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Evaluation of clinical decision support provided by medication review software

by

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Declaration of Originality

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Statement of Ethical Conduct

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

Colin Michael Curtain

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Publications

Peer-reviewed journal publications

Curtain C, Bindoff I, Westbury J, Peterson G. An investigation into drug-related problems identifiable by commercial medication review software. Australasian Medical Journal, 6(4) 2013, p183-188.

Curtain C, Bindoff I, Westbury J, Peterson G. A comparison of prescribing criteria when applied to older community-based patients. Drugs and Aging, 30(11) 2013, p935-943.

Curtain C, Peterson G. A review of computerised clinical decision support in community pharmacy. Journal of Clinical Pharmacy and Therapeutics, 2014. [In press]

Conference abstracts (oral)

Curtain C, Bindoff I, Westbury J, Peterson G. Can software assist the home medicines review process by identifying clinically relevant drug-related problems? ASCEPT-APSA 2012 Conference, 2-5 December 2012, Sydney, Australia.

Conference papers

Curtain C, Bindoff I, Westbury J, Peterson G. Validation of decision support software for identification of drug-related problems in home medicines reviews. 11th National Conference of Emerging Researchers in Ageing, 19-20 November 2012, Brisbane, Australia.

Curtain C, Bindoff I, Westbury J, Peterson G. An investigation into the types of drug related problems that can and cannot be identified by commercial medication review software. Second Australian Workshop on Artificial Intelligence in Health (AIH 2012), 4 December 2012, Sydney, Australia. Available from: http://ceur-ws.org/Vol-941/aih2012_Curtain.pdf

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Abstract

Aim

The purpose of this investigation was to evaluate the clinical decision support capacity of commercial computer software designed to assist pharmacists performing medication reviews.

The primary hypothesis was: If medication review software is related to pharmacist knowledge, then the detection of therapeutic problems will result in a similar frequency and scope of identified problems as those identified by pharmacists.

Method

Home medication review data collected during 2008 for a previous study were used for this investigation. The data contained original pharmacist findings of drug-related problems (DRPs), patient demographics, medications, laboratory results and diagnoses. Two commercial software applications advertising decision support were assessed, Monitor-Rx (MRX) utilising simple rules triggered by the presence of medication and Medication™ Review Mentor (MRM) utilising an advanced artificial intelligence rules-based approach. The previously collected data were entered into each of the applications and the DRPs identified by each tool were recorded. Additionally, published prescribing criteria, Beers (2003 and 2012 versions), Screening Tool of Older Person's Prescriptions and Screening Tool to Alert doctors to Right Treatment (STOPP/START) and Prescribing Indicators in Elderly Australians (PIEA) were also adapted so as to be applied computationally over the same set of patient data.

DRPs were assigned broad DOCUMENT classifications and examined by frequency and type. A common vocabulary of descriptive classifications capturing essential DRP concepts was developed to allow detailed comparison between the various DRP sources. The ability of software to identify the same classifications in the same patients as pharmacists was assessed as a crude measure of clinical relevance. A panel of pharmacology experts assessed the DRPs identified by pharmacists, MRM, MRX and the STOPP/START prescribing criteria for their

opinions concerning clinical relevance, excessive DRP findings, missed DRPs and the appropriateness of recommendations.

A qualitative survey of pharmacists who used MRM was also undertaken to obtain their opinions of the decision support capability of MRM.

Results

In total, across 570 patients, pharmacists identified 2020 DRPs, MRM 3209, PIEA 1492, STOPP 1032, Beers03 404 and Beers12 399. Ten percent of the volume of DRPs identified by MRM were found to be duplicated DRPs, where the same essential problem was identified more than once for a patients, typically via different rules. Using a smaller sub-sample of 100 patients, MRX identified 1265 DRPs. Pharmacist DRPs encompassed the widest range of DOCUMENT classifications, followed by MRM, then the sets of prescribing criteria and finally MRX.

A list of 141 descriptive classifications was developed which described the various DRP concepts in depth. Pharmacist-only descriptive classifications involving *compliance* and *not-classifiable* DRPs were excluded from assessment, since it was impossible to detect these DRPs without access to additional patient data that was not included in pharmacists written reports. Pharmacist DRPs were associated with 113 different descriptive classifications, MRM 100 and MRX 17. MRM was able to identify 90 differing classification types that were also identifiable by pharmacists. MRM was able to identify the same problems in the same patients as the reviewing pharmacists identified in 389 instances, whereas MRX identified the same problems in the same patients in only 11 instances.

Assessment of expert opinions found that experts generally agreed that MRM presented clinically relevant DRPs (80%) and appropriate recommendations for DRP resolution. This finding contrasted strongly for MRX, with experts of the opinion that MRX presented few clinically relevant DRPs (13%). Similarly, relatively few experts agreed that MRM presented too many DRP findings (19%) whereas the vast majority of experts agreed MRX presented an excessive number of findings (93% of opinions).

Pharmacists who used MRM agreed with the expert panel regarding MRM. These pharmacists also found MRM to be easy to use (mean 76 on scale of 0 to 100) and useful (mean 5.6 on a scale of 1 to 7). The pharmacists agreed that MRM identified clinically relevant DRPs (73%) and also agreed that MRM identified clinically relevant DRPs that would otherwise have been overlooked by pharmacists (73%).

Discussion

Both MRM and MRX identified a greater number of DRPs than pharmacists. However, MRM was considered, by both the expert panel members and pharmacist subscribers, to identify an acceptable number of mostly clinically relevant DRPs and to present appropriate recommendations to resolve DRPs. In contrast, the expert panel thought MRX identified an excessive number of mostly irrelevant DRPs. The contrast between the relevance of MRM and lack of relevance of MRX highlighted the different approaches used by each product. MRX utilised a simple approach through the identification only of medications of interest, whereas MRX incorporated a range of variables such as examining all medications, medication doses, medical history, laboratory results. The integration of a range of variables allowed MRM to provide far greater context to the DRPs found for each patient. Application of the DOCUMENT classifications and the descriptive classifications found that MRX was capable of identifying a very limited range of DRP types, whereas MRM was capable of identifying a wide range of DRP types, approaching the range of problem types identifiable by pharmacists.

The descriptive classification comparison of MRM and MRX findings with the sets of prescribing criteria found that MRX was more closely aligned with the Beers12 criteria, whereas MRM was more closely aligned with the STOPP/START criteria. Interestingly the STOPP/START criteria were also considered, by the expert panel, to provide clinically relevant findings. This may be due to patient contextualisation via the incorporation of medication-medication interactions and medication-diagnosis interactions within many of the STOPP/START criteria. However, compared to MRX, MRM and pharmacists' original findings, STOPP/START found the smallest number of problems. These findings were naturally limited to the set of 74 criteria which implemented in this investigation. An additional finding was the STOPP/START criteria were found to be the closest of all the sets

of prescribing criteria to the pharmacists' findings, both in terms of scope of problem types as well as by frequency.

Greater contextualisation of DRPs certainly provided greater clinical relevance, as shown with the STOPP/START prescribing criteria and exemplified by MRM. However, STOPP/START was limited to a set of specific consensus-based rules, limiting opportunities to expand on the identification of clinically relevant DRPs. MRM did not have this limitation, allowing an expert in the the knowledge domain of medication reviews to add and refine numerous rules incorporating patient-specific data to maximise the detection of clinically relevant DRPs. A strong rationale for the use of MRM, or similarly implemented technologies, was not only MRM's clinical relevance but also MRM's practical usefulness in the detection of missed opportunities – pharmacist subscribers confirmed that MRM did identify clinically relevant DRPs that the pharmacists themselves had missed.

Conclusion

The implementation of overly simple rules, such as the mere presence of a medication as was used by MRX, was insufficient to provide good decision support as it resulted in an excessive abundance of a narrow range of mostly clinically irrelevant DRPs.

Automated versions of the prescribing criteria STOPP/START, PIEA, and Beers proved to be a slightly better tool for identifying DRPs as took into account a broader spectrum of information about the patient’s condition (typically diagnoses), allowing them to identify more targeted and relevant problems.

However, the use of artificial intelligence technology by MRM allowed for both greater contextualisation and variety of clinically relevant DRPs. MRM identified a higher frequency of DRPs than did pharmacists. In part, the greater frequency of DRPs identified by MRM may represent clinically relevant DRPs that were missed by reviewing pharmacists. This capacity to supplement clinically relevant DRPs complements the consistency and thoroughness of the pharmacists medication reviews.

In light of the performance of MRM seen in this research, it is reasonable to expect that future clinical decision support system (CDSS) applications using the multiple-classification

ripple-down rules (MCRDR) approach could provide significant benefits over the much simpler technologies that are typically utilised, with very limited success, worldwide. These benefits include the identification of clinically relevant problems both more frequently, and more consistently, yet with very few clinically irrelevant problems identified. Furthermore, this consistently high performance level leads to better uptake and acceptance rates by users, ensuring that the problems are not only identified, but are actually acted upon when appropriate to do so. Such CDSS implementations might be successfully incorporated into a wide variety of healthcare settings, such as hospital, general and specialist practice, and community pharmacy. Given the results of this thesis, that the technology now exists, and that quality patient electronic health record (EHR) data is gradually becoming more available, it seems that the time has come for this technology to be applied more widely.

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Abbreviations

Abbreviation	Explanation
AACP	Australian Association of Consultant Pharmacy
ACEI	Angiotensin Converting Enzyme Inhibitor
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AF	Atrial Fibrillation
AI	Artificial Intelligence
ARB	Angiotensin Receptor Blocker
ASCP	American Society of Consultant Pharmacists
ATC	Anatomic Therapeutic Chemical classification system
Beers03	Beers criteria 2003 version
Beers12	Beers criteria 2012 version
BMI	Body Mass Index
BP	Blood Pressure
BSL	Blood Sugar Level
CAD	Coronary Artery Disease
Case	Generally represents a Home Medicines Review patient
CCB	Calcium Channel Blocker
CD4+	Cluster of Differentiation 4 positive T lymphocyte
CDSS	Clinical Decision Support System
CHF	Congestive Heart Failure
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
COX, COX2	Cyclo-oxygenase
CPOE	Computerised Physician Order Entry
CV	Cardiovascular
DDI	Drug-Drug Interaction
DEMS	Diabetes Electronic Management System
Df	Degrees of freedom
DMARD	Disease-Modifying Anti-Rheumatic Drug
DOCUMENT	Classification system for drug-related problems
DOUMET	DOCUMENT classifications excluding compliance and not-classifiable components
DRP	Drug-Related Problem
DVA	Department of Veterans Affairs
EBM	Evidence-Based Medicine
EHR	Electronic Health Record
EPG	Evidence-Practice Gap
EQ-5D	EuroQol group 5 Dimensions
EQ-VAS	EuroQol group Visual Analogue Scale
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume 1 second

Abbreviation	Explanation
GP	General Practitioner
GTN	Glyceryl Trinitrate
H2	Histamine type 2 receptor
HbA1c	Glycated haemoglobin
HF	Heart Failure
HIV	Human Immunodeficiency Virus
HMR	Home Medicines Review
HR	Hazard Ratio
ICD-9	International statistical Classification of Diseases and related health problems (version 9)
ICPC2-plus	International Classification of Primary Care (version 2 plus)
ID	Numeric patient identifier
IHD	Ischaemic Heart Disease
INR	International Normalised Ratio
ITT	Intention To Treat
L-DOPA	Levodopa
LABA	Long-Acting Beta Agonist
LDL	Low-Density Lipoprotein
MCRDR	Multiple-classification ripple-down rules
MDS	Minimum Data Set
MeSH	Medical Subject Headings
MI	Myocardial Infarction
mmHg	Millimetres of mercury
MMSE	Mini-Mental State Examination
MRM	Medication Review Mentor
MRX	Monitor-Rx
N	Number
NEHTA	National E-Health Transition Authority
NPS	National Prescribing Service
NSAID	Non-Steroidal Inflammatory Drug
NYHA	New York Heart Association
OR	Odds Ratio
PIEA	Prescribing Indicators in Elderly Australians
PPI	Proton Pump Inhibitor
PIM	Potentially Inappropriate Medication
PRN	*Pro re nata* (Latin), As the occasion arises (English)
QUM	Quality Use Of Medicine
RCT	Randomised Controlled Trial
RMMR	Residential Medication Management Review
SF-36	Short Form (36) health survey
Source	Generally represents a source of identified DRPs
SQL	Structured Query Language
SSRI	Selective Serotonin Reuptake Inhibitor
START	Screening Tool to Alert doctors to Right Treatment

Abbreviation	Explanation
statin	HMG-CoA reductase inhibitor
STOPP	Screening Tool of Older Person's Prescriptions
STOPP/START	Screening Tool of Older Person's Prescriptions and Screening Tool to Alert doctors to Right Treatment
TAM	Technology Acceptance Model
TCA	Tricyclic Antidepressant
TermID	A numeric field code referencing individual ICPC-2 plus classifications
TIA	Transient Ischaemic Attack
UTI	Urinary Tract Infection
VALMER	The economic value of home medicines reviews
vs.	versus

1 Introduction

Analogous with many developed nations in the early part of the 21st century, the Australian population is undergoing a shift towards an increased proportion of older citizens.[1,2] Older people are associated with greater frequency of chronic conditions, co-morbidity and medication use.[3] Expenditure on medications in Australia grew from $13.9 billion in 2007-08 to $18.4 billion in 2010-11, perhaps not surprising considering the shift toward an ageing population.[4,5]

Unfortunately, although mostly life enhancing, medications do contribute to patient harm including hospitalisations and death. Australian studies have identified that up to 5.6% hospital admissions were related to adverse drug events (ADEs), with a third of these associated with older people.[6,7] Activities, or interventions, to minimise such events may involve patient education, as well as prescriber education, such as the implementation of best practice guidelines. Interventions targeting improvements in the use of medications, particularly in older patients, may be expected to benefit society through better health and reduced healthcare utilisation.[8–10]

A range of medication safety intervention strategies were reviewed by Semple and Roughead which concluded that clinical pharmacist services showed benefit.[10] Pharmacists are extensively trained in pharmacotherapy and may reasonably be expected to possess a wider scope of pharmaceutical knowledge than other health professionals.[11] Such knowledge is suited to the task of patient medicines review for identification of drug-related problems and recommendations for improved therapy.[9,12]

Around the world medication review programs have been developed to capitalise on pharmacist drug knowledge. The United Kingdom National Health Service implements pharmacist initiated medicines reviews through several hospital and community programs (medicines use review, dispensing review of use of medicines, chronic medication service, comprehensive medication review, clinical medication review).[13] Finland has performed pharmacist-conducted medicines reviews since 2005 with aspects drawn from the Australian and USA programs, although this program has not been nationally funded.[14] Medication therapy review an element of medication therapy management is performed in pharmacy

practice in the USA and funded through Medicare Part D, to improve medicines use through patient targeted programs and healthcare collaboration.[15]

The Australian Government Department of Health and Ageing funds pharmacists who undertake additional training to become accredited to perform medicines review services. Such services are directed at aged care residents as well as patients who reside in their own homes and meet selection criteria which are designed to identify patients in need of this service. An example may be a patient who regularly consumes five or more medications on a daily basis.[16,17]

The medicines review task requires the pharmacist to obtain a range of information about the patient's current medication therapy and incorporate many factors which may actually or potentially impact on the best possible therapy. A critical step in the review process is the analysis of information to identify suboptimal treatment and provide relevant recommendations for consideration by the patient's GP. Such analysis requires the reviewing pharmacist to have proficient knowledge, not only of medications, but of medical conditions associated with the elderly, laboratory test results and familiarity with current evidence-based disease management and medicine guidelines.

There is some evidence that pharmacist medicines review can reduce polypharmacy and improve patient outcomes.[18–20] However, a 2008 Australian report of pharmacist medication reviews identified some reservations from GPs such as "... sometimes supply irrelevant or unhelpful information ...".[21] Also pharmacists had reservations including a lack of confidence in making clinical recommendations and concerns about time constraints.[21]

In Australia and overseas, software has been developed to aid pharmacist medicines review activities and some of this software has incorporated an additional clinical decision support functionality, see section 3.8. Clinical decision support systems (CDSS) may have a role to play, by assisting pharmacists with both the identification of suboptimal therapy and the provision of recommendations for their resolution. Such computerised clinical decision support may address some of the reservations by aiding pharmacist confidence and improving the clinical information that is provided to GPs in medicines review reports.

There have been numerous studies investigating the effects of CDSS on prescriber practice and patient outcomes.[22–24] However, little investigation has been undertaken on the capabilities of CDSS developed for medicines review in general or for pharmacist medicines review in particular, see section 3.7. Information technology is widespread in the health sector and electronic health records and system interoperability is improving. However, there has been limited investigation into the validation of commercial systems. This thesis evaluates two commercial products and investigates the applicability of CDSS for medicines review. It is important that commercial products of this nature are evaluated as they need to show they can support a fundamental activity such as healthcare. Both healthcare professionals and healthcare consumers need to be reassured that the products in use will benefit them, and if not, that such products are clearly identified and avoided.

