review service tailored to meet the needs of Indigenous, please note that the use of the term 'Indigenous' in this manuscript includes all Aboriginal and Torres Strait Islander people and acknowledges their rich traditions and heterogenous cultures, people, who experience some of the worst health outcomes of all Australians.

Design A modified Delphi technique was used to: (i) identify additional indicators for consideration, (ii) assess whether the original indicators were relevant in the context of Indigenous health and (iii) reach consensus on a final set of indicators. Three rounds of rating were used via an anonymous online survey, with 70% agreement required for indicator inclusion.

Setting The indicators were designed for use in Indigenous primary care in Australia.

Participants Thirteen panellists participated including medical specialists, general practice doctors, pharmacists and epidemiologists experienced in working with Indigenous patients.

Results Panellists rated 101 indicators (45 from the original set and 57 newly identified). Of these, 41 were accepted unchanged, seven were rejected and the remainder were either modified before acceptance or merged with other indicators. A final set of 81 indicators was agreed.

Conclusions
This study provides a set of clinical indicators to be used as a primary outcome measure for medication review services for Indigenous people in Australia and as a prompt for pharmacists and doctors conducting medication reviews.

Trial registration number The trial registration for the Indigenous Medication Review Service feasibility study is ACTRN12618000188235.

Strengths and limitations of this study

- This is the first set of clinical indicators developed to identify potentially preventable medication-related hospitalisations in Indigenous Australians;
- The set of clinical indicators developed can be used to measure serious medication-related problems in Indigenous Australians and be used as a resource by health professionals conducting medication review services;
- The set of clinical indicators forms the primary outcome measure of an Indigenous Medication Review Service feasibility study;
- The participant sample size for this study was limited, possibly due to workload constraints of clinicians working in Indigenous health in Australia;
- This study makes an important contribution to the literature by developing a quantitative measure that can be used to improve medication outcomes for Indigenous Australians.

INTRODUCTION

Aboriginal and Torres Strait Islander people in Australia experience higher rates of disease burden compared with other Australians, particularly for chronic disease.[1] As pharmacotherapy is one of the principal tools used to manage chronic conditions, this creates a challenge for health services providers to coordinate medication services within a culturally respectful and comprehensive primary healthcare system,[2] and minimise medication-related harm. Medication review is a structured evaluation of an individual's medications to optimise medication use and health outcomes.[3] An important component of a medication review involves a pharmacist identifying medication-related problems (MRPs) and, in consultation with the prescriber, suggesting management options.

Medication reviews have been shown to significantly increase the identification and resolution of MRPs, although there is limited

evidence to show that they reduce hospital admissions,[4] possibly because there are many types of MRPs with varying degrees of severity and preventability.[5–7] Although the most serious MRPs can lead to hospitalisation[8] some are unpredictable and therefore not considered preventable, for example, atypical adverse drug reactions. However other MRPs are potentially preventable, for example, where clinical care preceding the hospitalisation event is not in accordance with accepted clinical guidelines.

Potentially preventable medication-related hospitalisations (PPMRHs) are the result of a proportion of serious MRPs.[8] Clinical indicators have been developed and used in a number of countries to measure PPMRHs which link suboptimal care involving medication use with subsequent hospitalisation.[9–11] However, differences have been found, for example, between the UK and USA in terms of the inclusion of particular indicators, presumably guided by the prevalence of different health conditions in different population groups and health system differences.[12] Thus, although a set of PPMRH indicators have been developed for use in the Australian population,[13 14] it cannot be assumed that this is a robust measure for specific subsets of the Australian population with distinct healthcare needs, like Indigenous people.

There are a number of advantages of using PPMRHs as the primary outcome in a medication review intervention as they: (i) are prespecified, removing potential classification bias from the primary outcome; (ii) can be costed, for easy inclusion in an economic evaluation and (iii) offer a meaningful target for pharmacists and other clinicians undertaking medication reviews in clinical settings.

The Indigenous Medication Review Service (IMeRSe) feasibility study is being undertaken across nine Australian sites including remote, regional and urban locations, with the aim of developing and testing the feasibility of a culturally appropriate, strengths-based, medication review service.[15] The IMeRSe intervention is delivered by local community pharmacists (on a fee-for-service basis) integrated with local Aboriginal health services (AHSs). Previous research has shown that Indigenous people encounter barriers to accessing medication review services,[16 17] thus the aim of IMeRSe is to overcome these barriers and meet the health needs of the population.[15]

Here we report on the modification of the existing set of 45 PPMRH indicators which were originally developed for use in the general Australian population and validated using a large veterans cohort.[13 14] However, the indicators needed to be revised; to ensure: (i) utility, as an appropriate primary outcome measure in the IMeRSe feasibility study; and (ii) currency and applicability, in light of changes to clinical guidelines and best practice. Inclusion criteria for the IMeRSe study specifies participants to be over 18 years and identify as being Aboriginal or Torres Strait Islander,[15] meaning participants will likely be younger and experience different health conditions than the general Australian population.[1] Thus, the list of previously identified PPMRHs needs to be revised to reflect the health problems faced by this population.

