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Adaptation of potentially preventable medication-related hospitalisation indicators for Indigenous populations in Australia using a modified Delphi technique

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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 so that the revised indicators can be used to assess the effectiveness of a medication review service tailored to meet the needs of Indigenous[1] 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.

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

Results: Panellists rated 102 indicators (45 from the original set and 57 newly identified). Of these, 41 were accepted unchanged, 7 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. Rates of the cumulative incidence of these indicators should be identified using administrative databases

[1] 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.

to identify population rates of suboptimal care prior to hospital admission and as a prompt for pharmacists and doctors conducting medication reviews.

Article Summary

Strengths and limitations of the study:

- This is the first set of clinical indicators developed to identify potentially preventable medication-related hospitalisations (PPMRHs) in Indigenous Australians;
- The set of clinical indicators developed can be used to measure serious medication-related problems (MRPs) 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 (IMeRSe) 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.

Keywords: Indigenous health; potentially preventable medication-related hospitalisations; medication review; clinical indicators

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Competing interests statement: None declared.

Author contributions: JS was responsible for study concept, design, data collection and wrote the first draft of the manuscript. AJW designed the research protocol, is the principle investigator and was involved in the design and data collection. All authors were involved in the revision of this paper and made a contribution to the intellectual content and approved the final version of the paper.

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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 health care 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] There are a number of advantages of using PPMRHs as the primary outcome in a medication review intervention as they: (i) are pre-specified, 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.[9] The IMeRSe intervention is delivered by local community pharmacists (on a fee-for-service basis) integrated with local Aboriginal health services (AHSs).

Here we report on the modification of an existing set of 45 PPMRH indicators which were originally developed and validated for use in the Australian healthcare setting.[10, 11] The indicators needed to be revised, however, 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.

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.[12] 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,[13, 14] including the development of healthcare quality indicators.[15] Other consensus methods, such as the nominal group technique,[16] or the RAND appropriateness method,[17-20] may also be appropriate, however, the Delphi technique has the advantage of involving a sufficiently representative group of experts whilst 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).[9] 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. 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. Ethics approval was granted from Griffith University Human Research Ethics Committee (GU ref No:2018/126) for this study.

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[11] or email them after the interview, if preferred. Panellists were asked to only identify indicators that met the criteria of preventable drug-related morbidity, as defined by Hepler & Strand[21] 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.[22] 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.

<< Figure 1 about here >>

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.[23] 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 two 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 one week before the deadline and requests for additional time was granted for participants to complete 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 sub-group (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/AW).

Results

CVG panellists

A total of 13 panellists, five females and eight males, from five clinical areas participated between May and November 2018. They 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 from and from urban, rural and remote locations (detailed information is withheld to maintain the anonymity of panellists).

Table 1: Clinical Validation Group (CVG) Panel

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

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 102 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: Clinical indicators by clinical presentation and round

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

*NOTE: Totals are not cumulative as during the rating process, panellists suggested that some indicators should be merged or split.

At the end of Round 2 rating, 65 indicators (80% of the final total) were agreed upon by the panellists. The three-person sub-group of the CVG invited to undertake Round 3 rating formed consensus on the remaining 23 indicators during a two-hour face-to-face meeting (one panellist phoned-in), moderated by the research team (JS/AW). 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[2]. 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.

[2] NB. The final list of clinical indicators has not been considered as part of any independent Health Technology Assessment (HTA) for effectiveness/cost-effectiveness.