2 Inappropriate medication use in older people

This chapter covers some of the issues of the inappropriate use of medicines, or drug-related problems (DRPs), in older people. The factors associated with DRPs are discussed as well as their frequency. Two approaches which are synergistic and closely associated with the central work of pharmacists are discussed: the use of prescribing criteria - measures of good and bad prescribing, and medicines review also known as medication therapy management. The home medicines review (HMR) is talked about specifically as the data on which this thesis is based is drawn from HMR reports.[16,25]

Appropriate medication use is termed quality use of medicines (QUM); defined as "Selecting management options wisely; choosing suitable medicines if a medicine is considered necessary; and using medicines safely and effectively"[26] This is an ideal goal, however, there is a gap between knowing what best practice is, and actually implementing best practice. The difference between accepted current research identifying evidence of best medication therapy and the actual practice is known as the evidence-practice gap (EPG). Australian studies have identified EPGs for a range of medications.[27–30]

It is important to identify DRPs and do what can be done to improve QUM through resolving or minimising the potential for harm. Addressing DRPs in older people is important as adverse drug reactions (ADRs) lead to greater rates of hospitalisation in older people than in the general population, are costly to society and are detrimental to the individual's quality of life.[6,31]

2.1 Drug-related problems

A central component of pharmacist medicines review is the identification of DRPs.[25,32] DRPs are defined by the Pharmaceutical Care Network Europe as "... an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"[33] This definition is broad in that it covers actual problems that have occurred, that is ADEs, of which adverse drug reactions (ADRs) are a subset, as well as potential problems that may occur. The relationships between the components contributing to DRPs are shown in Figure 1 as a Venn diagram adapted from Nebeker *et al*.[34]

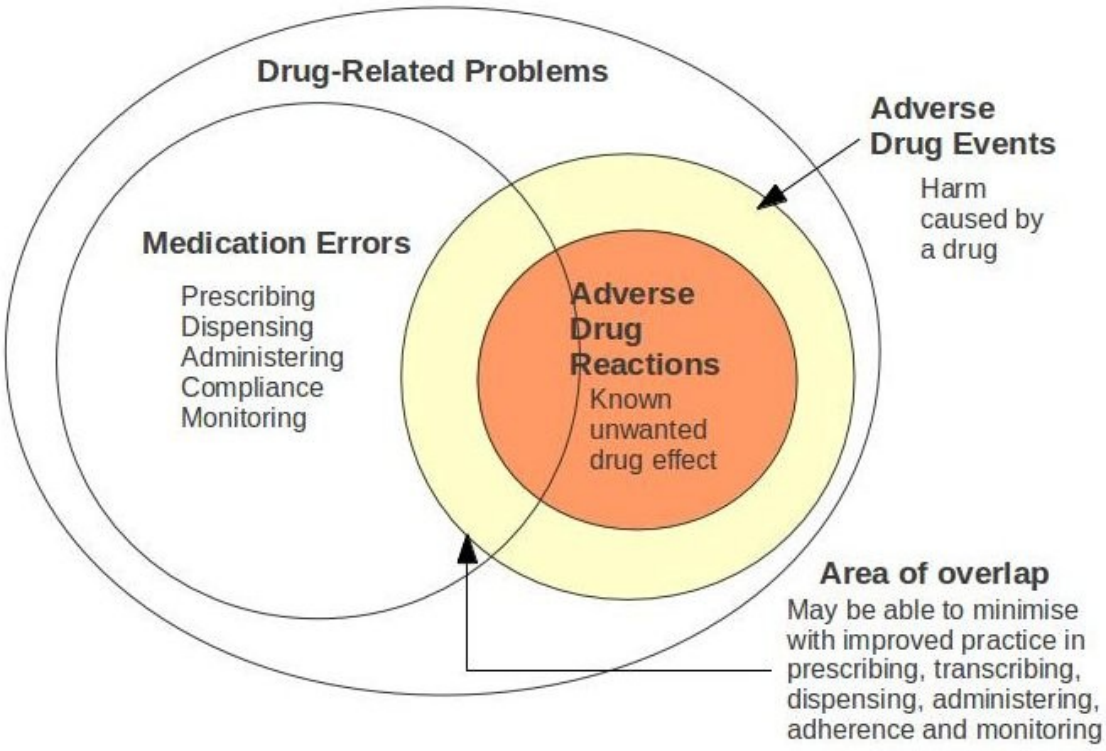


Figure 1: Relationship between medication errors, ADEs and ADRs

An example of a potential DRP is the prescribing of dextropropoxyphene, an opioid analgesic prescribed for pain management. Studies have shown both dextropropoxyphene and the metabolite nordextropropoxyphene accumulate in the elderly due to reduced hepatic and renal clearance[35], and cardiac toxicity.[36] Additionally, dextropropoxyphene is considered to be no more effective than paracetamol or aspirin and was considered to be relatively toxic even as far back as the 1970s.[37] As such dextropropoxyphene has been included in several iterations of the Beers criteria as a potentially inappropriate medication (PIM) in older people, and prescribing dextropropoxyphene in this cohort would be considered a potential DRP.[38,39]

Another type of DRP is lack of treatment for existing disease or symptoms, or lack of treatment to prevent a disease occurring. Examples include preventative therapy with antiosteoporotics, calcium and vitamin D to reduce incidence of osteoporotic fractures[40], or improved survival in patients with heart failure with the addition of angiotensin-converting

enzyme inhibitors (ACEIs) or beta-blocking drugs.[41] Several studies have identified problems relating to drug treatment omissions in hospitalised and community-based elderly ranging from 16% to 42% of patients.[42–45]

2.1.1 Factors associated with DRPs in older people

Studies have identified a variety of factors which have been associated with DRPs, not only drug specific factors but also factors involving organisational systems and patient-specific factors of compliance, cost of medications, health literacy, culture and language barriers.[6]

An Australian study published in 2004 by Roughead *et al*. identified a variety of factors associated with DRPs in older adults.[46] The majority of these DRPs were related to the prescriber and involved inappropriate medicines, inappropriate dosages or therapeutic or monitoring omissions. Proportions of DRP factors are illustrated in a National Prescribing Service (NPS) Medicinewise News publication,[47] see Figure 2.

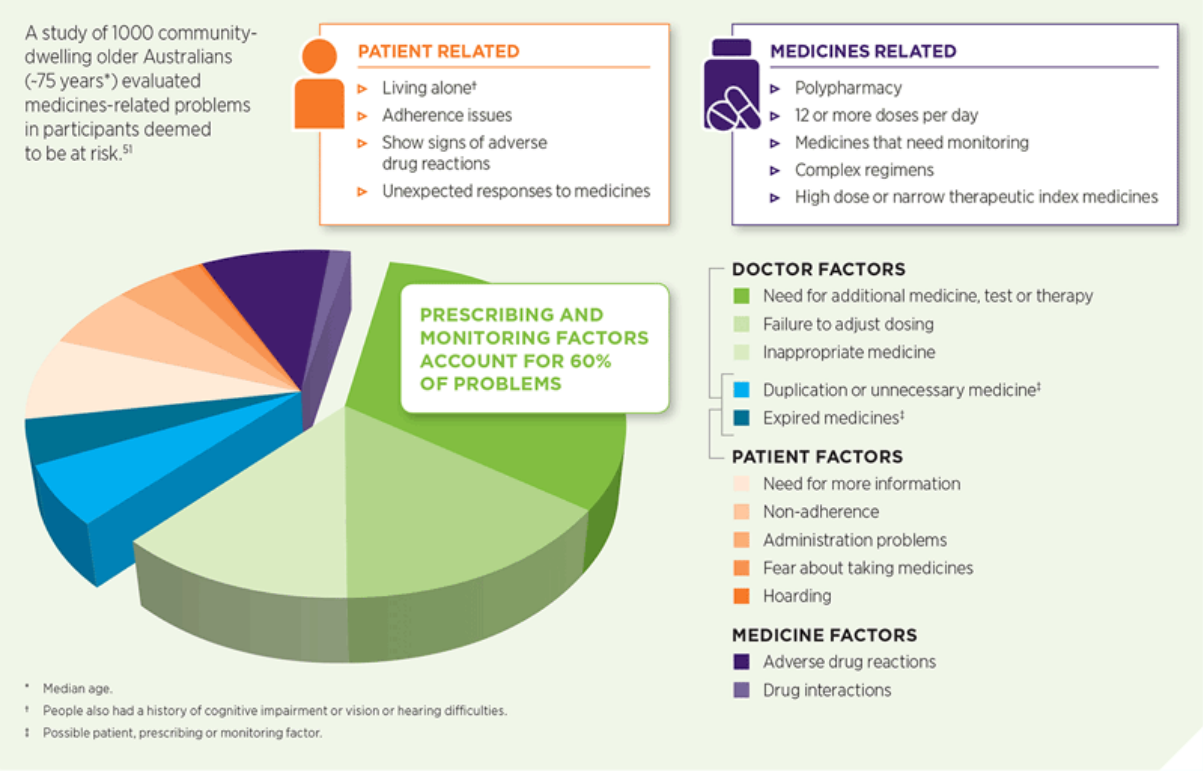


Figure 2: DRPs in older Australians. Figure reproduced from NPS Medicinewise News September 2013.[47] Data from Roughead *et al*.[46]

The following factors have been found to be associated with DRPs in older people. Such factors may not present in isolation and their additive or synergistic effects may enhance the opportunity for undesirable outcomes in older people.

Pharmacodynamics and pharmacokinetics

Older people have differing biological processes compared to younger people. Renal function declines reducing elimination of renally excreted medication.[3] Hepatic function declines which may have various consequences such as reduced first pass metabolism, reduced prodrug activation, and reduced or altered metabolism of active drugs and metabolites,[3] such as dextropropoxyphene mentioned earlier. The ability to maintain homeostasis (autonomic functioning, blood pressure, blood chemistry) is reduced. Pharmacodynamic responses to medications may be accentuated or diminished, examples are: a reduced response to β-agonist inhalers, or excessive sedation with the use of benzodiazepines.[3,48]

Medical conditions and co-morbidity

Chronic medical conditions occur more often in older people and co-morbidities occur with greater frequency with increased age.[49,50] Americans aged 65 and over had the highest proportion of one (87%) or more (67%) chronic medical conditions of any age group.[50] Co-morbidities have been identified as factors associated with DRPs.[51] Co-morbidity was also associated with conflicting treatment leading to DRPs.[52–54]

Co-morbidity of chronic medical conditions of diabetes mellitus, coronary artery disease (CAD), congestive heart failure (CHF), and geriatric syndromes of falls and incontinence were found to co-exist in substantial proportions of American patients.[49] Similarly, co-morbidity was not uncommon in Australian patients with one or more of arthritis, hypertension, cardiovascular disease, diabetes, asthma and mental health conditions found to co-exist.[55] Co-morbid hypertension and diabetes was found to exacerbate cognitive decline in older people.[56]

Polypharmacy

Polypharmacy is a common theme associated with ADEs in older people. As people age there is greater incidence of chronic disease and consequently the use of medications to treat

disease.[3] Polypharmacy is often defined as the use of 5 or more medications at the same time.[57] Polypharmacy has been identified as a factor in elderly hospital admissions.[51,58] Even after hospital discharge, polypharmacy in older people remained associated with ADEs.[59] An increase in the number of medications has been shown to have a linear relationship with increased DRP frequency, based on medicines review of hospital admissions in Norway.[57] A very similar result was found from a review of Australian general practice patient case notes.[60] Graphs of each of these study results are shown in Figure 3 and Figure 4. Polypharmacy has also been associated with inappropriate prescribing.[61]

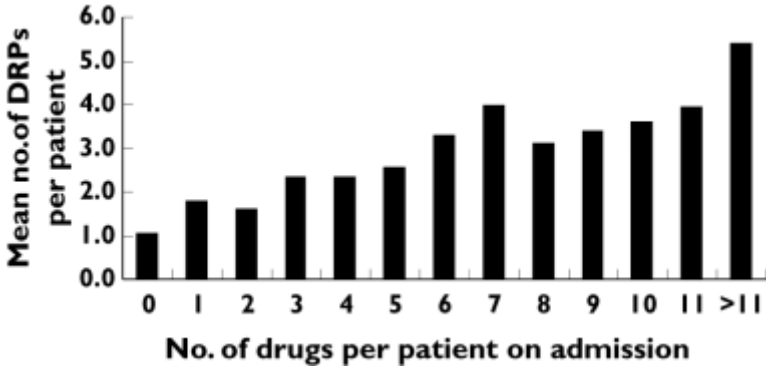


Figure 3: Linear increase of DRPs with greater polypharmacy, reproduced from Viktil *et al*.[57]

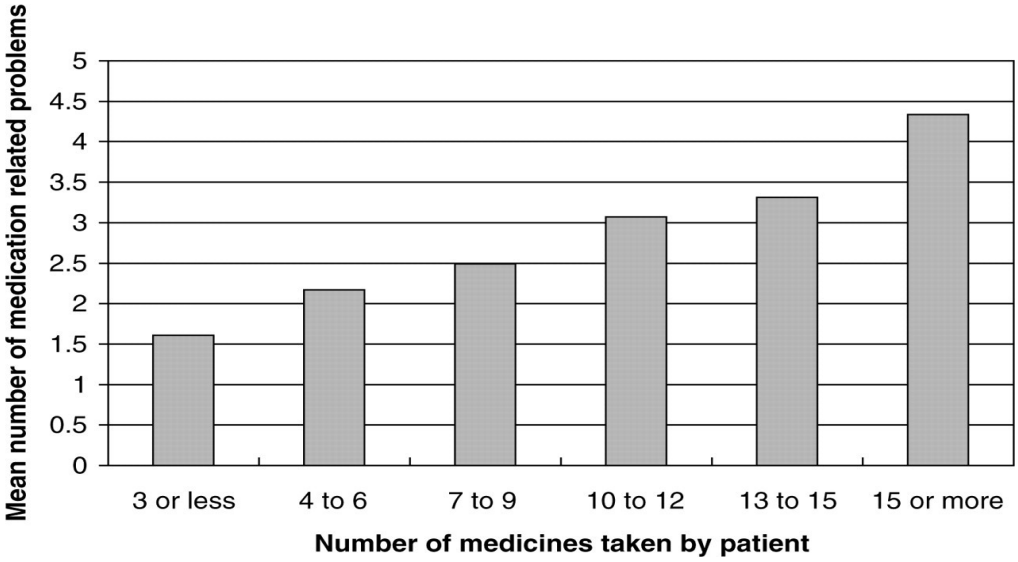


Figure 4: Increased medication problems with increased medication use, figure reproduced from Runciman *et al*.[75] based on data from Gilbert *et al*.[60]

Drug classes

Various classes of medications have been associated with ADEs in older people. Easton *et al.*[6] presented a table of drugs and drug classes involved in ADEs in older people, developed from a review of studies. Several drug classes were commonly associated with ADEs and included: antibiotics, cardiovascular drugs, anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs), hypoglycaemics, antidepressants and anticholinergics. Studies published since this review support these drug classes as key ADE contributors.[62–64]

Adherence

Adherence is a term commonly used to describe patient behaviour concerning medication-use. Adherence is defined as "the extent to which the person's behaviour – taking medication … corresponds with the agreed recommendations from a health care provider"[65] Non-adherence typically consists of never beginning treatment, not persisting with treatment or not conforming with the recommended treatment regimen.[66] These steps are illustrated in Figure 5 from Iron Health Alliance[67]. Several patient factors are implicated in non-adherence including: misunderstanding instructions, forgetfulness, fears and beliefs related to side-effects and regimen complexity.[66]

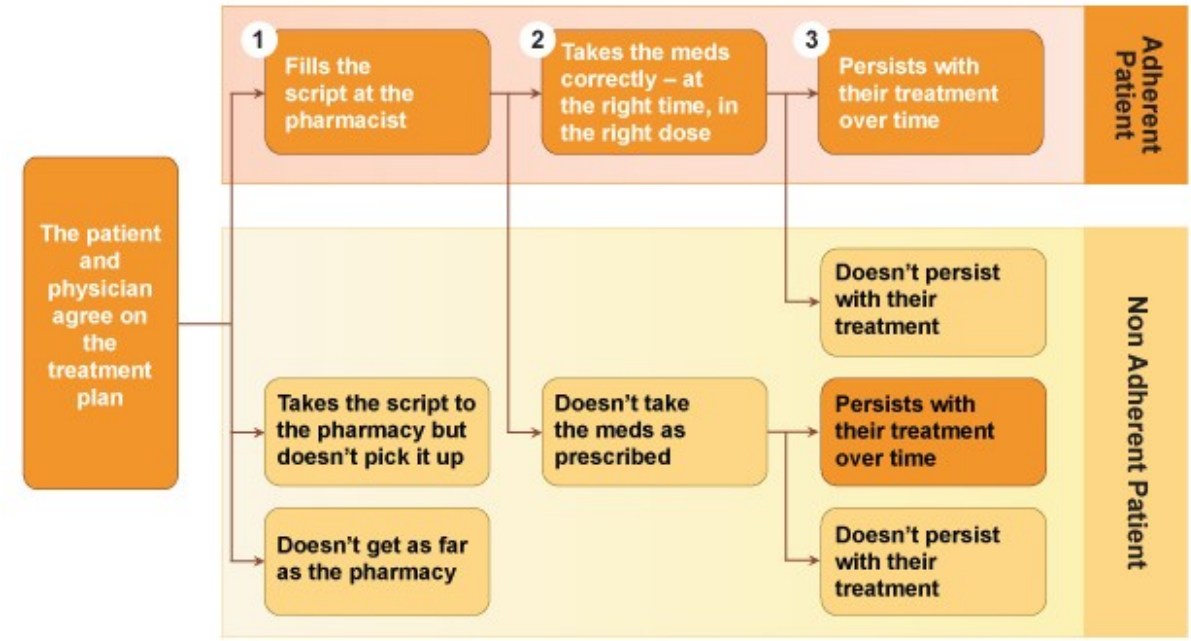


Figure 5: Adherence and patient actions. script = prescription, meds = medication. Figure reproduced from Iron Health Alliance[67]

A study in the Netherlands found impaired cognition and treatment non-adherence were associated with hospital admissions.[51] Lack of patient knowledge and related non-adherence have been associated with DRPs in several studies.[60,68,69] In Australia 26% of hospital admissions were related to not conforming or not persisting with therapy.[58] Higher mortality has been linked with poorer health literacy in a study of patient's ability to read and understand medication directions.[70] Financial limitations may also affect the purchase of medications resulting in non-adherence.[71]

Physical factors

Physical limitations may affect older peoples' ability to access or utilise medication, subsequently reducing adherence to therapy. Poor physical strength or dexterity may cause difficulty with opening medication containers, splitting tablets or actuating medication inhalers.[71,72] Reduced vision may affect interpretation of written labels and the consumption of the presumed correct medications.[71] Swallowing difficulties can affect medication adherence and may be compounded by drugs affecting saliva production or muscle

movement, tablet or pill size, or disease states resulting in reduced saliva or pharyngeal muscle movement.[73,74]

Health system factors

Health system factors encompass prescribing, dispensing and administration errors including communication failures, particularly informing health care professionals after hospital discharge.[7] Prescribing errors were not infrequent in hospital practice. A 2003 systematic review found administration errors occurred at rates ranging from 5% to 20%, typically involving dose timing being too early or late or dose omission.[75] Prescribing errors occurred in 2.4% of prescriptions, typically involving wrong, unclear or missing dosing.[75] Hospital dispensing errors also occurred with low frequency, 0.08% to 0.8% of prescriptions.[75]

A 2008 USA survey of pharmacy directors from over 1300 hospitals showed a range of measures were implemented to reduce the incidence of dispensing and administration errors, including robots and automated dispensing, smart infusion pumps, two-pharmacist checks for high risk medication, pharmacist review of emergency department medication orders and administration checks – verbally confirming the right patient or using bar-code confirmation.[76] A study in a English teaching hospital compared changes after automated dispensing, patient bar-code identification and electronic medication administration records were introduced. The study found significant reductions in prescribing errors (3.8% to 2.0%) and medication administration errors (7.0%% to 4.3%) and improved patient identity checking (17.4% to 81.1%).[77]

An observational study of administration errors in 12 assisted living centres found, after excluding wrong timing of medication administration, an error rate of 8.2% consisting of wrong, excessive or omitted doses and incorrect or unauthorised medication.[78] The assisted living centres primarily employed non-medically trained staff.[78]

2.1.2 Frequency of adverse drug events

ADEs have been defined as "Medication incidents that cause harm to the patient"[6] A subset of ADEs, ADRs have been defined as "A response to a drug that is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function".[79]

In Australia a study conducted in 1994 found hospitalisations associated with ADEs accounted for 5.7% of hospital admissions.[80] Additionally, a Canadian study conducted in 2006 found emergency department admissions from ADEs were associated with an almost doubled of cost of care compared to admissions due to other reasons.[81] ADEs were also a common event among ambulatory patients with 10% of Australian general practice patients having experienced an ADE within 6 months prior to GP consultation.[82] Overseas studies have shown roughly similar rates of ADEs, shown in Table 1.