The objective of this study was to develop a meaningful and clinically relevant outcome measure for use in the IMeRSe pilot study,[15] which is trialling the feasibility of a culturally appropriate, strengths-based, medication review service.

METHODS

In general terms, the selection of clinical indicators to measure processes and outcomes of primary care should meet the criteria of validity, reproducibility, acceptability, feasibility, reliability, sensitivity and predictive validity.[18] Consensus methods are one way of developing, or refining, a set of clinical indicators to meet these criteria. The Delphi technique has been widely used in health research to achieve consensus on a particular topic where expert opinion is the main source of evidence,[19 20] including the development of healthcare quality indicators.[21] Other consensus methods, such as the nominal group technique,[22] or the RAND appropriateness method,[23–26] may also be appropriate; however, the Delphi technique has the advantage of involving a sufficiently representative group of experts while being less resource intensive than alternative methods.

Selection of Delphi panellists

The IMeRSe feasibility study Expert Stakeholder Panel (which included Indigenous advisors) identified potential panellists for the Clinical Validation Group (CVG).[15] The function of the Expert Stakeholder Panel is to ensure that all aspects of the study are culturally appropriate and respect Indigenous practices, protocols and community engagement. Potential CVG panellists were identified by the Expert Stakeholder Panel as either having current clinical experience as a doctor or a pharmacist in an Indigenous health setting, or medication safety expertise from a public health perspective. Ideally, Indigenous clinicians and researchers would constitute the whole of the CVG, however while the CVG did have Indigenous representation and attempts were made to include more, we were not able to convene an entirely Indigenous CVG. Potential panellists were approached via email, provided with participant information forms and instructions, and contact details to obtain further information, as required. Panellists were made aware that informed consent was implied by acceptance of the invitation via return email. Of the 40 eligible panellists approached to participate, 13 agreed. Panellists were offered a small honorarium to compensate them for their time.

Rating rounds

Prior to the start of the first rating round, consented panellists were interviewed individually by a member the research team (JS) to ensure they had a chance to clarify the Delphi process. During the interview, panellists were asked to identify any additional indicators that they believed should be considered in addition to the original 45 indicators[14] or email them after the interview,

Griffith UNIVERSITY Online Research Survey Tool

Indigenous Medication Review Service - Clinical Validation Group

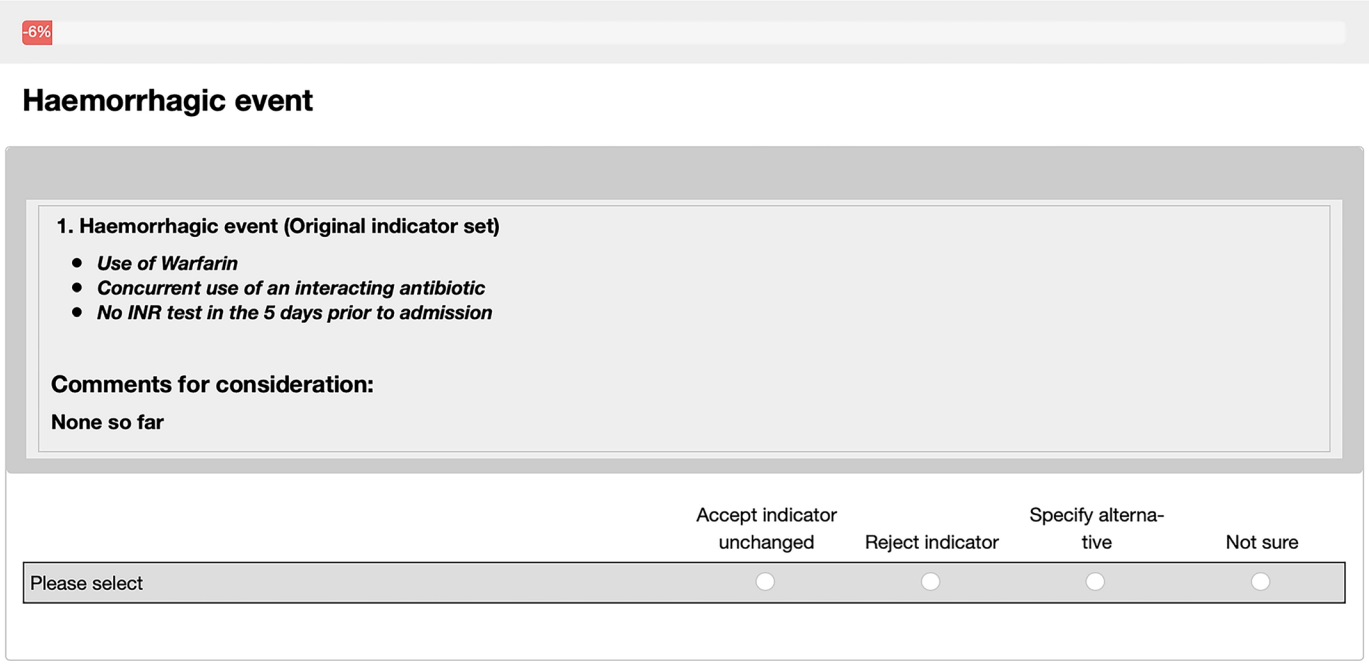

Figure 1 An example of the online presentation of a clinical indicator to panellists. INR, international normalised ratio.

if preferred. Panellists were asked to only identify indicators that met the criteria of preventable drug-related morbidity, as defined by Hepler & Strand[27] who specify three necessary elements:

1. The drug-related problem must be recognisable, and the likelihood of an undesirable clinical outcome must be foreseeable;
2. The causes of that outcome must be identifiable;
3. The causes must be controllable.