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

Number	Hospitalisation outcome to avoid	Process of sub-optimal clinical care prior to hospitalisation
Haemorrhagic event		
1	Haemorrhagic event	Use of warfarin;
		Concurrent use of an interacting antibiotic;
		No INR test in the 5 days prior to admission.
2	Haemorrhagic event	Use of warfarin;
		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
		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 one 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;
		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
		Use of gastric toxin (e.g. oral corticosteroids, NSAIDs, antiplatelet agents, bisphosphonates, anticoagulants, cholinesterase inhibitor) for a period of at least 3 months prior to admission; AND
		No cytoprotection (e.g. 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
`		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;
		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;
		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;
		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;
		No use of dual anti-platelet in 2 months prior to admission.
11	Thromboembolic cerebrovascular event	Prior diagnosis of atrial fibrillation;
		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;
		Not on lipid lowering therapy AND/OR antihypertensive therapy.
13	Transient ischaemic attack (TIA)/ Ischaemic stroke	Pulse quality/blood pressure not tested within past 24 months;
		No use of any of antiplatelet, antihypertensive, anticoagulant, lipid lowering therapy.
14	Ischaemic coronary event	History of angina or acute coronary syndrome;
		No use of beta-blocker, calcium channel blocker or nitrates.
15	Ischaemic event	History of diabetes;
		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);
		No complete blood count or platelet test in the 6 months prior to admission.
17	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Use of TCAs, carbamazepine, ACEIs, other antidepressants;
		No electrolyte test in the 12 months prior to admission.
18	Electrolyte imbalance	Use of diuretics, ACEI/ARB, spironolactone, potassium supplements or calcium supplements;
		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;

		No drug level test in the 6 months prior to admission.
20	Digoxin toxicity	Use of digoxin;
		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;
		No lithium drug level test in the 3 months prior to admission.
22	Clozapine-related blood dyscrasias	Use of clozapine;
		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;
		No baseline echocardiogram; OR
		ECG in the previous 12 months; OR
		troponin in the previous 12 months; OR
		CRP (C-reactive protein) in previous 12months before admission.
24	Clozapine toxicity/failure	Use of clozapine;
		Altered smoking status whilst on clozapine (may vary levels and result in toxicity or relapse).
25	Clozapine toxicity	Use of clozapine;
		Concurrent illness;
		No full blood count/ white blood count/ neutrophils/ eosinophils in > 1 month prior to admission.
Endocrine		
26	Hypoglycaemia	Use of insulin; OR
		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;
		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;
		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
		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;
		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;
		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;
		Not taking osteoporosis prevention therapy at time of admission.
Neurological		
33	Acute confusion	Urinary tract infection un/inadequately treated
34	Acute confusion	Use of two or more anticholinergic agents at the time of admission; OR
		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;
		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;
		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;
		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;
		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
		No review (including medication adherence) undertaken post previous admission.
40	Mania/hypomania	Use of antidepressants in the two months prior to admission;
		No use of mood stabiliser in the two months prior to admission.
41	Attempted suicide	Use of SSRI in adolescents (up to 20 years old);
		No psychiatric review in 12 months prior to admission.
42	Psychotic episode	History of psychosis/ mental illness;
		Reduced compliance with prescribed antipsychotic/ anxiolytic medication.
43	Antidepressant withdrawal symptoms	Abrupt cessation of antidepressant (especially short-acting such as paroxetine and venlafaxine).
44	Acute anxiety	Cessation of psychotropic medications (such as antidepressant and/or benzodiazepines) without monitoring.
45	Eating disorder / electrolyte imbalance	Excessive laxative use; OR
		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).
Renal		
47	Renal failure	Use of ACEI or ARB;
		No BUN or serum creatinine test in the 12 months prior to admission.
48	Renal failure	Use of allopurinol;
		No BUN or serum creatinine test in the 6 months prior to admission.
49	Renal failure	Use of lithium;
		No BUN or serum creatinine test in the 3 months prior to admission.
50	Renal failure	NSAID use for >3 months;
		BUN or serum creatinine not monitored in the previous 12 months.
51	Renal failure	Use of methotrexate;
		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
		No / inadequate maintenance therapy (LAMA, LABA, ICS); OR
		Poor inhaler technique; AND/OR
		No action plan in place; AND/OR