Table 1: Hospital admissions associated with ADEs

Study	Country	ADE-related hospitalisation rate
Hohl *et al*. 2011[81]	Canada	12%
Wu *et al*. 2010[64]	England	1.1%
Pirmohamed *et al*. 2004[83]	England	6.5%
Leendertse *et al*. 2008[51]	Netherlands	5.6%
Brvar *et al*. 2009[84]	Slovenia	5.8%
Kongkaew *et al*. 2008[85]	Various	0.16% - 15.7%

A study of Australian general practice patients aged 45 years old and older, from 2007 and 2010 data found an ADE rate of 11.6% made up primarily of known drug side effects from commonly used drug groups (opioids, lipid-modifiers, cardiovascular drugs, and anti-diabetic drugs).[86] Rates of ADEs among older people have been shown to be even higher, with up to a third of hospital admissions and discharges involving ADEs and higher rates among ambulatory older people.[58,59,82]

2.2 Prescribing criteria for older people

Attempts to reduce the incidence of DRPs have led to the development of various QUM guidelines designed to be applicable to older patients. Older patients are the typical cohort for medication reviews. Published prescribing criteria include: Beers 2003 version (Beers03)[38], the recently updated Beers 2012 version (Beers12)[87], Improved Prescribing in the Elderly Tool[88], Screening Tool of Older Persons Prescriptions and Screening Tool to Alert doctors to Right Treatment (STOPP/START)[89], McLeod criteria[90], Drug Burden Index (DBI)[91], Medication Appropriateness Index (MAI)[92] and an Australian specific tool Prescribing

Indicators in Elderly Australians (PIEA) developed in 2008, and further validated and refined in 2012.[93,94]

Prescribing criteria are intended to be broadly applicable to select patient populations yet require professional interpretation for each individual patient. Criteria cannot truly prescribe individual patient solutions as patient-specific context is lacking, although each set of prescribing criteria attempt to incorporate some patient-relevant factors to contextualise the relevance of any recommendations made.[38,89,90,93] True patient context is a conglomeration of unique factors including demographic information, co-morbidities, pathology, treatment goals, patient physical capabilities, patient understanding, and history of successful and unsuccessful treatments and treatment regimens.[95] Despite this caveat, prescribing criteria are intended to point the healthcare professional in the right direction by providing evidence-based rules of what are or are not suitable therapeutic options.

Many sets of prescribing criteria have been developed by expert consensus.[38,89,90,96–99] Prescribing criteria often cite evidence supporting their recommendations.[87,89,93,100] Several sets of prescribing criteria for use in older people have been compared and critiqued,[101–104] likely spurring the development of newer guidelines. Concerns have included: the lack of a holistic approach through the exclusion of patient's life expectancy, quality of life, social and financial factors[101,102]; Another concern is the time cost to apply prescribing criteria, particularly the MAI, taking about 10 minutes per drug assessed.[101,102]

Evidence behind prescribing criteria have also been critiqued and considered deficient.[105–108] The plethora of prescribing criteria and criteria fatigue has also been noted, perhaps limiting their application and effectiveness.[108,109] Prescribing criteria have been developed and trialled in older people, typically those aged 65 years old and older. However, their application in much older patients, such as those over 75 years old, may require greater caution.[102] To quote geriatrician Virginia Aylett:

> 'We care for the patient who would never be included in a randomised controlled trial: the cognitively impaired, the patient with multiple comorbidities, the patient with not long to live, the patient where the researcher stands at the end of the bed and says, "Perhaps not."' [106]

Another pertinent issue is the applicability of prescribing criteria developed in other countries. Prescribing criteria for older people have been developed specifically for use within many countries: Australia[93], Japan[110], Italy[96], France[98], Canada[90], Thailand[97], Norway[99], Germany[111] and USA.[38] The reason for such diversity appears to be the need to have criteria designed for medications available within each country. Despite these concerns, several trials have shown prescribing criteria do support the identification of clinically relevant DRPs, discussed in the following sub-sections.

2.2.1 Beers03

The Beers03[38] criteria were developed to bring up to date an earlier version published in the 1997[39] in the USA. It was acknowledge that the earlier Beers criteria required updating due to discontinuation of older drugs, new drugs becoming available and changed use of existing drugs. This version of the Beers criteria was developed using a modified Delphi technique which involved iterative feedback from a group of 12 medical experts to reach consensus or otherwise on the proposed criteria.

The Beers03 criteria was designed to be applicable to "... the general population of patients 65 years and older"[38]. Criteria were assembled into two tables: a table for PIMs, drugs to avoid or avoid at higher doses, totalling 49 criteria and; a table of 19 disease context PIM criteria. The criteria are detailed in Appendix 1. Each criterion was assigned a high or low severity rating to assist interpretation. Several studies have supported the use of the Beers03 criteria.[112–115] A recent study found Beers03 could be used as a measure to identify inappropriate prescribing more generally, beyond the medications listed in the criteria.[115] MAI scores for non-Beers03 listed medications were higher (indicating inappropriateness) in patients who were also prescribed Beers03 PIMs compared to patients who were not prescribed Beers03 PIMs.[115] An Australian study of nursing home residents (1993 to 2005) found the use of Beers03 criteria listed medications were not generally associated with increased hospitalisations.[116] However, high-care residents had a greater likelihood of hospital admissions that were attributable to Beers03 PIMs.[116]

Criticisms include: criteria recommending against the use of amiodarone or fluoxetine, these medications are considered useful if appropriately monitored; few drug-drug interaction

criteria; lack of drug-disease interactions such as NSAIDs in heart failure.[103] An investigation into emergency hospitalisations due to ADEs in older patients were not representative of Beers03 criteria and were mainly associated with four classes of medications: warfarin, insulins, oral antiplatelets and oral hypoglycaemics.[63] Steinman *et al.* study examined the drugs to avoid in older people according to the Beers03 criteria.[117] Through expert review they found the majority of drugs to avoid were not actually causing problems and concluded "...they are insufficiently accurate to use as stand-alone measures of prescribing quality"[117]

2.2.2 Beers12

Subsequent to criticisms and the publication of studies showing the comparative advantage of the newer STOPP criteria, an updated version of the Beers criteria (Beers12) was released in 2012.[87,103,118,119] Details of the Beers12 criteria are tabled in Appendix 1. It was again acknowledged that the earlier Beers criteria required updating due to new drugs becoming available and the use of existing drugs in line with best practice. The 2012 version of the Beers criteria was developed using a modified Delphi technique which involved iterative feedback from a group of medical experts to reach consensus or otherwise on the proposed criteria. Rarely used medications and medications no longer marketed in the USA were removed and newer medications or medication classes were added, details are shown in Appendix 2.

Recent studies have investigated the use of the Beers12 criteria. One study of patients in Lanzarote, Spain[120] found the Beers12 criteria had minimal overlap with the STOPP/START criteria and suggested the two tools were complementary, a finding similar to that published out of this thesis.[121] In an Italian study Pasina *et al*.[122] compared Beers12 with Beers03 in patients 3 months post-hospitalisation and concluded patient using criteria-listed medications were not more likely to be at higher risk of ADEs, re-hospitalisation or mortality.

We have since written an article utilising the Beers12 criteria which compared the frequency and type of DRPs identified alongside the STOPP/START and PIEA criteria as well as original reviewing pharmacist findings.[121] Of the three sets of criteria examined, the Beers12 criteria was found to be the least representative of the original pharmacist findings.[121]

2.2.3 STOPP/START

The STOPP and START (STOPP/START) criteria were published in 2008 and contained explicit criteria which had been validated by expert consensus.[89] STOPP/START was developed out of limited information of benefit pertaining to existing criteria such as the Beers and Zahn criteria. Additionally, the applicability of such criteria in everyday practice was considered to be limited.[89] The STOPP/START criteria were prepared from published details of inappropriate prescribing in older people. These sources included text on pharmacology in older people and the British National Formulary.[123–126] As with the Beers03 and Beers12 criteria, the draft STOPP/START criteria were validated through a Delphi process by a panel of experts in geriatric pharmacology.[89]

The 65 STOPP criteria identified instances of PIMs and the 22 START criteria identified instances of potential therapeutic omission. Details of the STOPP and START criteria are shown in Appendix 1.

An Irish study of acute hospital admissions related to ADEs found STOPP, unlike Beers03, was more strongly associated with detection of avoidable ADEs contributing to hospitalisations.[118] Study summary is shown in Figure 6.

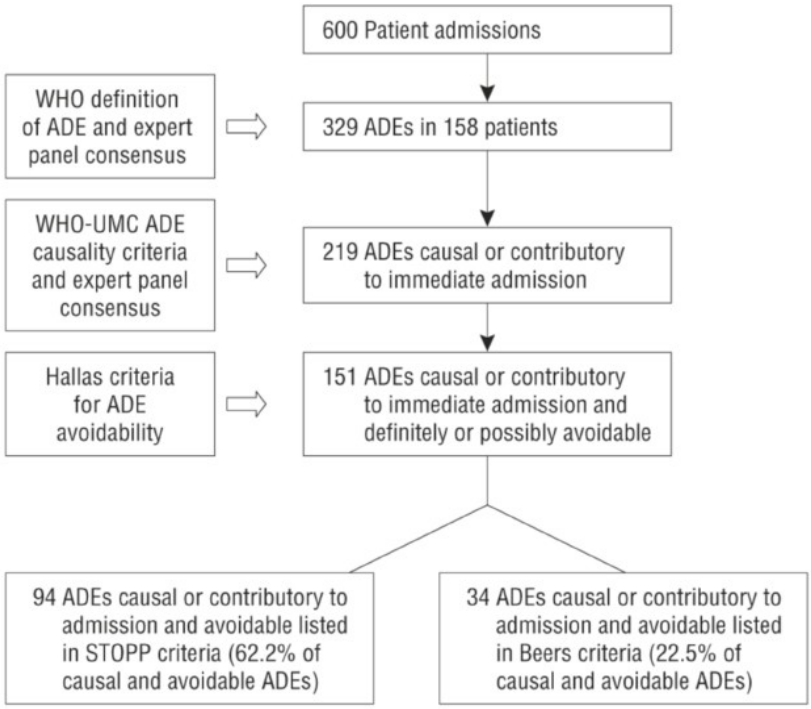


Figure 6: Avoidable ADEs associated with STOPP and Beers03.
Figure reproduced from Hamilton *et al*.[118]

A review of medication appropriateness tools recommended the use of STOPP over Beers03.[103] The START component was applied to elderly patients admitted to hospital and found to be simple to apply and effective in identifying prescribing omissions which were subsequently corrected in most patients.[127]

2.2.4 PIEA

The PIEA[93] was published in 2008 based on frequently prescribed Australian medications for common medical conditions rather than the expert panel consensus approach used with Beers and STOPP/START. The PIEA was developed from an investigation of frequent medical conditions of older people encountered by GPs in Australia as well as common reasons for hospitalisation in older people. These conditions were narrowed to those conditions for which treatment by medication was available. Medications commonly prescribed for these conditions were identified through the Australian Government funded Pharmaceutical Benefits Scheme. Australian drug information sources were used to create preferred treatment

options using these commonly prescribed medications for the various disorders experienced by older people. PIEA contained 45 explicit criteria (rules that could be directly applied and produce a true or false answer) and three implicit criteria (based on clinical judgement). The explicit criteria included 25 PIM criteria, 19 criteria relating to prescribing omissions and one monitoring criterion. Details of the criteria are shown in Appendix 1.

Only two studies were found which assessed the PIEA in practice.[128,129] The PIEA were applied to Spanish nursing home patients and were compared with the STOPP/START criteria. The PIEA were found to be more likely to detect DRPs in patients and more likely to detect more than two DRPs per patient. Similarities between the criteria involved: undertreatment with osteoporosis, undertreatment with statins, and inappropriate use of psychotropic drugs. The most frequent DRPs identified by the PIEA involved lengthy use of benzodiazepines, and psychotropic drug use in patients with a history of falling, and anticholinergic drug use in patients with dementia.[129]

A study by the authors of the PIEA applied the tool to hospital discharge patients who were using 5 or more medications.[128] Patients with dementia were excluded from the trial. This study found an average of 7 DRPs per patient involving both inappropriate prescribing and under-prescribing. The most frequent DRPs identified were inadequate treatment of pain, insufficient antihypertensive therapy, and similar to the Spanish study, undertreatment with statins. Lengthy use of benzodiazepines also featured prominently.[128]

It has been acknowledged that the use of the PIEA has been low, one reason provided was lack of awareness of the tool.[130] One drawback of the PIEA was it had not been independently validated. The original tool was subsequently validated in 2012 by an expert panel using the RAND/UCLA method (based on the Delphi method).[94] The 2012 validated PIEA resulted in 41 criteria, 9 original criteria deleted, 2 new criteria added, and some rewording of original criteria.[94] The revised criteria contained 38 explicit criteria and 3 implicit criteria.

Sets of criteria, as discussed here, are in essence tools to be employed by health professionals, such as pharmacists, to address deficiencies in medication use. Tools such as these are an important component in the medicines review process.

2.3 Home Medicines Reviews

Medicines review services are offered in various countries including the USA, the UK and Australia for community-based patients through specially trained community pharmacists.[13,15,16]

In Australia, the Commonwealth Government Department of Health and Ageing, through community pharmacy agreements, has provided funding since 2001 for Home Medicines Reviews (HMRs), a service for community-based patients. The HMR service has steadily grown with nearly 80,000 HMRs funded in the 2011/2012 financial year.[131] The purpose of HMRs is to reduce ADEs, improve QUM, improve health care professional collaboration and ultimately improve patient health outcomes.[16] Pharmacists are required to be accredited for provision of these services through the Australian Association of Consultant Pharmacy (AACP) or the Society of Hospital Pharmacists of Australia.[16] A similar process is in place for patients of aged care facilities and is called residential medication management review (RMMR).[17]

The HMR process is initiated with the identification of patients who are most likely to benefit from an HMR. Eligibility criteria include age, number of medications, changed medication plans, medications which require monitoring or have a narrow window of therapeutic effect, ADRs or other difficulties with patients managing their medications.[16] These criteria are drawn from the evidence pertaining to DRP factors discussed in section 2.1.1.

A GP identifies a patient who is eligible for the HMR service and once patient consent is obtained, an accredited pharmacist is contacted to conduct the HMR. The accredited pharmacist visits the patient, usually in the patient's home, to conduct a patient interview. The interview elicits information about the patient's medication use, health conditions and any other relevant factors. This information is analysed and a report is sent to the GP identifying DRPs and making suggestions for changes to the patient's existing medication management. The process culminates in a medication management plan with the aim of improving patient medication therapy. Patient follow-up is required to determine the success, failure, or need for further adjustment to the plan.

2.3.1 The HMR process

The medicines review task requires the pharmacist to obtain detailed medication-related information concerning the patient. The patient's GP can provide details of prescribed medications, diagnoses, observations and laboratory test results. The patient's regular community pharmacy can supplement the prescribed medications obtained through the GP with medications not prescribed by the GP, such as those obtained through medical specialists, pharmacists, optometrists and nurses. Medications dispensed at the community pharmacy can be reconciled with prescribed medications to assess adherence.

Much information is provided by the referring GP and patient's regular community pharmacy, however this is supplemented by pertinent information obtained by conducting a patient interview preferably at the patient's home. Alternatively, interviews may be conducted on pharmacy premises. HMR accredited pharmacist Grant Kardachi explained "...my experience shows me that in the home the patient is more comfortable and relaxed and offers information more readily"[132]

The patient interview, preferably in the patient's home, elicits additional information, such as: how the patient actually uses, or does not use, prescribed medication; the use of non-prescribed medications – over the counter medicines, herbal and vitamin supplements; an understanding of the patient's motivation behind the actual rather than directed medication use; patient understanding of their health condition(s) and the purpose of their medications for treating or preventing illness.[133] Apart from determining medication awareness and compliance, previously unknown medication toxicity and untreated illness may be identified.