Panellists were also asked to consider indicators that, from their own clinical experience, represented the greatest burden to population health for Indigenous Australians. Additional indicators considered to be relevant were added to the original list of 45 indicators to form a Master List. Three rounds of rating and consensus were then undertaken using this list as a starting point.

The first two rating rounds were sent to all panellists via email link in an online format hosted in LimeSurvey.[28] Panellists were asked to carefully consider each indicator presented and then choose from four options: (i) accept indicator unchanged, (ii) reject indicator, (iii) specify alternative or (iv) not sure. Panellists were asked to provide comments or a rationale for rejecting an indicator or providing an alternative. An example of the online presentation of a clinical indicator to panellists is shown in figure 1.

The indicator was accepted unchanged if at least 70% of panellists chose the option 'Accept indicator unchanged' or rejected if at least 70% of panellists chose the option 'Reject indicator' in accordance with previous modified Delphi methods.[29] The indicators which were accepted unchanged or rejected were removed and did not appear in subsequent rating rounds. All other indicators (where an alternative was proposed) were collated alongside the panellists' comments or rationale, by the researchers. The researchers considered the comments, consulted any relevant clinical literature and offered alternative wording for the disputed indicator. Panellists' comments were (anonymously) reported *verbatim* in the subsequent rating round, alongside the researchers proposed new wording of the indicator and links to any relevant clinical literature or guidelines. Researchers set a deadline of 2 weeks for responses after the online survey was opened. Panellists could login to the survey again if they had not completed it, and previous responses could be altered at any time prior to survey submission. Reminder emails were sent 1 week before the deadline and requests for additional time was granted for participants to complete

Table 1 Clinical validation group panel

Clinical expertise	Number	%
Pharmacist	5	39
Specialist doctor	3	23
General practitioner	2	15
Researcher	2	15
Epidemiologist	1	8

the rating round, if required. Every effort was made by the research team to enable all 13 participants to complete the first two rating rounds.

The third rating round involved a face-to-face meeting of an invited subgroup (n=3) of the larger consensus group; a representative from each main speciality area (specialist doctor, general practice doctor, clinical pharmacist) provided expert commentary regarding any remaining discrepancies. Consensus in this final round was achieved following open group discussion which was moderated by the researchers (JS/AJW).

Patient and public involvement

Patient and public involvement has been achieved in the IMeRSe feasibility study, and will be ongoing over the study lifetime, through extensive collaboration with the relevant representatives of both Partner organisations. As described above (*Selection of Delphi panellists*), working with key Indigenous groups, both locally and as members of the Expert Panel, will be integral to the ongoing engagement process (eg, via the inclusion of community juries, councils and boards). This process will be informed by the local requirements at each site throughout this feasibility study. Acceptability outcomes for consumer participants will be assessed as described previously.[15] Dissemination to Indigenous participants and communities will be a priority, with processes guided by the Expert Panel and informed by key stakeholders at a local site level.

RESULTS

CVG panellists

A total of 13 panellists, five females and eight males, from five clinical areas participated between May 2018 and November 2018. Panellists had a mean of 17 years experience in their clinical areas and 11 years experience working with Indigenous people in their current role (table 1); . Panellists were drawn from six of the nine states and territories across Australia and from urban, rural and remote locations (detailed information is withheld to maintain the anonymity of panellists).

Clinical indicators

In addition to the original 45 indicators,[11] panellists identified a further 56 new indicators. Hence, the Master List of indicators at the start of Round 1 rating comprised 101 indicators. During each of the rating rounds, panellists made suggestions to split and merge indicators, meaning the number of indicators for consideration could increase or decrease between rounds. The number of clinical indicators from the Master List accepted or rejected in each rating round, grouped by clinical presentation, are summarised in table 2.

Table 2 Number of clinical indicators, grouped by clinical presentation and round

Clinical presentation	Previous list*	Master list	Accepted round 1	Accepted round 2	Accepted round 3	Rejected
Neurological	7	17	7	11	**14**	0
Vaccine preventable diseases	0	12	11	11	**12**	0
Electrolytes and laboratory abnormalities	8	15	4	7	**10**	1†
Cardiovascular	6	12	1	6	**9**	0
Respiratory	4	6	4	5	**6**	0
Renal	3	5	1	3	**5**	0
Fracture or falls	4	6	3	3	**4**	0
Haemorrhagic event	3	5	1	2	**3**	0
Gastrointestinal	4	4	0	3	**3**	0
Endocrine	4	6	3	3	**3**	0
Genitourinary	2	3	1	2	**2**	0
Sexually transmitted infections	0	1	0	1	**1**	0
Other	0	10	5	8	**9**	0
Total†	**45**	**102**	**41**	**65**	**81**	**1**

*The list of PPMRHs previously developed for the general Australian population.[13 14]
†NOTE: Totals are not cumulative as during the rating process, panellists suggested that some indicators should be merged or split.
PPMRHs, potentially preventable medication-related hospitalisations.