		No smoking cessation advice given.
53	Asthma/COPD	Prior hospitalisation for/or diagnosis of asthma and/or COPD;
		Use of beta-blocker eye drops for glaucoma at the time of admission.
54	Chronic obstructive pulmonary disease (COPD)	Prior hospitalisation for/or diagnosis of COPD;
		Use of a betablocker at the time of admission.
55	Acute respiratory failure	Prior hospitalisation for/or diagnosis of COPD;
		Use of a medium to long-acting benzodiazepine at the time of admission.
56	Asthma	Prior hospitalization for/or diagnosis of asthma/COPD;
		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.
Genitourinary		
58	Urinary retention	Prior diagnosis of benign prostatic hyperplasia OR bladder atony due to diabetes mellitus;
		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.
Sexually Transmitted Diseases		
60	Chlamydia or gonorrhoea	Untreated with antibiotics for more than 1 week after results received.
Vaccine Preventable Diseases		
61	Pneumonia	No pneumococcal vaccine if 'at risk' (chronic illness or >50 years);
		No revaccination after 5 years.
62	Influenza	No influenza vaccination in the past 12 months.
63	Tetanus	No/incomplete vaccination.
64	Diphtheria	No/incomplete vaccination.
65	Whooping cough	No/incomplete vaccination.
66	Acute poliomyelitis	No/incomplete vaccination.
67	Varicella	No/incomplete vaccination.
68	Measles	No/incomplete vaccination.
69	Rubella	No/incomplete vaccination.
70	Mumps	No/incomplete vaccination.
71	Hepatitis A	No/incomplete vaccination.

72	Hepatitis B	No/incomplete vaccination.
Other		
73	Cellulitis	No treatment / inadequate treatment with antibiotics to treat staphylococcus aureus or streptococcus pyogenes with an appropriate antibiotic at time of admission.
74	Rheumatic fever (<21 years of age)	Prior diagnosis of rheumatic fever or rheumatic heart disease;
		No benzathine penicillin (or erythromycin if allergic) in the last 28 days.
75	Gout attack	Previous history of gout;
		Use of loop diuretics or thiazide diuretics.
76	Hepatitis C	No treatment with direct acting antivirals.
77	Methicillin resistant Staphylococcus aureus (MRSA) skin infection	Recurrent skin infection (>2 weeks);
		Continuing use of β-lactam antibiotic;
		No skin swab taken.
78	Jaw osteonecrosis	Use of a bisphosphonate or denosumab;
		No dental assessment within 6 months prior to admission.
79	Trachoma	Untreated with appropriate antibiotics.
80	Iron deficiency anaemia	Confirmed pregnancy;
		No FBE test during pregnancy.
81	Eclampsia	Prior diagnosis of hypertension (a systolic blood pressure of greater than or equal to 160mm Hg or a diastolic blood pressure greater than or equal to 110 mm Hg) during the current pregnancy;
		No treatment with antihypertensive agent (suitable for use in pregnancy) at time of admission.

DOAC = Direct oral anticoagulant; NSAID = non-steroidal anti-inflammatory; LMWH = low molecular weight heparin; GI = gastrointestinal; CHF = congestive heart failure; COX-2 = cyclooxygenase-2; ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II blockers; ARNi = angiotensin receptor-neprilysin inhibitors; MI = myocardial infarction; HMG-CoA = 3-hydroxy-3-methylglutaryl-CoA; 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]; CVD = cardiovascular disease; TIA = transient ischaemic attack; TCA = tricyclic antidepressants; SIADH = syndrome of inappropriate antidiuretic hormone secretion; ECG = electrocardiogram; CRP = C-reactive protein; HbA1c = glycolated haemoglobin; HRT = hormone replacement therapy; ATC = anatomical therapeutic chemical; SSRI = selective serotonin reuptake inhibitor; MAOI = monoamine oxidase inhibitor; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; LAMA = long-acting muscarinic antagonists; LABA = long-acting beta agonists; ICS = inhaled corticosteroids; SABA = short-acting beta-2 agonists; SAMA = short-acting muscarinic antagonist; MRSA = methicillin resistant Staphylococcus aureus; FBE = full blood examination; Hg = mercury.

* The original indicator (from Kalish 2012[11]) 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.