The home interview gives the pharmacist insight into the patient's physical, social and financial situation as well as their compliance with therapy. These factors may directly impact on therapy.[32,71] Many of these factors are associated with DRPs in older people, see section 2.1.1. Social factors such as family and peer support can be more readily understood when observing patient interactions with other family members or peers in the patient's own home. Such support has been acknowledged as an element of improved adherence to therapy.[65]

Once sufficient information is gathered, the pharmacist assesses the current therapy, comparing prescribed versus actual patient use, including potential or actual side effects,

costs, drug interactions, conditions requiring treatment and treatment complexity.[32] If treatment has been found to be suboptimal the pharmacist prioritises treatment recommendations in a report of findings. In Australia, the report is submitted to the patient's GP for consideration of changes to therapy, some issues within the pharmacist's capacity, such as patient education can be resolved without the GP.

A flowchart of the typical medicines review process, from Lowe *et al.*[32], is shown in Figure 7.

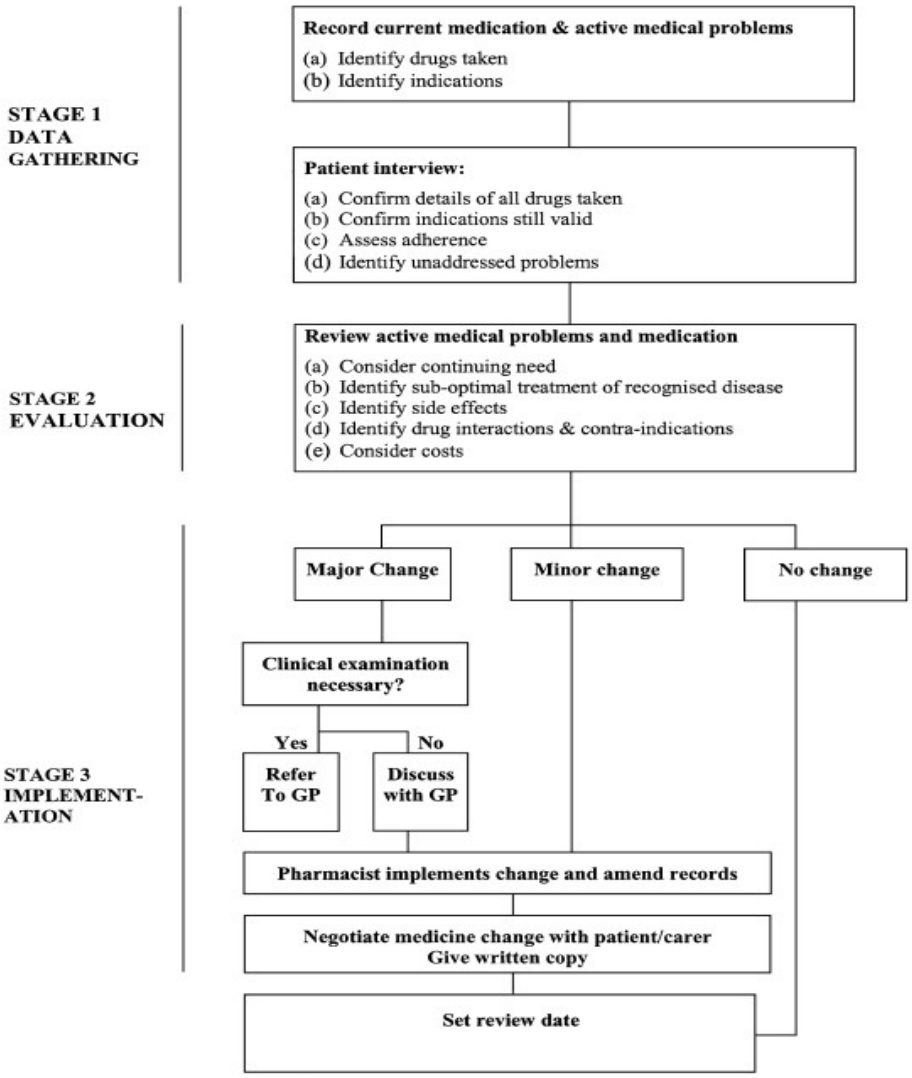


Figure 7: The medication review process; from Lowe *et al.*[32]

2.3.2 Benefits and limitations of HMRs

A retrospective analysis by Nishtala *et al*.[134] of 500 Australian medicines reviews of aged care residents, found pharmacists identified medication-related problems in 96% of residents. Similarly, an analysis of older, at-home, Australian patients by Castelino *et al.*[135], showed pharmacists identified medication-related problems in 99% of patients. Stafford *et al*.[136] found pharmacist HMRs identified nearly 5 DRPs per patient on average.

Several recent trials have shown evidence for the positive impact of medication reviews on patient health for various chronic conditions including HIV[137], heart failure[20] and diabetes.[138] A study by Ma *et al*. Which was through a hospital outpatient service, showed pharmacist medicines review involving medication changes and improvements to medication adherence in HIV positive patients improved CD4+ cell counts and increased the number of patients with undetectable HIV viral load.[137] Receiving an HMR was shown to delay a subsequent hospitalisation in patients with heart failure (45% reduction in hospitalisation rate).[20] Fornos *et al*. implemented a pharmacist care program for diabetic patients through which pharmacists reviewed medications and provided individualised patient education.[138] A range of measures were improved including reductions in HbA1c (mean 8.5 to 7.9%), total cholesterol (mean 217 to 202 mg/dl) and systolic blood pressure (mean 150 to 135mmHg).[138]

Medication specific benefits have shown reduced hospitalisations resulting from warfarin use (79% reduction in hospitalisation)[139] and a positive effect on polypharmacy through reduction of over-prescribed medications.[18,137]

Castelino *et al*.[42] investigated whether Australian pharmacists provided evidence-based recommendations, and found 94% of recommendations made were evidence-based. Castelino concluded "a suitable trained pharmacist, with full access to the patient, medical record and supporting resources, can help to improve the quality use of medicines…" Supporting this finding, a number of Australian and international medication reviews and studies have found improvements in patient outcomes, quality of life and reduced hospital admissions.[6,8,9,12,140] Although trials may not always show the ultimate benefit in terms of improved patient outcomes, positive findings include reduced polypharmacy,[18,137] and resolution of actual or potential DRPs.[9,139,141]

Conversely, several studies have not found improved patient outcomes.[142,143] The MEDMAN trial conducted in England during 2002 to 2004 found no improvement in appropriate medication use, nor improved quality of life in patients who received community pharmacist medicines review compared to a control group.[142] Additionally, the intervention arm was also found to incur greater cost.[142] Another similarly conducted English trial in 2002 found no change in the prescribing of appropriate medications, nor improved health outcomes.[143] A trial examining the impact of HMRs several weeks after hospital discharge actually found patients who were recipients of HMRs had a higher rate of hospital readmission.[144] Despite the lack of positive change shown from these trials, medicines reviews are broadly supported within England.[13]

Campbell Research and Consulting conducted qualitative research into HMRs in Australia published in 2008 and obtained consumer, pharmacist and GP perspectives concerning HMRs.[21] Consumer opinion was found to be positive with the main benefits seen from a consumers point of view being education, provided reassurance and the removal of out of date medication. However, despite positive opinion, consumers also reported that they did not consider the HMR to be a necessary service.[21] Strong consumer satisfaction with medicines review services was also documented in a large US study, which showed consumer-identified benefits of improved education and better health.[9]

The Campbell report highlighted several barriers to the implementation of the Australian HMR program by pharmacists, primarily time and resource limitations, communication problems and administrative problems.[21] Several problems raised by pharmacists from the report are listed:

- Lack of resources
- Quality of report compromised due to time constraints
- Poor communication between GPs and pharmacists, in particular lack of face-to-face communication and lack of professional relationship
- Lacking confidence in making clinical recommendations to GPs
- Accreditation process: lost clinical knowledge since university

- Older pharmacists feeling they have lost clinical knowledge

Some of these issues overlapped with concerns from the GP perspective, particularly the perception of inadequate clinical knowledge. GP perspectives from the report are listed:

- A feeling that community pharmacists were too busy to effectively participate in the HMR process
- A lack of training and qualification of pharmacists in medication management of this nature
- An inappropriate supply of information by pharmacists, who were reported to sometimes supply irrelevant or unhelpful information as part of HMRs

The report also noted positive GP perspectives including:

- Improving patient awareness of their medications
- Decreasing polypharmacy and costs to all
- Gaining a second opinion on prescribing trends
- Gaining a more complete understanding of the patient and their attitude towards their health and medications

Subsequent to the Campbell Report, a survey of HMR recipients and HMR naïve but eligible patients was conducted during 2008 and 2009.[145] The majority of recipients expressed opinions that they had better understanding of their medications and that they had reduced concerns about their medications compared to HMR naïve patients. The HMR recipients also preferentially rated saving money on medicines, taking fewer medicines and the ability to live independently at home compared to HMR naïve patients.[145]

The Campbell report showed the perspectives from both pharmacists and GPs of pharmacist lack of clinical knowledge, despite Castelino *et al.* finding Australian pharmacists were quite capable of identifying evidence-based problems.[21,42] CDSS that are custom-designed to aid pharmacist medication review may provide the support needed to address some of these concerns. CDSS is discussed in the next Chapter.

3 Clinical decision support systems

A HMR report must present an evaluation of a patient's medication therapy in light of a wide range of patient-specific factors, as discussed in section 2.3. CDSS may well have a part to play in the evaluation of patient medical information to assist with the detection of DRPs and potentially provide recommendations for their resolution. This chapter discusses the key issues of CDSS and what part these systems may play in assisting pharmacists with the task of medicines review.

3.1 CDSS Definition

CDSS have been simply defined as "access to knowledge stored electronically to aid patients, carers and service providers in making decisions on healthcare"[146] This definition includes passive CDSS and active CDSS. Passive CDSS requires an individual to actively search for information within an electronic system whereas active CDSS brings the information to the users attention, avoiding the individual's need for them to search.

A more detailed definition incorporates the important concept of rules – machine interpretable representations of human expert knowledge – that allow software to analyse cases in a similar manner to the human expert and actively present its findings:

"Electronic decision support systems have three main components: knowledge, rules, and software. Knowledge stored electronically includes published clinical practice guidelines, commercial databases, and custom-designed knowledge bases, based on expert opinion. Knowledge is translated into active rules used within the system. The software applies the knowledge, rules, and local patient and clinical data, and presents the electronic decision support functionality on the clinician's desktop"[146]

3.2 CDSS, electronic health records and data standardisation

The use of information technology, such as electronic health records (EHRs), has been promoted and implemented to various degrees by various Governments (Australia, Canada, France, USA) as an important driver to improve patient health outcomes.[147–151] This aim can be achieved through the use of electronic standards to collate and communicate health information to relevant parties, both patients and health care professionals.[152] Electronic

standards including EHRs provide a consistent structure on which to implement CDSS capabilities.[153] Data standardisation may also assist health-care professionals and organisations to screen patients for health problems and to assist health-care professionals implement best care practices through automated analysis of patient information (data mining).[154] Standardised formats are important to maximise communications between various electronic systems, which allows for efficiency gains, as the information must only be entered once, yet can be re-used many times by many different health providers.[153,155–159]

3.3 CDSS Role

CDSS encompass a range of electronic resources, from passive electronic reference material to software that interprets data to actively advise healthcare professionals.[160] CDSS can also have an impact on patient health management from a distance through the use of the internet and mobile technology.[161,162] For the purposes of this thesis, CDSS will apply to software that actively applies rules to interpret patient data. Active advice includes prepared templates for completing information (work-flow support) reminders regarding due clinical tests (process-based support), health condition screening, alerting (abnormal laboratory test values, allergy-drug- disease interactions), and therapeutic decision support.[163] A common use of CDSS have been in combination with computerised prescriber order entry (CPOE) software which checks drug interactions, dosing, or patient contraindications such as allergies.[164] Figure 8 shows an example of CDSS warning of multiple medications with sedative activity.[165]

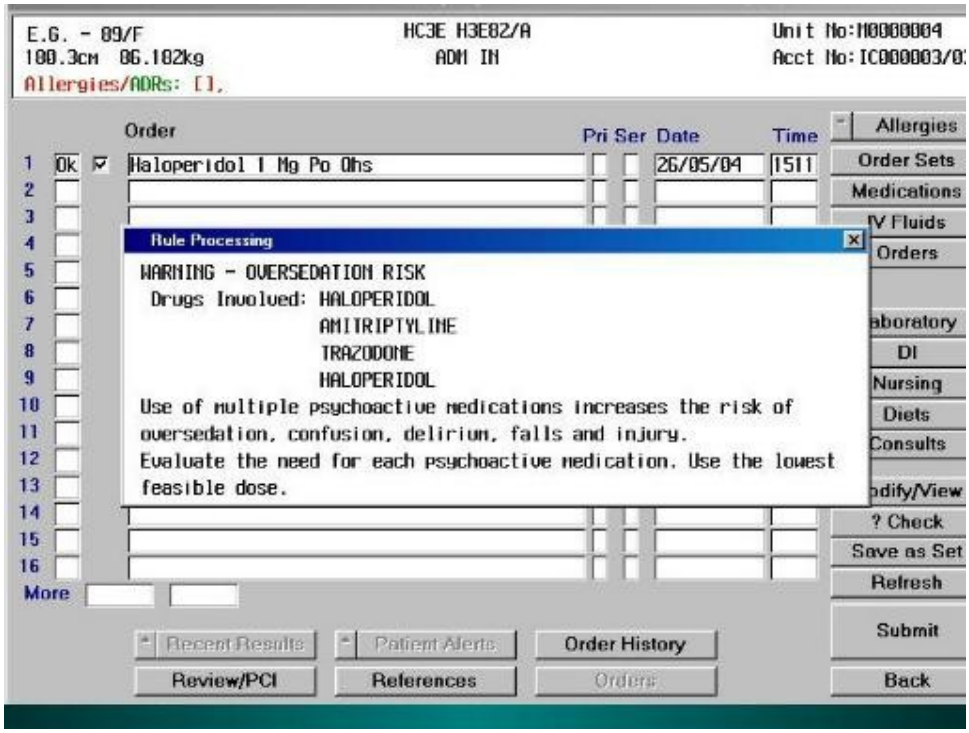


Figure 8: CDSS warning of multiple medications with sedative activity.[165]

3.4 CDSS Technology

CDSS implementations can vary from simple hard-coded static rules to complex artificial intelligence (AI). Knowledge based systems, also known as expert systems, are AI which have been developed based on various approaches.[164] Examples include rules-based, probability-based and neural network systems.[164] Expert systems have been defined as "... a computer model of expert human reasoning, reaching the same conclusions that the human expert would reach if faced with a comparable problem".[166]

Expert systems are an approach to replicate the problem solving reasoning of an expert typically through the incorporation of a database of facts (such as a patient dataset) and rules (a knowledge base), with the rules applied to the facts via an inference engine to produce solutions.[164,167–170] An overview of an expert system is shown in Figure 9.

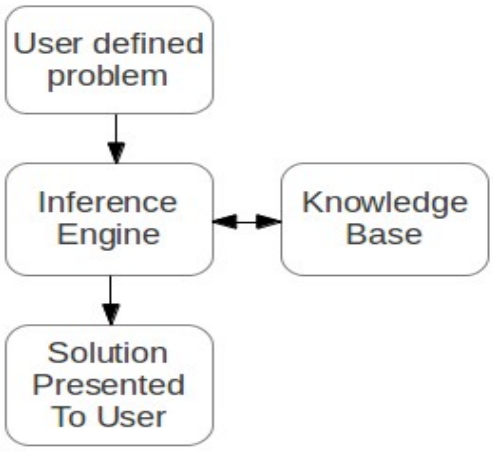


Figure 9: Components of an expert system

Case-based reasoning is a type of expert system in which the presenting problem is compared to similar cases stored in the knowledge base and solutions to the problem are presented. When a case is misclassified the correct classification is identified (usually by the expert user) and the case is stored in the bank as a new exemplar for that classification. As each new case is added and the knowledge base grows, incorrect solutions are gradually reduced.[167] The flow of assessing cases and adding to the knowledge base is shown in Figure 10. This figure, provided by Dr Ivan Bindoff, is for a specific kind of case-based reasoning called multiple-classification ripple-down rules (MCRDR).