At the end of Round 2 rating, 65 indicators (80% of the final total) were agreed on by the panellists. The three-person subgroup of the CVG invited to undertake Round 3 rating formed consensus on the remaining 23 indicators during a 2 hour face-to-face meeting (one panellist phoned-in), moderated by the research team (JS/AJW). One clinical indicator was rejected during this round, with the remaining 22 indicators either accepted or merged with other indicators.

The final list of accepted indicators is presented in table 3. Thirty-four indicators from the original list of 45 were accepted by panellists, although 21 of these were updated in some way to reflect: (i) changes in current guidelines or new medicines, (ii) having been combined with other similar indicators for simplification, (iii) having been split into additional indicators for clarity. Forty-seven new indicators were added, giving a final total of 81 indicators.

DISCUSSION

The development of this updated clinical indicator list is an important step in addressing MRPs for Indigenous Australians. This study builds on earlier work which identified a set of clinical indicators for use in a general Australian population.[13 14] The new list includes 81 indicators, sourced from 34 of the original 45 indicators and 47 newly identified indicators. In comparison to the general Australian population list, the new list contains more neurological indicators (expanded from 7 to 14), vaccine preventable diseases (expanded from 0 to 12) and 'other' indicators (expanded from 0 to 9), which better reflects the health burden of the Indigenous population. For example, trachoma and rheumatic heart disease are health issues seen in the Indigenous population, but rarely in the general Australian population.

Panellists included specialist and general practice doctors, pharmacists, epidemiologists and researchers, the majority of whom had extensive experience in providing healthcare for Indigenous populations. The purpose of conducting this research was two-fold: first to provide a prespecified list of PPMRHs to define the primary outcome measure for the IMeRSe feasibility study[15]; and as a resource for pharmacists conducting medication reviews for Indigenous Australians to assist in identifying suboptimal processes of primary care related to medication use, defined for the IMeRSe feasibility study as serious MRPs.[15]

AHSs offer Indigenous Australians access to holistic and person-centred primary care. The inclusion of pharmacists undertaking medication review services is important as much of the health burden experienced by Indigenous Australians results from chronic conditions such as renal and/or cardiovascular disease, type-II diabetes and mental illness, which in turn increases the requirement for ongoing medication regimens.[1 30] There are reports that the levels of MRPs among Indigenous populations are of concern,[31 32] although there is scant evidence of the size or extent of the problem. Further, Indigenous populations access the existing government funded medication review services, The MedsCheck and Diabetes MedsCheck Programme provides for in-pharmacy reviews of consumers who are taking multiple medications and/or have newly diagnosed or poorly controlled type 2 diabetes. These reviews are aimed at enhancing the quality use of medicines and reducing the number of adverse drug events experienced by consumers. A Home Medicines Review is designed to enhance the quality use of medicines and reduce the number of adverse medicine events by assisting consumers to better manage and understand their medicines through a medication review conducted by an accredited pharmacist in the patient's home (http://www.6cpa.com.au/medication-management-programs) at a lower rate than non-Indigenous Australian for reasons including the lack of culturally responsive services, not having established and trusting relationships with pharmacists and because pharmacists are not usually integrated into AHSs.[16 17]

The clinical indicator list developed in this study will be tested for predictive validity in two ways through the IMeRSe feasibility study: (i) as a primary outcome measure and as such, will be used to classify a set of serious MRPs which can be analysed against a list of all MRPs (regardless of severity); and (ii) to estimate the rate of PPMRHs in Indigenous populations using a linked administrative data set comprised of 5 years of hospital admissions from the state of Queensland, Australia. This data set will be combined with pharmaceutical and medical services usage for the same cohort of hospitalised individuals (collected by the national government). Thus, the background rate of PPMRHs can be identified, for arguably the most representative state in Australia in terms of Indigenous Australians, as urban, rural and remote populations are all included. However, it is anticipated that it will not be possible to measure some of the indicators using these existing administrative databases as insufficient clinical information (such as cardiovascular disease risk) will be available. It is possible that this problem may decline over time as individual health records become fully digitalised and shared in Australia.

The processes contributing to suboptimal clinical care specified in the final indicator list (table 3) are termed serious MRPs; these may, or may not, result in a hospitalisation. Only when a hospitalisation does occur is a PPMRH realised. Thus, we are interested not only in the rate of PPMRHs in the Indigenous population, but also the rate of MRPs and the translation rate of MRPs to PPMRHs. The reduction in MRPs of all severity, including serious MRPs, is a key outcome of IMeRSe feasibility study.