The final list of clinical indicators has not been considered as part of any independent Health Technology Assessment (HTA) for effectiveness/cost-effectiveness.

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.[10, 11] The new list includes 81 indicators, sourced from 34 of the original 45 indicators and 47 newly identified indicators. 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: firstly to provide a prespecified list of PPMRHs to define the primary outcome measure for the IMeRSe feasibility study;[9] and as a resource for pharmacists conducting medication reviews for Indigenous Australians to assist in identifying sub-optimal processes of primary care related to medication use, defined for the IMeRSe feasibility study as serious MRPs.[9]

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, 24] There are reports that the levels of MRPs amongst Indigenous populations are of concern,[25, 26] although there is scant evidence of the size or extent of the problem. Further, Indigenous populations access the existing government funded medication review services[3] at a lower rate than non-Indigenous Australian for reasons including the lack of culturally responsive services, not

[3] 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 (HMR) 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).

having established and trusting relationships with pharmacists and because pharmacists are not usually integrated into AHSs.[27, 28]

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 five 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. It is anticipated, however, 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 sub-optimal 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 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. 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,[10] 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.

By classifying a list of serious MRPs, the importance of other MRPs may be discounted. The lack of adherence to medication regimens amongst 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.[25] 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 sub-optimal processes of care and then institute corrective processes to prevent a potential hospitalisation.

List of Abbreviations

AHS – Aboriginal health service

CVG – clinical validation group

IMeRSe - Indigenous Medication Review Service

MRPs – medication-related problems

PPMRHs – potentially preventable medication-related problems

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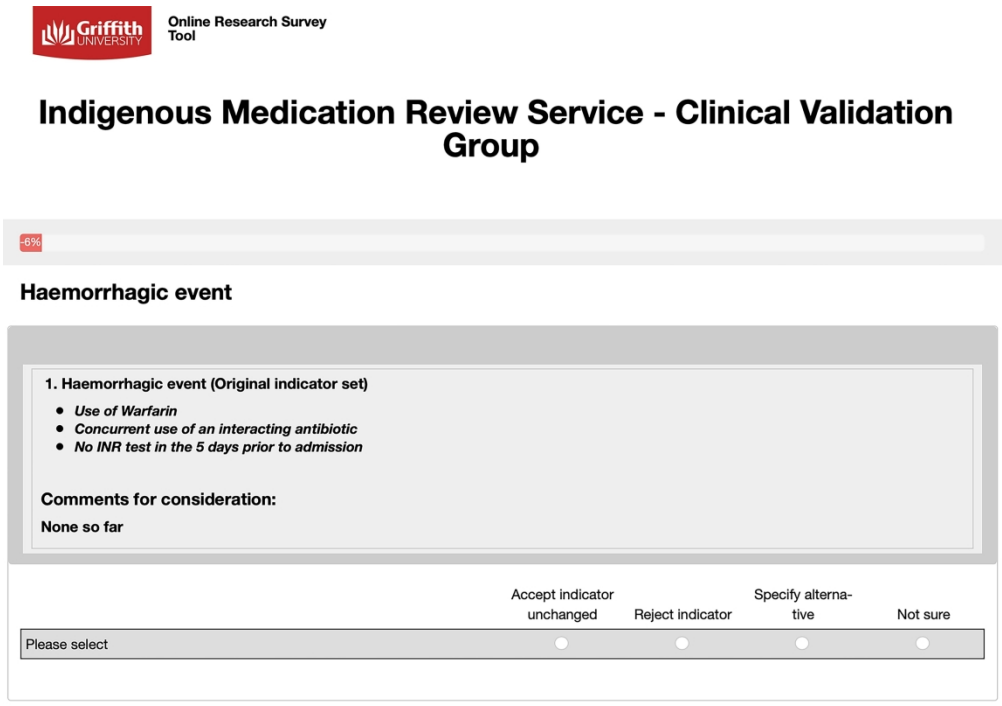

Figure 1: Example of online survey question

358x249mm (300 x 300 DPI)

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Adaptation of potentially preventable medication-related hospitalisation indicators for Indigenous populations in Australia using a modified Delphi technique

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Adaptation of potentially preventable medication-related hospitalisation indicators for Indigenous populations in Australia using a modified Delphi technique

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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[1] 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 102 indicators (45 from the original set and 57 newly identified). Of these, 41 were accepted unchanged, 7 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.