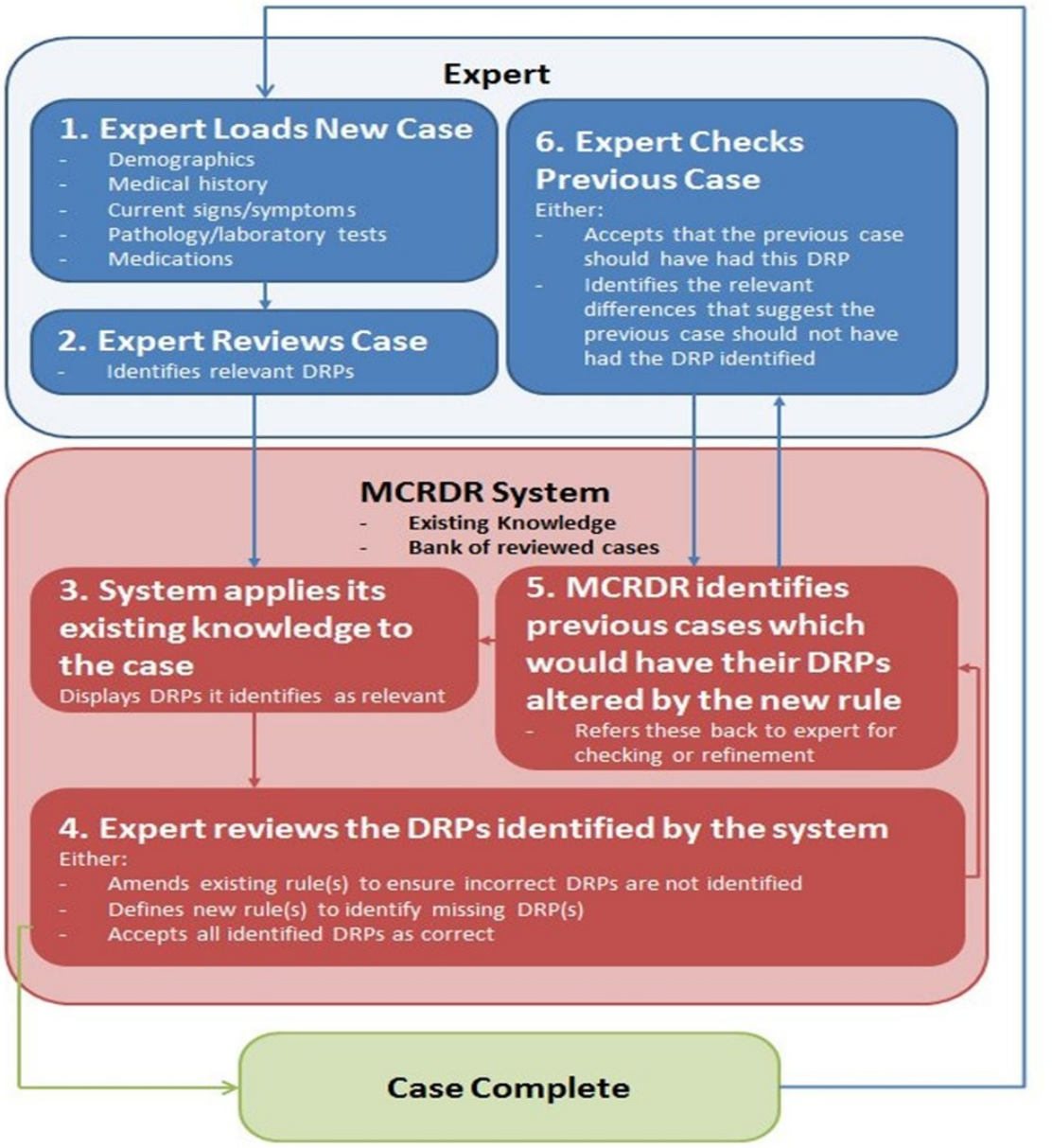


Figure 10: Flow of case assessment and development of the knowledge base

CDSS in general and expert systems in particular need to be validated to ensure they produce accurate results. Validation is defined as the "Determination of the correctness of the final program or software … with respect to the user needs and requirements"[171] Flaws in software accuracy do occur, see section 3.6.2.

3.5 CDSS Benefits

CDSS has generally been found to be beneficial providing assistance in areas of patient screening, prescribing, diagnosis, and preventative health.[22,172–175] A comprehensive and oft cited review by Garg *et al.*[22] found CDSS did improve healthcare professional performance in the majority of studies in the areas of diagnosis, disease prevention, disease management and prescribing. Despite improved healthcare performance, reviews of CDSS articles have found few have investigated or shown improved patient outcomes.[22,176,177]

3.5.1 Consistent advice

A second potential advantage of CDSS is an expectation of improved consistency of therapeutic decision-making.[153,167,178] One of the fundamental problems of medical decision making was and is the explosion of knowledge; this quote captures the enormity of the problem:

> 'Medical educators of the middle and latter 19th century were the first physicians in history to feel the real shock of the information explosion in medical science. By the 1870s, an enormous increase in medical information was radically transforming medical thought and practice, and the amount of medical literature began to become overwhelming.'[179]

Guidelines exist for the management of many diseases, apart from the prescribing criteria discussed previously in section 2.2. Australian guidelines have been developed by several organisations including: NPS (www.nps.org.au) and Therapeutic Guidelines (www.tg.org.au) covering many health conditions, as well as disease-centred guides from specific health organisations such as: The Heart Foundation (www.heartfoundation.org.au) and Diabetes Australia (www.diabetesaustralia.com.au). CDSS advice can be tailored from such guidelines to be displayed to the healthcare professional.

Many CDSS have been successfully trialled focussing on specific disease states and/or drug interaction and dosage checking.[170,175,180–186] Reviews of CDSS have generally shown improved practitioner adherence to guideline-based recommendations.[22,24,174,176,187]

3.5.2 Capacity to screen many patients

The ability to screen a database of patients to identify patients who require additional care such as routine monitoring, or risk of DRPs is a distinct advantage over manually searching patient records.[188] CDSS screening can also raise health care practitioner awareness of patients who may require additional treatment or monitoring at the time of presentation.[181]

3.6 CDSS Limitations

The use of CDSS involves a broad range of factors beyond simply the decision support itself. An attempt to classify the CDSS workflow was undertaken by Sim and Berlin.[189] A figure from their article highlights some core components of any CDSS, particularly considerations of *knowledge source, the decision support itself, information delivery, context of use* and *work-flow*, detailed in Figure 11. This figure raises awareness of the many factors that are involved in the development or implementation of CDSS solutions.

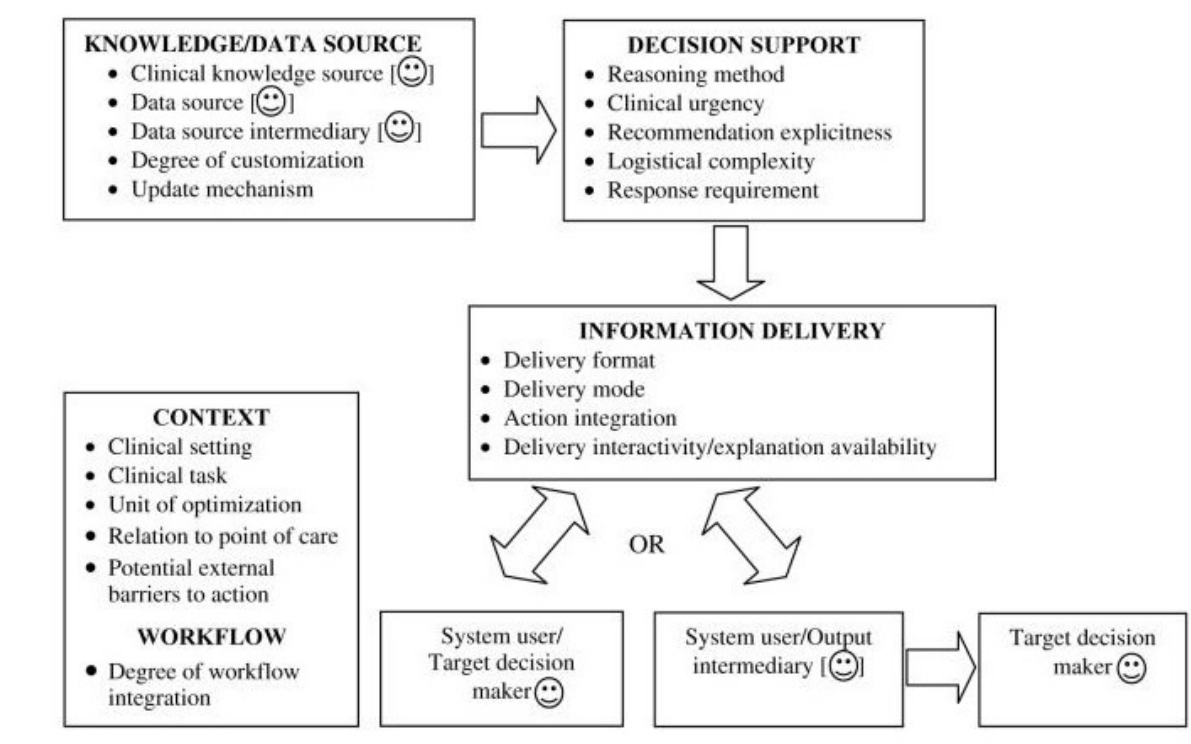


Figure 11: CDSS workflow and factors from Sim and Berlin[189]

Many factors for successful implementation of CDSS are not immediately apparent, yet may be essential for user acceptance and ultimately the success or failure of the software. Factors

include: work-flow integration and ease of use, CDSS in context to the setting or task, organisational support, and user acceptance of CDSS recommendations.[172,189] Authors from health disciplines have investigated and suggested factors that may impact on the end user's acceptance of such technology,[181,190–192] yet few studies provide sufficient design detail to allow for identification of detrimental or beneficial design features. [23,193,194]

The technology acceptance model (TAM) developed by Fred Davis was based on the theory of reasoned action, to help explain the acceptance and use of technology.[195,196] Several modifications have been proposed, however the model comprises two core components: *perceived usefulness* and *perceived ease of use*.[197] *Perceived usefulness* was defined as "the degree to which a person believes that using a particular system would enhance his or her job performance" and *ease of use* was defined as "the degree to which a person believes that using a particular system would be free of effort".[195]

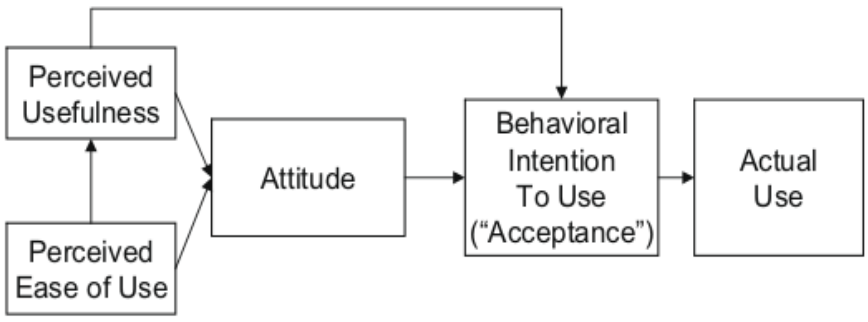


Figure 12: Technology Acceptance Model from Holden and Karsh[197]

In a review of health information technology *perceived usefulness* was considered the prime factor in intention to use or actual use of technology.[197] *Ease of use* was found to correlate with *perceived useful*ness although both components have been confirmed to be distinct factors.[197,198] The authors investigating health information technology stated the TAM "did a fair job predicting … end-user acceptance" in the health care environment although further improvements may increase acceptance predictions.[197]

Perceived usefulness implies confidence, or trust, in the appropriateness of findings presented by CDSS. However, too much or too little trust in the findings of a decision aid can result in undesirable outcomes; Parasuraman and Riley provide examples of aviation disasters

associated with both too much and too little trust in automation.[199] The authors provide the following useful terms:

> '*Misuse* refers to the overreliance on automation, which can result in failures of monitoring or decision biases. Factors affecting the monitoring of automation include workload, automation reliability and consistency, and the saliency of automation state indicators.
>
> *Disuse*, or the neglect or underutilization of automation, is commonly caused by alarms that activate falsely. This often occurs because the base rate of the condition to be detected is not considered in setting the trade-off between false alarms and omissions.'[199]

Addressing human/computer factors of *misuse*, *disuse*, *ease of use* and *perceived usability* may lead to improvements in the uptake of CDSS. Reviews of CDSS studies identified the need to incorporate these factors.[23,177] Several of these factors are described below.

3.6.1 Alert fatigue

One of the well-established issues experienced with many CDSS is the excessive display of unsuitable alerts or reminders that leads to desensitisation to the proffered warning, known as alert fatigue.[200–203] This may be due to overly simple rules triggering an alert, rather than taking a wide range of patient factors into context as has been noted by several authors.[184,200,204] A number of CDSS studies have looked at health care professionals overriding CDSS alerts, finding the majority of alerts were ignored.[205–207]

Instead of simple static rules, more robust AI approaches such as expert systems may be less likely to produce alert fatigue if sufficient data were available to apply intelligence and produce more specific and sensitive responses.

As concluded by Taylor *et al.* "Non-adherence to alert information appears to be associated with additional knowledge of the clinical situation, beyond that inherent in the decision support tool, for the specific patient context."[204] And, "We have really great technology for simple rules … The problem is getting beyond these simple rules," Mark Musen, MD, PhD, professor of medicine, Stanford University.[208]

3.6.2 Information accuracy

Apart from alert sensitivity, alert content has also been questioned. An Australian study identified the lack of alert sensitivity involving selected major drug interactions in investigated GP and community pharmacy software, and also a general lack of management advice within these alerts.[209] Similarly an American study found a commercial database, First DataBank, classified investigated drug interactions with greater severity than was considered appropriate, also contributing to alert fatigue.[210]

3.6.3 Commercial interest

Commercial interest may not generally be viewed as a limitation of CDSS, in all likelihood CDSS may promote commercial interest in a positive way through advertising of such a service to healthcare professionals, see Table 6 for examples of companies who promote decision support capabilities of their products to health professionals. Yet commercial interest in CDSS has been shown to be detrimental, and potentially damaging, as was the case to the Australian pharmacy profession during 2011.

The Pharmacy Guild of Australia, an organisation representing community pharmacy proprietors, formed a partnership with Blackmores Pty Ltd, a company producing vitamin and herbal supplements. The partnership centred on adding CDSS to existing pharmacy dispense software which prompted pharmacists when dispensing medications for several health conditions to suggest Blackmores companion products for these patients.[211–215] The products had no or minimal scientific evidence to support their use.[216] The inflammatory "coke and fries" comment which likened the pharmacist's role to a fast food outlet, expressed by Blackmores chief executive Christine Holgate, made national television and newspaper headlines.[211,214,215,217] Subsequently the plan for the CDSS deal was dropped.[218]

3.7 Literature review of CDSS

Healthcare professionals, particularly pharmacists, undertake patient medication reviews to maximise QUM. It has been shown that pharmacists identify many DRPs and do provide evidence-based recommendations to resolve DRPs.[42,134–136] Studies have generally shown medication reviews result in improved patient outcomes.[8,9,12,18,20,137,138,219] Pharmacists

generally rely on passive guidelines, and sometimes drug interaction checking software to assist in the identification and resolution of DRPs.[42]

CDSS have been shown to improve the performance of healthcare professionals with diagnosis, disease prevention, disease management, drug dosing and drug prescribing.[22,172–175]

Medication reviews assisted by CDSS can be anticipated to benefit in terms of improved prescribing of medications and/or improved patient outcomes, as both medication reviews and CDSS were independently associated with improved performance, as discussed above. A literature review was undertaken to determine if the combination had previously occurred, and what benefits occurred, if any.

The aim of this review was to identify and summarise literature about CDSS which actively assisted the healthcare provider in the context of general or disease-specific medication review to identify problems and, if possible, provide recommendations for improved patient therapy.

3.7.1 Search terms and criteria

Articles describing the use of CDSS for the purpose of actively assisting decision making during the medication review process were selected. Studies were excluded if they focused on a specific medication, review articles, software description articles, passive electronic reference materials, exclusive patient disease screening software, exclusive drug interaction/dose check computerised provider order entry (CPOE) decision support and manual medication review combined with electronic dissemination of results.

PubMed and Embase databases were searched from 1990 to 2014. The PubMed search terms are shown in Table 2. No unique articles were found in Embase. A total of 4,649 PubMed articles were found via search criteria. Additional studies were identified by screening the references in included articles, and through the PubMed related citations index. From these sources 23 articles matched the inclusion criteria.

Table 2: PubMed search terms to July 2014

Search Term
(decision support medication review ambulatory) AND "1990/01/01"[Publication Date] : "2014/07/14"[Publication Date]
("1990/01/01"[Publication Date] : "2014/07/14"[Publication Date]) AND home medication reviews
("1990/01/01"[Publication Date] : "2014/07/14"[Publication Date]) AND inpatient medication reviews
("1990/01/01"[Publication Date] : "2014/07/14"[Publication Date]) AND medication therapy management software
(Drug Utilization Review/methods*[MeSH Terms]) AND "1990/01/01"[Publication Date] : "2014/07/14"[Publication Date]
(("1990/01/01"[Publication Date] : "2014/07/14"[Publication Date]) AND Evidence-Based Medicine[MeSH Terms]) AND Decision Making, Computer-Assisted[MeSH Terms]
("1990/01/01"[Publication Date] : "2014/07/14"[Publication Date]) AND Drug Therapy, Computer-Assisted[MeSH Terms]
(Medical Records Systems, Computerized/utilization[MeSH Terms]) AND "1990/01/01"[Publication Date] : "2014/07/14"[Publication Date]

3.7.2 Literature Results

Twenty-three articles were found concerning the use of CDSS assisting the medication review process, summarised in Table 3. These were utilised by pharmacists, nurses and medical practitioners. Articles were specific to practice settings: hospital, general practice, pharmacy and shared care. The articles have been divided into general review or related to specific conditions such as: CHF, CAD, angina, diabetes, asthma, chronic obstructive pulmonary disease (COPD), hypertension and lipid management.

Five articles[220–224] describing one CDSS identified through a Google search in Section 3.8 were not located through the above search terms and are not included in this section.

General patient medication review

Medication reviews of hospital patients aged 65 or over were undertaken by nurses briefly trained in pharmacology compared with control in a Swedish study by Bergqvist *et al*.[225] The Janus web application[226] assisted in calculating creatinine clearance and drug-drug interactions (DDIs). Outcomes investigated were re-admission within three months, inappropriate drug use (anticholinergics, long acting benzodiazepines, multiple psychotropics) and the number of DRPs detected. No significant differences were found for

readmission or inappropriate drug use. Utilisation of the CDSS identified 86 clinically significant DRPs in 53 patients, which would have otherwise been missed. The number of clinically insignificant alerts was not mentioned.