A modified Delphi technique was used in this study to reach consensus between experts. The Delphi technique allows for anonymity in responses, which permits all panellists an equal chance to have their opinion considered. A majority consensus was reached for 65 (80%) of the total number of indicators at the end of Round 2 rating. Of the remaining indicators (n=23), the majority required only

Table 3 Final list of potentially preventable medication-related hospitalisations for Indigenous Australians[#]

Number	Hospitalisation outcome to avoid	Process of suboptimal clinical care prior to hospitalisation	Source
Haemorrhagic event			
1	Haemorrhagic event	Use of warfarin;	Original
		Concurrent use of an interacting antibiotic;	
		No INR test in the 5 days prior to admission.	
2	Haemorrhagic event	Use of warfarin;	Original†
		No INR test in the 6 weeks prior to admission.	
3	Haemorrhagic event	Use of one or more antithrombotics (warfarin, DOAC, aspirin, NSAID, clopidogrel, LMWH); AND	Original†
		No haemoglobin test within the past year; OR	
		No monitoring of renal function in the previous 6 months; OR	
		Use of triple therapy (dual antiplatelet plus oral anticoagulant) for more than 1 month prior to admission.	
Gastrointestinal			
4	Gastritis, GI bleed, GI ulcer or GI perforation	History of or prior hospitalisation for GI ulcers or GI bleed;	Original†
		Use of NSAID (including aspirin) for a period of at least 1 month prior to admission.	
5	Gastritis, GI bleed, GI ulcer or GI perforation	History of prior hospitalisation for GI ulcers or GI bleed; AND	Original†
		Use of gastric toxin (eg, oral corticosteroids, NSAIDs, antiplatelet agents, bisphosphonates, anticoagulants, cholinesterase inhibitor) for a period of at least 3 months prior to admission; AND	
		No cytoprotection (eg, proton pump inhibitor).	
6	Bowel impaction	Use of two or more medications known to retard gastrointestinal motility (including anticholinergic agents, calcium channel blockers, antacids and iron preparations) at the time of admission; OR	Original†
		Use of a highly anticholinergic agent at the time of admission; OR	
		Use of an opioid analgesic without concurrent use of a laxative at the time of admission.	
Cardiovascular			
7	Congestive heart failure or fluid overload	Prior hospitalisation for/or diagnosis of high blood pressure or CHF;	Original†
		Use of an agent known to exacerbate CHF including NSAIDs, COX-2 inhibitors, anti-arrhythmics (apart from beta-blockers or amiodarone), non-dihyropyridine calcium-channel blockers in systolic CHF (verapamil, diltiazem), corticosteroids, clozapine, tricyclic anti-depressants, tyrosine kinase inhibitors, thiazolidinediones or tumour necrosis factor antagonists at time of admission.	
8	Congestive heart failure or fluid overload	Prior hospitalisation for/ or diagnosis of heart failure;	Original
		No use of ACEI, ARB or ARNi (angiotensin receptor neprilysin inhibitor) at time of admission.	
9	Myocardial Infarction	History of acute coronary syndrome / previous MI;	Original†
		No use of anti-platelet(s) OR beta-blocker (reduced left-ventricular systolic function only) OR HMG-CoA reductase inhibitor in the 3 months prior to hospitalisation.	
10	Myocardial infarction	Insertion of stent within the previous 12 months;	New
		No use of dual anti-platelet in 2 months prior to admission.	
11	Thromboembolic cerebrovascular event	Prior diagnosis of atrial fibrillation;	Original†

Continued

Table 3 Continued

Number	Hospitalisation outcome to avoid	Process of suboptimal clinical care prior to hospitalisation	Source
		No use of anticoagulant in the 3 months prior to admission in a patient with high risk according to CHA2Ds2Vasc score.	
12	Acute coronary syndrome	CVD risk known to be >15% prior to admission;	New
		Not on lipid lowering therapy AND/OR antihypertensive therapy.	
13	Transient ischaemic attack/ ischaemic stroke	Pulse quality/blood pressure not tested within past 24 months;	New
		No use of any of antiplatelet, antihypertensive, anticoagulant, lipid lowering therapy.	
14	Ischaemic coronary event	History of angina or acute coronary syndrome;	New
		No use of beta-blocker, calcium channel blocker or nitrates.	
15	Ischaemic event	History of diabetes;	New
		History of ischaemic event;	
		No antiplatelet or lipid lowering therapy.	
Electrolytes and laboratory abnormalities			
16	Blood dyscrasia	Use of an agent known to cause blood dyscrasias (including carbimazole, sulphonylureas, propylthiouracil, methotrexate, sulphasalazine);	Original†
		No complete blood count or platelet test in the 6 months prior to admission.	
17	Syndrome of inappropriate antidiuretic hormone secretion	Use of TCAs, carbamazepine, ACEIs, other antidepressants;	Original†
		No electrolyte test in the 12 months prior to admission.	
18	Electrolyte imbalance	Use of diuretics, ACEI/ARB, spironolactone, potassium supplements or calcium supplements;	Original†
		No electrolyte test in the 12 months prior to admission; AND	
		No renal function test in the 12 months prior to admission.	
19	Anticonvulsant drug toxicity	Use of anticonvulsant requiring therapeutic drug monitoring;	Original
		No drug level test in the 6 months prior to admission.	
20	Digoxin toxicity	Use of digoxin;	Original†
		No renal function test in the 12 months prior to admission; AND	
		No potassium serum level in the 6 months prior to admission.	
21	Lithium toxicity	Use of lithium;	Original
		No lithium drug level test in the 3 months prior to admission.	
22	Clozapine-related blood dyscrasias	Use of clozapine;	New
		No full blood count/white blood count/neutrophils/ eosinophils in >1 month prior to admission or within the previous week in the first 18 weeks of therapy.	
23	Clozapine-induced myocarditis/cardiomyopathy	Use of clozapine;	New
		No baseline echocardiogram; OR	
		ECG in the previous 12 months; OR	
		troponin in the previous 12 months; OR	
		CRP in previous 12 months before admission.	
24	Clozapine toxicity/failure	Use of clozapine;	New
		Altered smoking status while on clozapine (may vary levels and result in toxicity or relapse).	
25	Clozapine toxicity	Use of clozapine;	New