[1] 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.

Article Summary

Strengths and limitations of the study:

- This is the first set of clinical indicators developed to identify potentially preventable medication-related hospitalisations (PPMRHs) in Indigenous Australians;
- The set of clinical indicators developed can be used to measure serious medication-related problems (MRPs) 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 (IMeRSe) 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.

Keywords: Indigenous health; potentially preventable medication-related hospitalisations; medication review; clinical indicators

Trial registration: The trial registration for the IMeRSe feasibility study is ACTRN12618000188235.

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Competing interests statement: None declared.

Author contributions: JS was responsible for study concept, design, data collection and wrote the first draft of the manuscript. AJW designed the research protocol, is the principle investigator and was involved in the design and data collection. LK, GS, TT & DW

contributed to methodology and data collection. All authors were involved in the revision of this paper and made a contribution to the intellectual content and approved the final version of the paper.

Availability of data and materials

The dataset generated and analysed for this study is not publicly available as consent from participants was not sought to share the data more widely than for the purpose of this study.

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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 health care 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 sub-optimal 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 pre-specified, 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 geneal 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 Indigenous Medication Review Service pilot study (IMeRSe)[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 whilst 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 whilst 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. Ethics approval was granted from Griffith University Human Research Ethics Committee (GU ref No:2018/126) for this study.

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, 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.

<< Figure 1 about here >>

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 two 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 one week before the deadline and requests for additional time was granted for participants to complete 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 sub-group (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/AW).

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 (e.g. 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 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); one panellist identified as being an Aboriginal or Torres Strait Islander person. Panellists were drawn from six of the nine states and territories across Australia from and from urban, rural and remote locations (detailed information is withheld to maintain the anonymity of panellists).

Table 1: Clinical Validation Group (CVG) Panel

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

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[a]	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 (STIs)	0	1	0	1	**1**	0
Other	0	10	5	8	**9**	0
Total*	**45**	**102**	**41**	**65**	**81**	**1**

*NOTE: Totals are not cumulative as during the rating process, panellists suggested that some indicators should be merged or split.

[a] The list of PPMRHs previously developed for the general Australian population[13, 14].

At the end of Round 2 rating, 65 indicators (80% of the final total) were agreed upon by the panellists. The three-person sub-group of the CVG invited to undertake Round 3 rating formed consensus on the remaining 23 indicators during a two-hour face-to-face meeting (one panellist phoned-in), moderated by the research team (JS/AW). 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.

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

Number	Hospitalisation outcome to avoid	Process of sub-optimal 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 one 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 (e.g. oral corticosteroids, NSAIDs, antiplatelet agents, bisphosphonates, anticoagulants, cholinesterase inhibitor) for a period of at least 3 months prior to admission; AND	
		No cytoprotection (e.g. 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*
		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 (TIA)/ 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 (SIADH)	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 (C-reactive protein) in previous 12months before admission.	
24	Clozapine toxicity/failure	Use of clozapine;	New
		Altered smoking status whilst on clozapine (may vary levels and result in toxicity or relapse).	
25	Clozapine toxicity	Use of clozapine;	New
		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
		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 two months prior to admission;	New
		No use of mood stabiliser in the two 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	
		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 (COPD)	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 hospitalization 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
		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 (MRSA) 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 160mm 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 original indicator (from Kalish 2012[11]) 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.
DOAC = Direct oral anticoagulant; NSAID = non-steroidal anti-inflammatory; LMWH = low molecular weight heparin; GI = gastrointestinal; CHF = congestive heart failure; COX-2 = cyclooxygenase-2; ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II blockers; ARNi = angiotensin receptor-neprilysin inhibitors; MI = myocardial infarction; HMG-CoA = 3-hydroxy-3-methylglutaryl-CoA; 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]; CVD = cardiovascular disease; TIA = transient ischaemic attack; TCA = tricyclic antidepressants; SIADH = syndrome of inappropriate antidiuretic hormone secretion; ECG = electrocardiogram; CRP = C-reactive protein; HbA1c = glycolated haemoglobin; HRT = hormone replacement therapy; ATC = anatomical therapeutic chemical; SSRI = selective serotonin reuptake inhibitor; MAOI = monoamine oxidase inhibitor; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; LAMA = long-acting muscarinic antagonists; LABA =