Bindoff *et al*.[167] developed a prototype CDSS expert system, using MCRDR technology[227], specifically for patient medication review. Patient medication review data for 126 real cases were sequentially entered into the expert system by a medication review accredited pharmacist. This resulted in 250 rules which included information of patient symptoms, demographics, medical history, medications and pathology results. The expert system was able to identify 80% of the potential problems detected by the medication review pharmacist. Less than 10% of the problems identified by the expert system were incorrect, reducing to 0% during entry of the final 15 cases. Based on the entered rules which covered 80% of potential DRPs detected by the pharmacist, the expert system identified at least one more DRP than the pharmacist per case entered. This suggested the pharmacist missed problems even though the pharmacist knew about the same problems, and had at some point entered a rule into the expert system for these problems. Interestingly, the pharmacist routinely identified problems with later cases that they had previously missed on earlier cases.

A subsequent article by Bindoff *et al*.[178] discussed the progression of the prototype CDSS. Improvements were enacted in the way medications and medical conditions were portrayed enabling the pharmacist expert training the system to develop suitable rules with greater ease. The revised system was trained with 244 patient cases resulting in 383 rules which covered 90% of the potential DRPs detected by the pharmacist. The authors concluded that the pharmacist expert in the study, and likely experts in general, do appear to routinely miss relevant DRPs and this type of software can help to reduce this issue. A limitation of this finding was the use of only one pharmacist expert.

Another Swedish study by Bladh *et al*.[228] investigated CDSS-assisted hospital medication reviews vs. control, assessing patient quality of life, DRPs and drug appropriateness. Reviews were assisted with use of CDSS which incorporated electronic guidelines for DDIs and drug appropriateness in the elderly. The CDSS was not well described but may have been similar to the Janus application. Patient self-rated health was improved using a post-six month analysis of the medication review intervention. Health-related quality of life was improved in

the intervention group mean 3.14 ± 0.87 compared with the control mean 2.77 ± 0.94, p = 0.02, using a one to five rating to the question "In your opinion, how is your state of health?" Other self-rated quality measures were not significant using EuroQol-5 dimensions (EQ-5D) or EuroQol Visual Analogue Scale (EQ VAS). A reduction was found in the prescribing of three or more psychotropic drugs per patient (percentage of patients: control: 9.4%, intention to treat analysis: 7.9%, per protocol analysis: 2.3%, p = 0.034). Whilst CDSS was involved in this trial, it may not have been the only factor leading to the positive results. The intervention group included additional interventions of medication discussions with patients and medication reports sent to patients' GPs. The positive results shown in this study may not be entirely due to the use of CDSS.

Software, titled Pharmanurse, was developed to assist nurses to identify ADRs as a component of medication review of nursing home residents.[229] The software presented nurses with resident-individualised lists of potential DRPs for 418 residents from eight nursing homes. The nurses identified a mean of 3.7 DRPs per resident of which GPs agreed in 54% of DRPs implementing 214 medication changes in 88 residents. Health professionals were generally satisfied with Pharmanurse which scored 7 out of 10 for the potential to improve pharmacotherapy. As with the study by Bladh *et al.* the DRPs identified and changes implemented were not entirely due to the CDSS.

In a year-long trial by Monane *et al*.[230], 2.3 million elderly patients were automatically screened according to Beers criteria to initiate a short medication review. Pharmacists were alerted to 43,007 potential problems. Subsequently, pharmacists were able to contact 19,368 GPs regarding 24,255 alerts to discuss potential DRPs and recommendations for resolution. Change of therapy was determined through GP telephone contact and through analysis of subsequent patient prescription claims. Change of therapy to more suitable medications occurred at differing rates depending on the class of medication. The largest medication groups resulted in significantly changed prescribing: 24% change for most long-acting benzodiazepines (11,344 alerts, p<0.001), 40% change for flurazepam (1,679 alerts, p < 0.001), 25% change for shorter-acting benzodiazepines exceeding the recommended daily dose (4,532 alerts, p < 0.001), 17% change for anticholinergic antidepressants (2,856 alerts, p

< 0.001). The strength of this study was the very large number of patients involved, finding a small proportions of DRPs which resulted in substantial therapy changes.

Tamblyn *et al*.[231] compared the effect of an active computer-triggered CDSS alert against a passive physician activated analysis alert by comparing follow-up prescription information. CDSS was triggered during CPOE as well as when a patient chart was opened. Alert sensitivity settings were available to either group and could be adjusted in display sensitivity by physicians in either group. In both groups not all physicians actively used patient EHRs reducing the opportunity to detect changes. The active CDSS identified 6,505 problems of which 668 alerts were displayed to the physician and 81 prescribing problems were revised. The passive physician activated alerts identified 4,445 problems of which 41 were seen by physicians and 31 were revised. At the end of the follow-up period no difference in the number of prescribing problems was identified, yet there was a significant reduction in the number of therapeutic duplication problems (odds ratio (OR) = 0.43, 95% confidence interval (CI) 0.29 – 0.64, $p < 0.001$). It is of interest to note the active CDSS alerts were ignored in 88% of alerts. Physician reasons mostly concerned lack of benefit or clinical irrelevance. The high number of false positive alerts, even with adjustable alerting sensitivity was of interest, as it highlighted the issue of providing patient contextually relevant alerts, which was suggested by the authors as a cause of alert fatigue and for future improvement of the software.[200,201]

Another Swedish study by Ulfvarson *et al*.[232] utilised the Janus software for medication reviews in 233 elderly patients. Medication review included pharmacologist opinions and CDSS advice concerning DDIs and medication appropriateness from patient data entered into CDSS software. Measurements were conducted for DRP frequency, dosage changes, number of drugs used, and frequency of inappropriate drug use before and after. Evaluation of the CDSS itself, or its impact on the medication review process, was not investigated. Initial review found a mean of 10.4 drugs and a mean of 1.5 DRPs per patient. Three or more psychotropic drugs were used by 34% of elderly patients. The pharmacologist issued a mean of 3.3 physician recommendations per patient. A follow-up at two months found a mean 9.5 drugs per patient was observed. Reductions were found for: drugs associated with kidney impairment (17%), anticholinergics (40%), long-acting benzodiazepines (17%), drug

duplication (30%), and use of three or more psychotropics (19%). At two months the adoption of recommendations did not affect patient health in 213 patients and improved health in 51 patients, yet worsened health in 30 patients as assessed by researchers and health care staff.

Specific disease management

An English study by Eccles *et al*.[233] looked at adherence to asthma and angina management guidelines with assistance of CDSS. The CDSS was activated to provide guidelines for each condition based on the patient EHR. Data was collected from one year prior to CDSS implementation and until one year post implementation. No significant changes were found regarding medications prescribed or in other care actions such as smoking education provided or inhaler technique assessed. At the end of the study, 2,241 angina patients and 1,760 asthma patients completed the one year prior, midpoint and one year post implementation quality of life questionnaires. There was low use of the software and no changes were identified between control or intervention groups.

Modest improvements were found in a three year study of lipid management by Gilutz *et al*.[234] The CDSS implemented in the study identified patients with CAD and produced monitoring and treatment recommendations which were mailed to GP clinics. GP clinics were randomised to control (56 clinics, 3753 patients) or intervention (56 clinics, 3695 patients). A health maintenance organisation obtained data from GP clinics and laboratory and pharmacy data for the CDSS. Study variables were lipid monitoring, statin initiation or optimisation and treatment trends. Investigators also looked at mortality and cardiovascular associated hospitalisations. Intervention patients had significantly greater history of myocardial infarction and angioplasty at the trial start. Overall, the intervention group recorded better lipid monitoring (54.8% vs. 48.7%, $p < 0.001$) and a comparison of non-hospitalised patients showed a strong improvement (relative risk = 1.423, CI 1.24 - 1.64, $p < 0.001$). Slightly improved statin prescribing occurred in the intervention group (59.1% vs. 53.7%, $p < 0.003$). Patient compliance determined via drug usage indicated only 28% of patients were therapy compliant (defined at taking 75% or more of their medication) with 47% of patients obtaining less than a quarter of the expected medication. The low rate of compliance impacted on the potential for improvement in LDL outcomes. Low-density lipoprotein (LDL) levels showed a

marginally improved reduction in the intervention group (16.2% vs. 14.8% reduction, $p < 0.02$) for patients whose initial LDL levels were over 120mg/dl. Clinical outcome showed a slight but significant reduction in all-cause mortality and hospitalisation (57.1% vs. 59.2%, $p < 0.03$). This important finding that points to the ultimate benefit of CDSS, improved patient outcomes, achieved through prescriber targeted activities.

A rule-based CDSS which provided advice on lipid management was tested by Hobbs *et al*.[235] in 21 GP practices against 4 control practices during 1992. Measured outcomes after six months included changes in laboratory testing, changes in referral to a specialist and changed prescribing. Data from one control and seven intervention practices were unable to be collected due to various issues. No details of drug prescribing were presented although no change in drug costs between groups was found. A slight increase in full lipid profile tests occurred in the intervention group ($\chi^2 = 49.5$, df = 3, $p < 0.05$) but overall no significant change occurred. Hobbs noted the CDSS was used infrequently, as noted with other CDSS studies, although a particular limitation was the requirement to manually enter information into the software and the slow speed of the computers used.

Management of diabetics was investigated using a CDSS diabetic module with EHR in a study by Hunt *et al*.[236] at baseline and two years after implementation (4,265 patients from start to finish). The CDSS included alerts for diabetic care during patient visit, daily identification of patients who were overdue for routine tests, benchmarking and feedback regarding physician and clinic performance regarding diabetic measures, and, access to electronic resources for physician and patient. LDL goal (<100mg/dl)) attainment improved from 32% to 56% patients ($p = 0.002$), average LDL decreased by 0.003 mmol/l ($p = 0.002$). Blood pressure (BP) goal (<130/80 mmHg) was attained from 30% to 52% patients ($p = 0.002$). Mean HbA1c was not changed overall but the number of patients who attained an HbA1c of 7% or less improved from 47% to 50% patients ($p = 0.002$). Increased proportions of patients received laboratory tests for LDL (16% increase, $p = 0.002$) and HbA1c (7% increase, $p = 0.002$). Greatly increased recorded use of lipid therapy (48% to 70%, $p = 0.002$), angiotensin-converting enzyme inhibitor(ACEI) or angiotensin receptor blocker (ARB) (54% to 69%, $p = 0.002$), oral hypoglycaemics (56% to 68%, $p = 0.002$) and antiplatelet therapy (54% to 88%, $p = 0.002$) occurred. Increased retinal (39% to 59%, p =

0.002) and foot examinations occurred (26% to 79%, p = 0.002). Patient satisfaction did not change, nor was there an association with improved clinical outcomes. It would have been interesting to determine the impact of the feedback mechanism on physician use of the CDSS module. It would also have been desirable to compare the results against a control group as it could be difficult to determine whether GP education regarding diabetes care had generally improved over the two years of the study, independent of the CDSS module.

An expert system, Hypercritic[237], provided review of hypertension treatment. Independently, Hypercritic and eight physicians reviewed 20 randomly selected patient records making comments concerning patient treatment to assess of the capability of the CDSS. The physicians then compared their findings with Hypercritic findings. Majority agreement among the physicians determined 260 physician findings were appropriate of which 118 were also identified by Hypercritic. Several barriers were identified concerning both the applicability of the software and regarding medical judgement in general: Findings outside the scope of knowledge (rules not incorporated for problems other than hypertension) of Hypercritic and knowledge based on free text (not coded for computer analysis) accounted for 99 of the missed findings. The researchers also noted low agreement between physicians as to the most appropriate standard of care.

The identification of adherence to asthma and COPD guidelines were investigated retrospectively using EHR data from 28 GP clinics over a one year period by Kuilboer *et al*.[238] AsthmaCritic a knowledge based CDSS was designed to screen EHRs, identify DRPs and provide GPs with recommendations for specific patients. AsthmaCritic identified 8,412 asthma or COPD patients who visited a GP at least once during the trial period (total 74,709 visits, average 9 per patient). AsthmaCritic found an average of 3.4 DRPs per patient per visit (total 255,664). In patients aged 12 years old or over the main DRPs consisted of non-compliance (1,467) and contraindications - use of anti-inflammatory medication (1,381). In patients less than 12 years of age non-compliant route of administration (691) and non-compliance (304) were the most frequent types of DRPs. Non-compliant route of administration was the use of an inhaled device that was considered by guidelines to be inappropriate for the age of the patient, an example was provided of the use of a powder inhaler in a 3 year old child. Whilst this retrospective, feasibility study is of interest, it would

have been beneficial to have collected information regarding GP acceptance and implementation of the recommendations, and perhaps in those patients where follow up was possible, outcome measures.

An expert system for hypertension management, ATHENA-HTN, was tested for accuracy by Martins *et al*.[239] A series of 92 patient cases were entered and ATHENA drug recommendations were compared with GP review for the same cases. ATHENA produced 181 recommendations, the GP made 184 recommendations. Difference of opinion occurred in 19 recommendations. For 15 of these ATHENA was found to be more thorough concerning the change of drug therapy. Three cases resulted in the need to update ATHENA rules. This CDSS was able to match GP recommendations in the majority of cases and importantly the CDSS was considered to be more thorough in a number of recommendations. This highlights the usefulness of such a tool as an aid to GP review.

Diabetic care was also examined in a before and after trial involving GP practices by Montori *et al*.[240] using a Diabetes Electronic Management System (DEMS) which included action plan recommendations, clinical alerts and medication warning advice.[241] The intervention also included implementation of planned care headed by a practice diabetes nurse educator. Diabetic care measures included frequency of laboratory test performance (lipids, HbA1c), physical examinations (foot, retina), counselling (exercise, smoking, diet), health care usage and patient metabolic outcomes for HbA1c, lipid profile and BP. DEMS was associated with significant improvements in implementation of examinations, advice and test requests (OR ranged from 1.6 to 5.0) except total cholesterol. DEMS alone was not associated with improved patient metabolic outcomes.

Perlini *et al*.[242] developed a prototype expert system, using IBM ESE[243], designed to assist GPs with choice of CHF drug treatment. This pre-EHR system required entry of relevant patient data such as demographics, existing diagnoses and medications. For 20 test cases CDSS therapy recommendations were compared against cardiologist recommendations. CDSS drug recommendations covered all cardiologist drug recommendations in 9 cases. Recommendations mostly matched in another 5 cases and partially matched in 5 cases, the recommendation discrepancies were considered minor. Recommendations were completely different in one case involving a patient with arrhythmia. In 6 cases the CDSS recommended

an additional drug and in 7 cases the cardiologist recommended an additional drug. Overall the CDSS recommendations were comparable to cardiologist advice.

An expert system using the ILOG rules engine[244] was developed for general practice use by Schnipper *et al*.[245] This software provided a template for disease data entry with free text and coded data, to support patient management by providing recommendations for due tests (e.g. cholesterol) and medications (e.g. antiplatelets). Schnipper *et al*.[246] trialled the CDSS with intervention GPs (3441 patients) against control GPs (3578 patients) among CAD and diabetic patients. They measured the number of care deficiencies addressed within 30 days of the patient consultation. Results showed the system was used by intervention GPs for only 5.6% of their eligible patients. The intervention group as a whole compared to control had more resolution of care deficiencies (OR = 1.14; 95% CI 1.02-1.28, p = 0.02). However, those 5.6% patients with whom the expert system was used, had greater resolution of care deficiencies such as tests, documentation of results and prescription of recommended medication compared with control plus intervention patients in whom the expert system was not used (OR = 1.58, 95% CI 1.31 - 1.90, $p < 0.001$). In this group antiplatelet prescribing, or documented reason for not prescribing, was significantly increased (4 prescribed or documented per 101 patients vs. 111 per 7379, p = 0.02). The system showed promise, but its use was low due to GP reluctance to change their existing documentation habits, and due to the need to spend time to learn how to use the system. Unfortunately, no investigation of the appropriateness of the CDSS recommendations was undertaken.

The use of CDSS guideline reminders for diabetic and CAD patients was trialled by Sequist *et al*.[247] The guidelines included recommendations for routine tests, and for diabetics, initiation of ACEI or statin therapy, and for CAD patients, initiation of aspirin, beta-blockers or statins. Medication recommendations were triggered by medical condition and lipid results. Reminders were displayed on a patient summary screen, yet both GP groups could print a paper patient summary which included the CDSS reminders. GPs were also surveyed concerning use of the guidelines and attitude to the CDSS. Control had 3,319 patients and intervention had 2,924 patients. There were significant differences between the groups with higher age, more white patients, more male patients and more Medicare insurance patients in the control group. The CDSS improved the use of three of nine guidelines, for cholesterol

testing of diabetics (Hazard Ratio (HR) = 1.41, 95% CI 1.15 - 1.72, $p < 0.001$), and in CAD patients, use of aspirin (HR = 2.36, 95% CI 1.37 - 4.07, $p = 0.002$) and statins (HR = 1.51, 95% CI 1.05 - 2.17, $p = 0.03$). Only one third of GPs noticed the CDSS reminders, yet of these 70% said they had acted on the recommendations. GPs thought the reminders were useful for disease management (53% CAD, 68% diabetes).

Cardiac care with GPs and pharmacists exposed to CDSS evidence-based medication and lifestyle guidelines via CPOE compared with control was trialled by Tierney *et al*.[248] Patients were associated with intervention GPs only (N = 197), intervention GPs plus intervention pharmacists (N = 170), intervention pharmacists only (N = 158), or no intervention GPs nor pharmacists (control, N = 181). Patient medication adherence and quality of life were measured at baseline and at 12 months. EHR data was collected to assess therapeutic modifications according to the guidelines (unmeasurable lifestyle recommendations were excluded). No significant improvements in compliance with guidelines (initiation or improved therapy with ACEIs, β-blockers, aspirin, antihyperlipidaemic drugs, diuretics, nitrates or calcium channel blockers) occurred (pharmacists and GPs $p > 0.8$, GPs only $p > 0.7$, pharmacists only, $p > 0.4$). There were no differences in patient quality of life or medication compliance, emergency department visits or hospitalisations. A survey of GP attitudes found the CDSS was a source of advice but too simplistic to apply to individual patients. The CDSS reminders were passive and able to be ignored and pharmacists rarely contacted the GPs concerning the recommended guidelines.