Continued

Table 3 Continued

Number	Hospitalisation outcome to avoid	Process of suboptimal clinical care prior to hospitalisation	Source
		Concurrent illness;	
		No full blood count/ white blood count/ neutrophils/ eosinophils in >1 month prior to admission.	
Endocrine			
26	Hypoglycaemia	Use of insulin; OR	Original†
		Use of long-acting sulfonylurea in the 3 months prior to admission; AND	
		Inadequate blood glucose monitoring OR reduced adherence to diabetes treatment plan.	
27	Diabetic complications (including hyperglycaemia)	Previously diagnosed with diabetes;	Original†
		Use of a hypoglycaemic in the 6 months prior to admission; AND	
		No HbA1c in previous 6 months.	
28	Hypothyroidism or thyrotoxicosis	Use of amiodarone or lithium;	Original†
		No thyroid function test in the 6 months prior to admission.	
Fracture or falls			
29	Hip fracture or other fracture/break	Aged 65 years or older; AND	Original†
		Use of long-term corticosteroids (>1 month); AND/OR	
		Use of sedating psychotropic medication (including TCAs, benzodiazepines, antipsychotics, opioids); AND/OR	
		Use of cardiovascular drugs with high potential to cause postural hypotension (including nitrates, centrally acting adrenergic blockers and alpha-receptor blockers).	
30	Hip fracture	Female gender;	Original
		Prior fall from the standing level resulting in fracture;	
		No use of HRT, bisphosphonate or other osteoporosis medicine in the 6 months prior to admission.	
31	Hip fracture	Male gender;	Original
		Prior fall from the standing level resulting in fracture;	
		No use of bisphosphonate or other osteoporosis medicine in the 6 months prior to admission.	
32	Low-trauma fracture	Previous low-trauma fracture;	New
		Not taking osteoporosis prevention therapy at time of admission.	
Neurological			
33	Acute confusion	Urinary tract infection un/inadequately treated	New
34	Acute confusion	Use of two or more anticholinergic agents at the time of admission; OR	Original†
		Use of a highly anticholinergic agent at the time of admission; OR	
		Use of two or more of sedating prescription drugs and/or sedating antihistamines; OR	
		Use of multiple psychotropic medicines (≥3 unique medicines from ATC groups, N05 or N06) at the time of admission.	
35	Seizure	Use of an anticonvulsant;	Original†
		Concurrent use of a medication which lowers the seizure threshold (as specified in the Australian Medicines Handbook); AND/OR	
		Reduced compliance with anticonvulsant medication.	
36	Bipolar disorder	Prior hospitalisation for bipolar disorder;	Original