long-acting beta agonists; ICS = inhaled corticosteroids; SABA = short-acting beta-2 agonists; SAMA = short-acting muscarinic antagonist; MRSA = methicillin resistant Staphylococcus aureus; FBE = full blood examination; Hg = mercury.
The final list of clinical indicators has not been considered as part of any independent Health Technology Assessment (HTA) for effectiveness/cost-effectiveness.

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: firstly 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 sub-optimal 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 amongst 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[2] 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 five 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 sub-optimal 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

[2] 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 (HMR) 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).

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 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 fed-back 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 amongst 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 sub-optimal processes of care and then institute corrective processes to prevent a potential hospitalisation.

Figure 1 Legend

Figure 1: An example of the online presentation of a clinical indicator to panellists

List of Abbreviations

AHS – Aboriginal health service

CVG – clinical validation group

IMeRSe - Indigenous Medication Review Service

MRPs – medication-related problems

PPMRHs – potentially preventable medication-related problems

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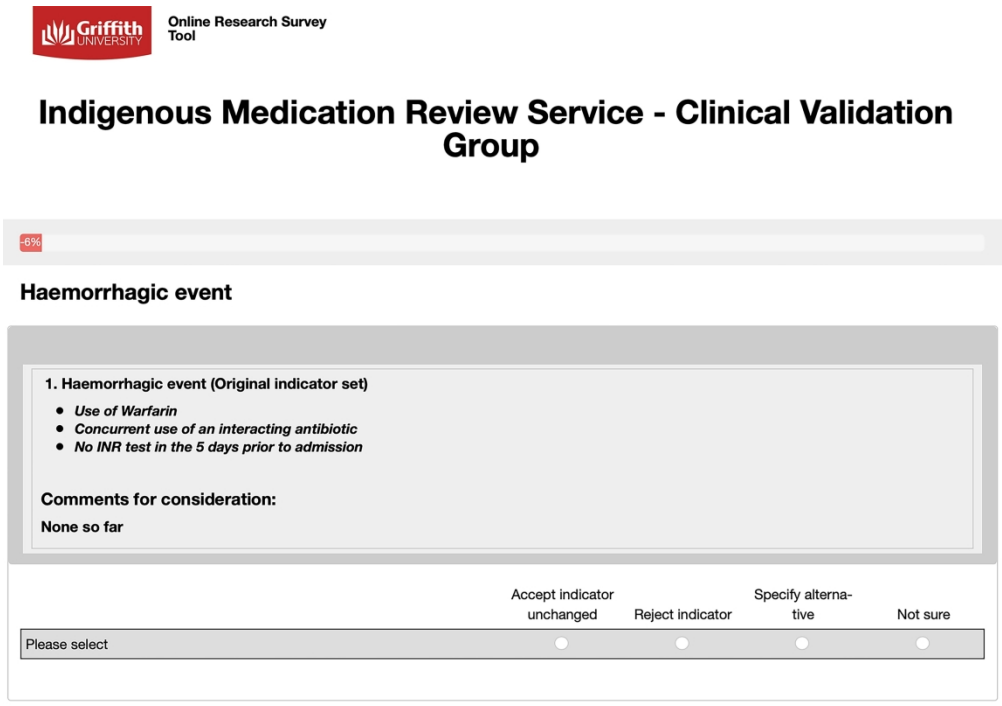

Figure 1: Example of online survey question

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