The same Indiana University research group (as Tierney) undertook a subsequent study by Subramanian *et al*.[249] of CDSS and EHR via CPOE for chronic heart failure and investigated similar outcomes, patient quality of life and physician adherence to guidelines, and health care utilisation. Control (365 patients) and intervention GPs (355 patients) were provided with ACEI, beta-blocker or diuretic recommendations but intervention GPs had additional recommendations triggered by patient symptoms (e.g. oedema). No overall differences in adherence to guidelines (initiation or improved therapy with ACEIs, β-blockers, diuretics, digoxin or referral to heart failure clinic) were found at 6 months ($p = 0.5$) or 12 months ($p = 0.4$). Yet, at 12 months intervention patients had increased guideline use of diuretics ($p = 0.05$). Control patients were more satisfied, scored with the 36 item Short Form (SF-36)

Physical Component Score (p = 0.03). Intervention patients were more satisfied with their GPs at 6 and 12 months. The authors noted less than half of enrolled patients were prescribed beta-blockers or ACEIs indicating the need for trialling an intervention, although both groups were provided with recommendations for beta-blocker or ACEI use. A significant response may have occurred if these recommendations were applied to the intervention group only.

Tierney *et al*.[250] again with the Indiana University research group investigated CDSS and EHR via CPOE with evidence-based asthma and COPD guidelines. Guidelines included pulmonary tests, vaccinations, prescribing of inhaled steroids and inhaled anticholinergics, step up beta-agonist use and smoking cessation. Patient groups were studied based on intervention GPs (N = 194), intervention pharmacists (N = 161), both (N = 182) or none (N = 169), as occurred in the earlier Tierney study.[248] No significant changes occurred in any group for guideline adherence. No significant changes occurred with patient medication adherence, emergency department visits or hospitalisations. Patient quality of life was significantly improved for the SF-36 Physical Component Score only for patients in the combined GP and pharmacist intervention group ($p < 0.05$). As with the two previous studies by this research group, GPs were surveyed concerning the CDSS, with similar results suggesting the guideline recommendations were a good idea but too simplistic to apply to individual patients. As with the prior Tierney study, little communication occurred between pharmacists and physicians.

A small Swedish study of 48 CHF patients by Toth-Pal *et al*.[251] looked at GP confidence regarding diagnosis, investigations and prescribed medications. The Evibase®[252] CDSS provided recommendations concerning diagnosis, further investigations and prescribed medications based on available patient data. The CDSS increased GP diagnosis confidence in 6 cases, and reduced diagnosis confidence in 6 cases. The GPs considered 31 investigations of which 14 were recommended by the CDSS. The CDSS recommended adding ACEI treatment to 11 patients whereas GPs added ACEIs to 5 patients. In 17 of the 48 cases, GPs considered CDSS support to be substantial. Some limitations of the CDSS were: inability to decide between dose adjustments or recommend additional medications, and having sufficient data to analyse. The CDSS affected GP confidence in their diagnosis and treatment plans by both agreement with GP decisions and by disagreement with GP decisions allowing further GP reflection of the case at hand.

Table 3 summarises the various studies. The complexity of approach used by each of the CDSS is shown in the integration of assessment factors column. The various relevant assessment factors were considered to be medications, diagnoses, laboratory results and demographics. The CDSS findings were then classified based on the integration of one factor, two factors or multi-factorial, determined from the study methodology.

Table 3: Studies of decision support assisting medication reviews

Author	Setting and study Type	Integration of assessment factors	Study Measures	Conclusion
Bergqvist 2009[225]	Hospital. Historical control	Two factors	Hospital readmission. Inappropriate drug use. DRPs detected.	No significant outcomes were found. Additional 86 DRPs were identified in 53 patients
Bindoff 2007[167]	Pharmacist and software. Case series comparison	Multi-factorial	Number of DRPs identified, accuracy of DRP identification	80% pharmacist DRPs were identified by the CDSS. Less than 10% DRPs were incorrectly identified by software
Bindoff 2011[178]	Pharmacist and software. Case series comparison	Multi-factorial	Number of DRPs identified, accuracy of DRP identification	90% pharmacist DRPs were identified by the CDSS. 4% DRPs were incorrectly identified by the software
Bladh 2011[228]	Hospital. Randomised controlled trial	One factor	Self-rated quality of life (global, EQ-5D, EQ-5D VAS), medication appropriateness	Improvement in global health rating score (p=0.02). Reduction in prescribing three or more psychotropic drugs. (p=0.034). EQ-5D was insignificant.
Dilles[229]	Nursing homes pre /post	Multi-factorial	Number of DRPs identified, Number of DRPs agreed by GPs, Number of medication changes implemented	1527 DRPs identified by nurses in 339 residents, 821 DRPs in 251 residents agreed by GPs, 214 medication changes implemented in 88 residents
Eccles 2002[233]	General practice. Cluster randomised controlled trial. One group asthma interventions and angina control. Other group angina intervention, asthma control.	Two factors	Adherence to guidelines – general care or drugs prescribed. Patient quality of life questionnaires	No significant results regarding physician adherence to guidelines. No significant results regarding patient quality of life.

Author	Setting and study Type	Integration of assessment factors	Study Measures	Conclusion
Gilutz 2009[234]	General practice. Cluster randomised trial	Multi-factorial	Lipid monitoring, statin initiation or optimisation, LDL levels, mortality, associated hospitalisations	Improved lipid monitoring (54.8% vs. 48.7%, p<0.001). Improved statin prescribing (59.1% vs. 53.7%, p<0.003). Reduced LDL in patients with high LDL levels (16.2% vs. 14.8% reduction, p<0.02). Reduced mortality/hospitalisation (57.1% vs. 59.2%, p<0.03).
Hobbs 1996[235]	General practice, Randomised controlled trial	Multi-factorial	Laboratory tests, changed lipid medication prescribing, patient referrals	Improved full lipid profile testing (χ^2=49.5, df=3, p<0.05). No change identified in other tests performed, referrals or prescribed medication
Hunt 2009[236]	General practice. Pre/Post	Two factors	LDL, BP, HbA1c, anti-platelet therapy, foot and retinal exams	Improved LDL goal attainment (p=0.002), BP goal attainment (p), HbA1c below 7% (p=0.008). Increased retinal and foot examinations (p=0.002). Increased use of diabetic (p=0.002), lipid, (p=0.002) antiplatelet (p=0.002) medications.
Kuilboer 2002[238]	General practice. Case series – post-test	Multi-factorial	Number of patients identified with asthma and COPD, number and type of recommendations produced	Identified 8,412 patients who visited GP during study period. Produced 3.4 therapeutic recommendations per patient.
Martins 2006[239]	GP and software. Case series comparison	Multi-factorial	Number of hypertension DRP recommendations, accuracy of DRP identification	In 92 cases, CDSS made 181 recommendations, GP made 184 recommendations. Discrepancy in 19 recommendations of which CDSS was considered more thorough
Monane 1998[230]	Pharmacy / General Practice Cohort study	One factor	Number of potential Beers criteria DRPs alerted, number of GPs contacted, number of therapy changes by drug type	43,007 alerts for 2.3 million patients, 19,368 GPs contacted about 24,255 alerts. Change of therapy varied according to drug class: main types: 24% change long-acting benzodiazepines, 40% change flurazepam, 25% change excess dosing of shorter-acting benzodiazepines, 17% change for anticholinergic antidepressants. All changes p<0.001
Montori 2002[240]	General practice, Cluster	Two factors	Frequency of laboratory tests,	Improved provision of advice, examinations, test requests (OR

Author	Setting and study Type	Integration of assessment factors	Study Measures	Conclusion
	randomised trial		examinations, advice. Patient outcomes for HbA1c, BP, lipid profile	ranged from 1.6 to 5.0). No improved patient outcome measures associated with DEMs use.
Perlini 1990[242]	Cardiologist and software. Case series comparison	Two factors	Number of matching, similar or wrong CHF drug recommendations	9 cases: cardiologist recommended drugs were matched by CDSS 10 cases: partial but non-harmful match 1 case: inappropriate conclusion
Schnipper 2010[246]	General practice. Randomised controlled trial	Multi-factorial	Number of care deficiencies for coronary artery disease and diabetes resolved within 30 day of patient visit	Low use of system by GPs (5.6% of eligible patients). Care deficiencies significantly resolved in this group compared to all other patients, OR=1.58; 95% CI, 1.31-1.90, p<0.001
Sequist 2005[247]	General practice. Randomised controlled trial	Two factors	Adherence to care guidelines. Physician attitude	3 of 9 guidelines showed significant improvement. Improved cholesterol testing of diabetics (Hazard Ratio (HR) 1.41 (1.15-1.72) p<0.001) CAD patients improved use of aspirin (HR 2.36 (1.37-4.07), p=0.002) and statins (HR 1.51 (1.05-2.17), p=0.03)
Subramanian 2004[249]	General practice. Randomised controlled trial	Two factors	Adherence to guidelines, patient quality of life, healthcare utilisation, GP attitude	No improvement in guideline adherence. No improvement in patient quality of life, except SF-36 physical component in control group
Tamblyn 2008[231]	General practice. Cluster randomised controlled trial	Two factors	Difference in prevalence of prescribing problems	With CDSS reduced therapeutic duplication (p=0.02), no difference in overall prescribing problems.
Tierney 2003[248]	General practice and pharmacy. Randomised controlled trial.	Multi-factorial	Adherence to care recommendations, quality of life, exacerbations, medication compliance. GP attitude. Healthcare utilisation	No improvement in adherence to care guidelines or patient outcomes. GPs thought guidelines were a good idea but too simplistic for individual patients
Tierney 2005[250]	General practice	Multi-factorial	Adherence to	No improvement in guideline

Author	Setting and study Type	Integration of assessment factors	Study Measures	Conclusion
	and pharmacy. Randomised controlled trial.		care recommendations, quality of life, exacerbations, medication compliance. GP attitude. Healthcare utilisation and cost	adherence. Generally no improvement in patient quality of life except SF-36 physical component ($p<0.05$) in combined intervention group.
Toth-Pal 2008[251]	General practice Case series comparison	Two factors	Confidence change in diagnosis, further tests, medication change	Diagnosis confidence increased and decreased 25% cases, 31% cases further investigations considered (45% agreement with CDSS). Medication changed 19% cases (40% agreement with CDSS). Perception of substantial CDSS support 35% of GPs
Ulfvarson 2010[232]	Pharmacy/General practice. Pre/post	Multi-factorial	DRPs identified, changes in drugs used and dosages, total drugs used, number of inappropriate drugs	Reduction of average drugs used from 10.4 to 9.5 per patient. 343 DRPs identified. Reductions in inappropriate drug use: 40% anticholinergics, 17% long-acting benzodiazepines, drug duplication 30%, 3 or more psychotropics 19%.
Van der Lei 1991[237]	General practice case comparison	Multi-factorial	Number of comments in agreement with expert assessment	118 of 260 comments in agreement with experts. 99 comments outside of knowledge domain or in free text.

3.7.3 Discussion

The positive findings in 15 of 20 studies[167,178,228–232,234,236,237,239,240,242,246,247] were encouraging. Several further studies provided results that did not provide insight into how successful the CDSS was.[237,238,251] However, proof of positive benefit on actual patient outcomes that can be attributed to the CDSS was limited.[232,234] Most of the studies investigated improved prescribing or investigative tests, and about half of studies did not examine CDSS versus control.[167,178,229,230,232,238,239,242,251]

Several studies focussed on identifying DDIs, or where additional data was available, drug appropriateness and dosage in the patient population (notably: excess use of psychotropics

and anticholinergics in the elderly).[225,228–232] Studies investigating specific disease management looked at guidelines for test frequency, lifestyle management and appropriate drug and dosage use.[233–236,238–240,242,246–251]

One study noted an excess of clinically insignificant alerts produced by CDSS[231] which was also suggested by three others.[248–250] The authors of the Tamblyn study[231] suggested patient context was lacking, with similar findings concerning the application of simple guidelines in other studies.[248–250] Two thirds of GPs in the Sequist study[247] reported not noticing the reminders, which may have been in some part due to alert fatigue. Whilst details of the types of approaches, or rules used, for the various CDSS are unclear, many studies appeared to use simple conditional rules.[228,230,231,233,234,236,240,247–251]

One study using Janus provided results of CDSS alerts of clinically significant incidences, but did not say how often insignificant alerts occurred.[225] The Swedish Janus application was previously identified with excessive alert production by Mannheimer *et al*.[253], yet no mention of this effect was provided in the two reviewed studies.[225,232] Mannheimer noted clinical monitoring context was not incorporated and would have been likely to reduce the high number of clinically unimportant DDI alerts issued, again highlighting the issue of alert fatigue (Janus employed a severity coded DDI database[253]).

Although the Janus application classified alerts by severity, and the Tamblyn study[231] allowed GPs to modify alert sensitivity, the issue of displaying reminders and alerts in the context of patient health factors remained.

Eight studies involved the use of CDSS for the general medication review process.[167,178,225,228–232] Most of these studies targeted patients who would have been likely to benefit from medication review, being the elderly or hospitalised patients.[225,228–230,232] Of the studies[225,228–232] measuring the effect of the CDSS intervention, five found positive benefit.[228–232]

Many studies utilised CDSS for specific disease management.[233–240,242,246–250] Many of the diseases studied (CHF, hypertension, CAD, angina, diabetes, asthma, COPD, lipid management), were more common conditions which typically involved the use of complex management guidelines. Many of these conditions have been associated with evidence-practice gaps, CHF[254], CAD[28,29], asthma[40,255], lipid management[29], diabetes.[29,256] The

complexity of management suggested CDSS could have a positive impact in the management of patients with these conditions, yet of the eleven studies[233–236,240,242,246–250] which investigated guideline adherence or patient outcome, only six showed at least some positive benefit.[234,236,240,242,246,247]

Half of the studies[228,231,233–235,246–250] used a randomised controlled trial (RCT) design which provided a more rigorous basis for comparison of the effect of CDSS intervention, with or without any associated interventions, of which six produced some positive results.[228,231,234,240,246,247]

The three studies associated with the Indiana University research group used the Regenstreif Medical Record System (www.regenstreif.org) resulted in virtually no improvements in guideline adherence or patient outcomes.[248–250] Tierney suggested the reminders were invasive and time consuming. Tierney also stated GPs could easily skip past the reminder by pressing a key rather than read and provide a response.[248] The subsequent studies by Tierney and Subramania may have also had this limitation.[249,250]

Six[167,178,232,239,242,246] of eight[167,178,225,232,235,239,242,246] studies using knowledge based systems showed positive results. Two studies of knowledge based systems did not assess change in terms of patient or healthcare practitioner outcomes.[237,238] Six knowledge based system studies were either pre-deployment or prototypes.[167,178,237–239,242] The advantage of knowledge based CDSS is the capacity of the system to integrate a wide range of patient contextual information to provide a more considered response. This is shown by the majority of positive studies of expert systems found in this review. Unlike simple conditional rules which were apparently used in many of the reviewed studies, expert systems may be expected to be able to provide more suitable, patient-contextual alerts and reminders, minimising the excessive alerting effect mentioned or suggested in several of the studies.[231,248–250]

An interesting observation was of three studies that utilised knowledge based systems. These were found to be more thorough (or perhaps more consistent) in detecting DRPs than their human counterparts.[167,178,239]

Lack of uptake by health professionals of the trialled systems was noted in several studies.[235,246–248] This lack of uptake also could have affected other studies, though no clear

mention of this was made. Several reasons for lack of uptake were discussed in some of the studies: CDSS advice was too simplistic, advice was not tailored for the needs of individual patients, CDSS advice was passive and as a result easy to ignore and practitioner reluctance to change existing processes.

There have been other articles which have discussed the possible lack of effectiveness of CDSS in general.[153,257,258] More than half of the studies examined support the effectiveness of CDSS, particularly when implemented with rules that incorporate individual patient detail. Utilising such detail has provided conclusions of greater complexity when drawn from such individualised patient context, particularly as can occur with expert systems.

3.7.4 Conclusion

Excluding the studies by Bergqvist, Bindoff, Martins, Perlini, Kuilboer, Toth-Pal and Van Der Lei which did not measure practitioner change of therapy or patient outcome, ten[228–232,234,236,240,246,247] of fifteen[228–236,240,246–250] CDSS applications, did improve at least some aspects of patient medication therapy or care, yet the intensity of effect was generally modest.

Aspects of CDSS that appear to require improvement include: overcoming health professional inertia to improve user uptake of these tools; and improved specificity of CDSS advice utilising patient contextual rules, of which judging from this review, expert systems may have the potential to achieve. Of great interest were three recent knowledge based system studies[167,178,239] which produced more comprehensive identification of DRPs than their human counterparts, perhaps pointing a way forward for the improved use of CDSS.

3.8 Google search for medication review software

As discussed in section 3.7, there were a variety of published studies involving CDSS with medication review capabilities. A background search of medication review software was undertaken to identify commercial products that were able to to be evaluated for this thesis.

A search was undertaken to determine how many software companies provided medication review software, and particularly whether the software provided was advertised with decision support capability. The first twenty links for the Google search term “medication therapy management software” and the first twenty links for the Google search term “medication

review software" were investigated. The initial search was undertaken 3 March 2011. The search criteria were applied using only English wording to identify websites of companies producing English language software.