Continued

Table 3 Continued

Number	Hospitalisation outcome to avoid	Process of suboptimal clinical care prior to hospitalisation	Source
		Use of lithium;	
		No lithium drug level in the 3 months prior to admission.	
37	Bipolar affective disorder/ psychotic disorder	Prior hospitalisation for bipolar disorder;	New
		No use of/ poor compliance with a mood stabiliser; OR	
		Reduced compliance with long acting injection and/or oral medication.	
38	Depression	Prior diagnosis of depression;	Original
		Concurrent use of a moderately highly lipophilic beta blocker.	
39	Depression (readmission)	Reduced compliance with antidepressant or augmenting medications (mood stabiliser or antipsychotic); AND/OR	New
		No review (including medication adherence) undertaken post previous admission.	
40	Mania/hypomania	Use of antidepressants in the 2 months prior to admission;	New
		No use of mood stabiliser in the 2 months prior to admission.	
41	Attempted suicide	Use of SSRI in adolescents (up to 20 years old);	New
		No psychiatric review in 12 months prior to admission.	
42	Psychotic episode	History of psychosis/ mental illness;	New
		Reduced compliance with prescribed antipsychotic/ anxiolytic medication.	
43	Antidepressant withdrawal symptoms	Abrupt cessation of antidepressant (especially short-acting such as paroxetine and venlafaxine).	New
44	Acute anxiety	Cessation of psychotropic medications (such as antidepressant and/or benzodiazepines) without monitoring.	New
45	Eating disorder/electrolyte imbalance	Excessive laxative use; OR	New
		Use/abuse of medications altering electrolyte levels (for example, loop diuretics).	
46	Serotonin toxicity	Use of multiple serotonergic agents that may contribute to serotonin toxicity (desvenlafaxine, duloxetine, MAOIs including moclobemide, SSRIs, TCAs, venlafaxine, fentanyl, tramadol, selegiline, lithium, tryptophan, St. John's Wort).	New
Renal			
47	Renal failure	Use of ACEI or ARB;	Original†
		No BUN or serum creatinine test in the 12 months prior to admission.	
48	Renal failure	Use of allopurinol;	Original
		No BUN or serum creatinine test in the 6 months prior to admission.	
49	Renal failure	Use of lithium;	Original
		No BUN or serum creatinine test in the 3 months prior to admission.	
50	Renal failure	NSAID use for>3 months;	New
		BUN or serum creatinine not monitored in the previous 12 months.	
51	Renal failure	Use of methotrexate;	New
		No BUN or serum creatinine test in the 6 months prior to admission.	
Respiratory			
52	Asthma AND/OR COPD	Prior hospitalisation for/or diagnosis of asthma/COPD; AND	Original†
		No / inadequate maintenance therapy (LAMA, LABA, ICS); OR	
		Poor inhaler technique; AND/OR	
		No action plan in place; AND/OR	

Continued

Table 3 Continued

Number	Hospitalisation outcome to avoid	Process of suboptimal clinical care prior to hospitalisation	Source
		No smoking cessation advice given.	
53	Asthma/COPD	Prior hospitalisation for/or diagnosis of asthma and/or COPD;	Original
		Use of beta-blocker eye drops for glaucoma at the time of admission.	
54	Chronic obstructive pulmonary disease	Prior hospitalisation for/or diagnosis of COPD;	Original
		Use of a betablocker at the time of admission.	
55	Acute respiratory failure	Prior hospitalisation for/or diagnosis of COPD;	Original
		Use of a medium to long-acting benzodiazepine at the time of admission.	
56	Asthma	Prior hospitalisation for/or diagnosis of asthma/COPD;	New
		High use (>2X per week) of a short-acting bronchodilator (SABA, SAMA);	
		No use of maintenance therapy (LAMA, LABA, ICS).	
57	Bronchiectasis	Two or more admissions with bronchiectasis exacerbations in last 12 months; No prophylactic azithromycin trialled in the 12 months prior to admission.	New
Genitourinary			
58	Urinary retention	Prior diagnosis of benign prostatic hyperplasia OR bladder atony due to diabetes mellitus;	Original†
		Current use of a drug with anticholinergic effects or an opioid at the time of admission.	
59	Recurrent urinary tract infection	No test for organism identification and sensitivity undertaken.	New
Sexually transmitted diseases			
60	Chlamydia or gonorrhoea	Untreated with antibiotics for more than 1 week after results received.	New
Vaccine preventable diseases			
61	Pneumonia	No pneumococcal vaccine if 'at risk' (chronic illness or>50 years);	New
		No revaccination after 5 years.	
62	Influenza	No influenza vaccination in the past 12 months.	New
63	Tetanus	No/incomplete vaccination.	New
64	Diphtheria	No/incomplete vaccination.	New
65	Whooping cough	No/incomplete vaccination.	New
66	Acute poliomyelitis	No/incomplete vaccination.	New
67	Varicella	No/incomplete vaccination.	New
68	Measles	No/incomplete vaccination.	New
69	Rubella	No/incomplete vaccination.	New
70	Mumps	No/incomplete vaccination.	New
71	Hepatitis A	No/incomplete vaccination.	New
72	Hepatitis B	No/incomplete vaccination.	New
Other			
73	Cellulitis	No treatment / inadequate treatment with antibiotics to treat staphylococcus aureus or streptococcus pyogenes with an appropriate antibiotic at time of admission.	New
74	Rheumatic fever (<21 years of age)	Prior diagnosis of rheumatic fever or rheumatic heart disease;	New

Continued

Table 3 Continued

Number	Hospitalisation outcome to avoid	Process of suboptimal clinical care prior to hospitalisation	Source
		No benzathine penicillin (or erythromycin if allergic) in the last 28 days.	
75	Gout attack	Previous history of gout;	New
		Use of loop diuretics or thiazide diuretics.	
76	Hepatitis C	No treatment with direct acting antivirals.	New
77	Methicillin resistant Staphylococcus aureus skin infection	Recurrent skin infection (>2 weeks);	New
		Continuing use of β-lactam antibiotic;	
		No skin swab taken.	
78	Jaw osteonecrosis	Use of a bisphosphonate or denosumab;	New
		No dental assessment within 6 months prior to admission.	
79	Trachoma	Untreated with appropriate antibiotics.	New
80	Iron deficiency anaemia	Confirmed pregnancy;	New
		No FBE test during pregnancy.	
81	Eclampsia	Prior diagnosis of hypertension (a systolic blood pressure of greater than or equal to 160 mm Hg or a diastolic blood pressure greater than or equal to 110 mm Hg) during the current pregnancy;	New
		No treatment with antihypertensive agent (suitable for use in pregnancy) at time of admission.	

*The final list of clinical indicators has not been considered as part of any independent Health Technology Assessment (HTA) for effectiveness/cost-effectiveness.
†The original indicator (from Kalisch *et al*[14]) forms the basis of this indicator but it has been modified either to (i) update the indicator to reflect current guidelines or new medicines in the class; (ii) combine with another indictor/s for simplification or (iii) has been split into more indicators for clarity.
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II blockers; ARNi, angiotensin receptor-neprilysin inhibitors; ATC, anatomical therapeutic chemical; BUN, blood urea nitrogen; CHA2Ds2Vasc, congestive heart failure, hypertension, age, diabetes and stroke/TIA vascular disease (peripheral arterial disease, previous MI, aortic atheroma) (female gender is also included in this scoring system); CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; COX-2, cyclooxygenase-2; CRP, C-reactive protein; CVD, cardiovascular disease;DOAC, Direct oral anticoagulant; FBE, full blood examination; GI, gastrointestinal; HbA1c, glycolated haemoglobin; Hg, mercury; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HRT, hormone replacement therapy; ICS, inhaled corticosteroids;INR, international normalised ratio; LABA, long-acting beta agonists; LAMA, long-acting muscarinic antagonists; LMWH, low molecular weight heparin; MAOI, monoamine oxidase inhibitor; MI, myocardial infarction; MRSA, methicillin resistant Staphylococcus aureus; NSAID, non-steroidal anti-inflammatory drug; SABA, short-acting beta-2 agonists; SAMA, short-acting muscarinic antagonist; SIADH, syndrome of inappropriate antidiuretic hormone secretion; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants; TIA, transient ischaemic attack.

a short discussion and/or brief changes to wording to reach consensus Round 3 rating. The researchers considered that this meeting expediated consensus on the remaining indicators and was a strength of the study. It must be noted that use of the term 'consensus' here, especially in the early phases of the Delphi process, is in fact 'convergence' of expert opinion. However, consensus has been assumed because : (i) panellists were made aware that they were involved in a decision-making process at the start, (ii) justification for non-acceptance was fedback to the group between rounds and (iii) face-to-face discussions were held to reach agreement in Round 3.

Unlike the RAND appropriateness method, the modified Delphi rating process did not incorporate a formal mechanism for considering the strength of evidence of the proposed indicators. This aspect could not be incorporated into the present study, due to the lack of relevant research specifically involving Indigenous Australians, and hence the lack of evidence for this specific patient population. However, the existing indicator list, which was adapted for the present study was developed using the RAND appropriateness measure,[13] and considered the strength of evidence underpinning each indicator during the indicator development process. Thirty-four of the indicators accepted in the present study were based on existing indicators, so nearly half of the indicators were developed by explicitly considering the strength of evidence for the particular indicator. During the moderated online and face-to-face discussions, the researchers observed that clinicians incorporated current clinical guidelines into their decision-making processes, although this was not undertaken in a formal way. This

could be viewed as a potential limitation of the study. Another possible limitation was the relatively small number of panellists who agreed to participate, which could be due to workload pressures for clinicians working in Indigenous health in Australia. Finally, the authors note that the final list of clinical indicators developed here are not necessarily independent of each other, nor are they of equal weighting of clinical seriousness. Thus, this issue will need to be accounted for in the data analysis of the PPMRHs for the IMeRSe study.

By classifying a list of serious MRPs, the importance of other MRPs may be discounted. The lack of adherence to medication regimens among Indigenous populations is of particular concern, especially given the high rates of chronic disease such as diabetes, cardiovascular disease, severe mental illness and renal disease that require regular medication. Barriers that limit adherence including poor health literacy, lack of access to medications (cost and physical access) and medication sharing with relatives and friends can all negatively impact on health through uncontrolled illness.[31] In the short-term, health decrements due to low medication adherence may not result in hospitalisation, it may nonetheless contribute to life-threatening outcomes in the medium-to-longer term. It must be stressed that the final clinical indicator list developed here should only be used by pharmacists and other health professionals undertaking medication review services as a resource to optimise medication management. It does not provide a definitive list of the most serious problems, nor does it replace clinical judgement.

CONCLUSIONS

The final list of clinical indicators developed in this study represents an initial, but important, step in quantifying serious MRPs and PPMRHs in Indigenous Australian populations. Such a list is not static and should be regularly updated in light of changes to clinical guidelines and medicines formularies. The health of Indigenous Australians may be enhanced by using this list as a resource during the process of medication review to identify suboptimal processes of care and then institute corrective processes to prevent a potential hospitalisation.

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