Table 4: Google search term "medication therapy management software"

Website (from the first 20 links)	Website refers to	Software	Data collection	Reporting	Decision Support
http://en.wikipedia.org/wiki/Medication_therapy_management	www.mirixa.com	Mirixa	√	√	
	www.medsmanagement.com	Assurance System	√	√	√
	From www.medsmanagement.com	Monitor-Rx	√	√	√
http://www.pharmacychoice.com/marketplace/category.cfm/listing/MTM_Medication_Therapy_Management	http://csshealth.com/products.php	Medication Pathfinder	√	√	
http://www.pharmacychoice.com/marketplace/category.cfm/listing/MTM_Medication_Therapy_Management	www.pharmacychoice.com/marketplace/link.cfm/mp_link_id/F9DCCBF0-64A7-4749-ACDC-20128F460C46	CommunityMTM No information available – failed link			
http://www.pharmacychoice.com/marketplace/category.cfm/listing/MTM_Medication_Therapy_Management		See Assurance system			
http://www.pharmacychoice.com/marketplace/category.cfm/listing/MTM_Medication_Therapy_Management		See Medication Pathfinder			
http://www.pharmacychoice.com/marketplace/category.cfm/listing/MTM_Medication_Therapy_Management	www.nexdose.com/for_hcp/MTM.htm	NexDose	√	√	
http://www.pharmacychoice.com/marketplace/category.cfm/listing/MTM_Medication_Therapy_Management	www.getoutcomes.com/	Outcomes Pharmaceutical Health Care	√	√	
http://rxinsider.com/medication_therapy_management.html		See Assurance system			
http://rxinsider.com/medication_therapy_management.html		See Outcomes Pharmaceutical Health care			

Website (from the first 20 links)	Website refers to	Software	Data collection	Reporting	Decision Support
http://rxinsider.com/medication_therapy_management.html		See Medication Pathfinder			
http://rxinsider.com/medication_therapy_management.html	http://www.mediware.com/	WORx Dispense System not medication review			√
www.pillhelp.com/	www.pillhelp.com/	PillHelp Works Consulting service	√	√	
http://www.silverscript.com/en-US/medication-therapy-management-programs.aspx		SilverScript Patient focussed site	?	?	

Table 5: Google search term "medication review software"

Google Link (related information from first 20 links)	Link refers to	Software	Data collection	Reporting	Decision Support
www.mediflags.com/		MediFlags	√	√	√
www.medscope.com.au/		Medscope	√	√	√
http://mediview.com.au/		PharmSoft MediView	√	√	
www.guild.org.au/mmr/content.asp?id=423		List of Referral Templates for various medical systems			
www.hrdcd.com/HRDMedRev.htm		Health Reference Disk	√	√	
www.pillpedia.com.au/		Pillpedia	√	√	
https://www.aacp.com.au/FourpointRoot/portal/shared/Assets/mmr_manual_09/AACP_Manual_2009_Ch4.pdf	www.guild.org.au/research/project_display.asp?id=257	Review of Domicillary Medication Management Review (DMMR) Software Reviews: Health Reference disc MediFlags Miracle MMR Pharmcare Other products mentioned: Cognicare EyreCare HomeR MediTrax Medreviewer			

Google Link (related information from first 20 links)	Link refers to	Software	Data collection	Reporting	Decision Support
	http://www.miraclemmr.com/	Miracle MMR	√	√	
	http://www.healthcaresoftware.com.au/pharmcare_index.html	PharmCare	√	√	
	Deregistered company. ASIC Gazette 11/08	Cognicare			
	http://www.pfizer.com.au/facts/EffectiveDiseaseMgt.aspx	EyreCare	?	?	
	Could not find web site	HomeR			
	www.meditrax.com	Meditrax	√	√	
	Could not find web site	Medreviewer			
http://investing.businessweek.com/research/stocks/private/snapshot.asp?privcapId=113629414		Medication Review Inc. Telepharmacy services	?	?	

The searches identified 20 unique commercial software applications, shown in Table 4 and Table 5, of which several were able to be further examined, shown in Table 6. Four software applications were either de-registered or no information was available, Cognicare, HomeR, Medreviewer, CommunityMTM. One application was for patient use (SilverScript), one application was a dispense system (WORx), and one application was for general practice care plan management (EyreCare).

On further investigation, the Health Reference Disk website was out-dated with computer requirements stated as "Pentium II/III/IV computer with Windows 98/2000/ME or Windows 95 with Internet Explorer 5 installed." On attempting to email to "webenquiry@mediview.com.au" the email was undeliverable.

Likewise, the MiracleMMR website was inoperable, with all website links inoperable, including links to "contact us" and "order form". Table 6 shows the medication management software applications which were current and available during April 2011 and able to be further investigated. These applications indicated medication review assistance was available via the software.

Table 6: Summary of medication management software found through Google search

Software	Link	Data Collection	Reporting facility	Decision Support
Mirixa	www.mirixa.com	√	√	√
Medscope	www.medscope.com.au/	√	√	√
PharmSoft MediView	http://mediview.com.au/	√	√	
Pillpedia	www.pillpedia.com.au/	√	√	
PharmCare	http://www.healthcaresoftware.com.au/pharmcare_index.html	√	√	√
Meditrax	www.meditrax.com	√	√	
Assurance System	www.medsmanagement.com	√	√	√
Monitor-Rx	www.monitor-rx.com	√	√	√
Medication Pathfinder	http://csshealth.com/products.php	√	√	
NexDose	www.nexdose.com/for_hcp/MTM.htm	√	√	
Outcomes Pharmaceutical Health Care	www.getoutcomes.com/	√	√	
MediFlags	www.mediflags.com/	√	√	√

Each software product shown in Table 6 offered data collection and reporting functionality. Six advertised CDSS as a software capability: Assurance System, MediFlags, Medscope, Mirixa, Monitor-Rx and PharmCare.

3.8.1 Assurance system

The Assurance system (www.medsmanagement.com) is based in the USA. The advertised decision support was stated as:

> "Triggers that identify a problem situation suggest appropriate interventions and indicate which parameters need monitoring on an ongoing basis." and "Access to Monitor-Rx module to aid in identifying medications that may cause, aggravate, or contribute to common geriatric problems and provide medication-monitoring recommendations"
>
> (www.medsmanagement.com/Pharmacists/MTM_Practice/tools.html accessed April 2011).

Assurance was medication review software which provided patient data collection, decision support, report generation and administrative services. The CDSS as suggested in the advertising appeared to be a rule-based system. A development in January 2011 incorporated Monitor-Rx for analysis of geriatric DRPs.[259] This software is discussed below.

No studies from the Assurance system were identified though PubMed (searched April 2011).

3.8.2 Monitor-Rx

Monitor-Rx (MRX)[260] was based in the USA and was developed by the American Society of Consultant Pharmacists Foundation. It was initially developed and known as the MDS-Med Guide in 1999, then redeveloped as the Geriatric Risk Assessment Med Guide (GRAM) in 2002.[260] MRX was software that provided patient data collection, decision support, report generation and administrative services.

The decision support was advertised as:

> "Monitor-Rx identifies medications that may … contribute to common geriatric problems, including identification of potentially inappropriate medications and drugs with anticholinergic properties; and provides medication-monitoring recommendations to foster early recognition of medication problems..." (https://www.monitor-rx.com/ accessed April 2011)

The purpose of the software was to identify DRPs, mainly PIMs, in elderly patients (60 years old and older), and to raise awareness of prescribed inappropriate medications and awareness of the need to monitor for medication-related detrimental effects. MRX identified medications that caused or worsened common problems in the elderly, grouped by care areas from the Resident Assessment Instrument Minimum Data Set 3.0[261] (MDS 3.0): daily living activities, behavioural symptoms, cognitive loss or memory impairment, dehydration, delirium, dental care, falls, mood, nutritional status, pressure ulcers, psychotropic drug use, urinary incontinence and visual function.[260] The software also identified PIMs based on the Beers[38] criteria such as medications with anticholinergic activity. Coded information could be entered for diagnoses using the international classification of diseases, 9th revision (ICD-9)[262] coding system yet this coding was not incorporated into the decision support functionality.

One small study of 29 elderly patients compared MRX and pharmacist review of patient medication lists to identify those at risk of drug-related geriatric syndromes (MDS 3.0 care areas) and the use of PIMs.[220] Based on medication lists, both MRX and pharmacists found all patients were at risk of falls. MRX identified more patients using medications with risk for geriatric syndromes than the pharmacist (175 vs. 124) whereas the pharmacist identified more PIMs (41 vs. 36 PIMs).

Papers concerning the MRX predecessor, GRAM, were identified[221–224], one study showed results from the use of GRAM.[222]

Lapane *et al.*[222] utilised the GRAM software to assist pharmacist medication review in a control versus intervention study in 25 aged-care homes. The GRAM software assisted pharmacist identification of residents taking medications associated with falls and delirium, as well as assisting in providing a guide to monitor these residents. Falls and delirium were two care areas within the MDS, and a fraction of the care areas that could be shown in MRX. A reduced delirium rate was found in the intervention homes, HR = 0.42, 95% CI 0.35-0.52. No reduction in falls was found.

No other studies were identified involving MRX (July 2014). MRX was superseded by MedOptz during 2013, shortly after feedback was provided on the MRX product, see Appendix 3. The uniform resource locator (URL) www.monitor-rx.com now (July 2014) points to a completely different blogging site, shown in Appendix 3. In finalising this thesis it was discovered in July 2014 that the MedOptz website www.medoptz,com had closed, see Appendix 3.

3.8.3 MediFlags

Mediflags (www.mediflags.com) is based in Australia. Advertised decision support stated:

> "Flags identify clinical scenarios encountered in medication reviews and are accompanied by background information (statements) and suggested recommendations…" (https://www.mediflags.com/MediFlags_features_-_sample_statements.pdf accessed April 2011)

MediFlags is medication review software which provides patient data collection, decision support recommendations, report generation and access to clinical resources. The CDSS uses a flag associated with a medical condition. The pharmacist can choose to view the information associated with the flag and incorporate the flag information into the HMR report. Mediflags is essentially a passive reference tool. The flags can be extended by the pharmacist to cover various routine scenarios. The CDSS also contained HMR relevant reference materials concerning evidence-based medical information.

The author briefly examined Mediflags. The software was found to be a passive implementation of CDSS wherein the user of the software identifies the problem and assigns a prepared flag containing generic advice to resolve the problem.

One study was found in PubMed which appeared to be a paper-based precursor to the MediFlags software.[263] The study was trialled by GPs in over 700 patients. The study showed therapeutic flags resulted in medication changes in 14.5% of patients' medications and changes in other recommended activities such as therapeutic monitoring (7%). No further studies were found to July 2014, however a Mediflags press release dated 16h December 2013 (available from www.mediflags.com/MediflagsPresselease.pdf) stated Medscope had acquired Mediflags.

3.8.4 Medscope

Medscope (www.medscope.com.au) is based in Australia. Medscope provided decision support through software called Medication Review Mentor (MRM).

Advertised decision support stated:

> "MRM is an 'expert system'. This means that it draws upon thousands of existing cases for knowledge on how to deal with the presented case. However, if an issue is presented for the first time, MRM will be unable to identify it. This is where the enormous advantage of the expert system technology used by MRM comes in. Pharmacists using the system can add new issues, and these are included in the knowledge base after being assessed by Medscope's clinical team. MRM, by design, grows in knowledge every time it is used." (www.medscope.com.au/index.php?lMenuId=154 accessed April 2011)

Medscope is medication review software which organises referrals, collates patient data, produces reports and uses decision support to detect DRPs and provide recommendations. The CDSS is a knowledge based system using MCRDR, discussed in section 3.4, and based on the work of Dr. Ivan Bindoff.[167]

Apart from studies published as a part of this thesis, no studies were found in PubMed (searched to July 2014).

3.8.5 Mirixa

Mirixa (www.mirixa.com) is based in the USA.

Advertised decision support: "…our sponsored MTM services include flagged clinical alerts…" (http://mirixa.com/pdf/PharmacySlipsheet.pdf accessed April 2011)

Mirixa is a software application which assists pharmacists with identifying patient medication non-adherence and drug interactions. It collates patient data and generates reports. It also contains packages which train pharmacists to educate patients. The CDSS as suggested in the advertising appears to be a rule-based system. However, very little detail of this product was available.

On searching for 'Mirixa', five studies were found in PubMed (searched to July 2014).[264–268] Of these, one study measured clinical effect in diabetics[264] and showed improved low density lipoprotein cholesterol (LDL-C), diastolic and systolic blood pressure and body mass index (BMI), although the specific effect of the CDSS component was not examined.

3.8.6 Pharmcare

Pharmcare (www.healthcaresoftware.com.au) is based in Australia.

> Advertised decision support: "The HCS Clinical Suite is a comprehensive collection of decision support tools, assisting hospital and community care providers in delivering a complete continuum of care for their patients." (http://www.healthcaresoftware.com.au/portal_cm.html accessed April 2011)

Pharmcare is medication review software which collates patient data, provides decision support, produces reports, provides access to clinical resources, patient support and education

material and administrative services. The type or capability of the CDSS is unclear. The author was briefly shown the system implemented at the Royal Hobart Hospital, Tasmania. It appeared to highlight drug interactions rather than provide a more comprehensive medication review.

No studies were found in PubMed (searched July 2014).

4 Thesis Outline

Medication review is within the scope of practice of pharmacists and is performed in various countries world-wide. Previous published studies have shown generally positive results of the benefit of CDSS to improve medication management. However, alert fatigue and lack of relevance, is a known problem with CDSS and occurred in some of the reviewed studies. Several studies of knowledge based expert systems showed the potential of more thorough assessment of patient medication management, although these studies were in prototype systems.

This investigation aimed to evaluate CDSS that were in active use by pharmacists to assist the medication review process. The evaluation was aimed at determining how successful different commercially implemented technologies were at the medication review task.

This thesis aims to address several questions concerning the commercial CDSS:

- Did they provide useful, clinically relevant decision support?
- Did they address or succumb to alert fatigue?
- Was the end user satisfied and accepting of the decision support?
- Did the knowledge based CDSS provide more thorough reviews as suggested in prototype articles?[167,178]

The core of this research was to examine the potential of the decision support systems developed for the medication review domain to identify clinically relevant DRPs and to make recommendations to resolve identified DRPs. Essentially, can CDSS be considered useful tools in assisting pharmacists with the medication review process? The fundamental features of CDSS in this domain is the identification of clinically relevant DRPs, to identify those DRPs without missing important DRPs, and to do so without presenting excessive irrelevant material, a known problem of many CDSS.

The actual clinical relevance of identified DRPs was the central problem within this investigation. Clinical relevance depends on the subjective interpretation of the likelihood of harm resulting from a particular DRP in a particular patient considering that particular

patient's circumstances. Clinical relevance of DRPs was defined for the expert panel assessors as: “If [the DRP was] unresolved [the DRP] would have resulted in suboptimal outcome for this patient”. I will define clinical relevance in the context of DRP identification more generally as “Any DRP that would have reasonably been expected to have resulted in a suboptimal outcome considering the patient's individual circumstances”.

An evaluation of the decision support required measurement of two principal and interacting concepts. The first was the clinical relevance of identified DRPs and the second was the scope of DRP detection. To give an example of this scope, consider a patient whose medication therapy has been assessed by a pharmacist and found to have five clinically relevant DRPs. This same patient is then assessed using software. If the software found only one DRP yet this DRP was clinically relevant, then one could say the software could identify clinically relevant DRPs but it's scope of detection was narrow and other clinically relevant DRPs were missed. This narrow scope may have a negative impact on the opinion of the end user of such software. Similarly, software finding numerous clinically irrelevant problems may also have a negative impression on the end user. Negative opinion of the usefulness of the software through poor relevance and scope may then lead to lack of use of such software, or at least of the decision support component.

The evaluation incorporated several distinct yet complementary methods of assessment. Assessment was undertaken using the DOCUMENT classification system, examination of descriptive classifications of DRPs - the concepts capturing the core of the DRP allowing comparison between DRP sources, and examination through expert opinion. Standards of measure for comparative purposes were the original pharmacists DRP findings and sets of prescribing criteria (Beers03, Beers12, PIEA, STOPP/START).

A final approach to determining clinical relevance and usefulness of the MRM product, was a survey of pharmacists who used this product.

Medication review has been defined as:

> “the process where a health professional reviews the patient, the illness, and the drug treatment during a consultation. It involves evaluating the therapeutic efficacy of each drug and the progress of the conditions being treated. Other issues, such as compliance,

> actual and potential adverse effects, interactions, and the patient's understanding of the condition and its treatment are considered when appropriate. The outcome of the review will be a decision about the continuation (or otherwise) of the treatment"[269]

I have defined medication review software as:

The process where software reviews the patient, the illness, and the drug treatment for the therapeutic efficacy of each drug and the progress of the conditions being treated. Other issues, such as compliance, actual and potential adverse effects, interactions, and the patient's understanding of the condition and its treatment are considered when appropriate. The outcome of the review will be decisions about the continuation (or otherwise) of treatments.

The primary hypothesis was:

Medication review software with clinical decision support capabilities based on pharmacist knowledge should detect DRPs at a similar frequency and of a similar scope to those detected by pharmacists. Secondarily, if recommendations presented to resolve therapeutic problems by medication review software are representative of contemporary therapeutic practice, then recommendations presented for problem resolution will be appropriate.

5 General methods

This investigation aimed to evaluate CDSS that were in active use by pharmacists to assist the medication review process. The search for commercial CDSS medication review products in section 3.7 uncovered a range of possibilities, from these, MRM and MRX were selected to be evaluated. The reasons for selection were: the products were available in the English language and approval for use of the software was provided.

MRM was chosen because it was developed in Australia and designed for the requirements of the medication review process in Australia. It also was advertised as providing "intelligent decision support".[270] MRX as a second source of software was found in the United States of America. This software was also advertised as a product which "... assists in identifying, resolving and preventing medication-related problems among older adults"[260] This source was chosen because it was English language software which provided decision support, its predecessor had a published article[222] showing benefit regarding reduction of potential delirium and the software was an international comparator.

To assess the capacity of MRM and MRX to detect DRPs, a rich source of patient data was obtained. This data also needed to have the original reviewing pharmacist-identified DRPs to allow for comparison between software and pharmacist findings. Patient details also needed to be entered into each software application to obtain the core DRP data for analysis.

A schema of the various projects to achieve the aims of this thesis is presented in Figure 13.

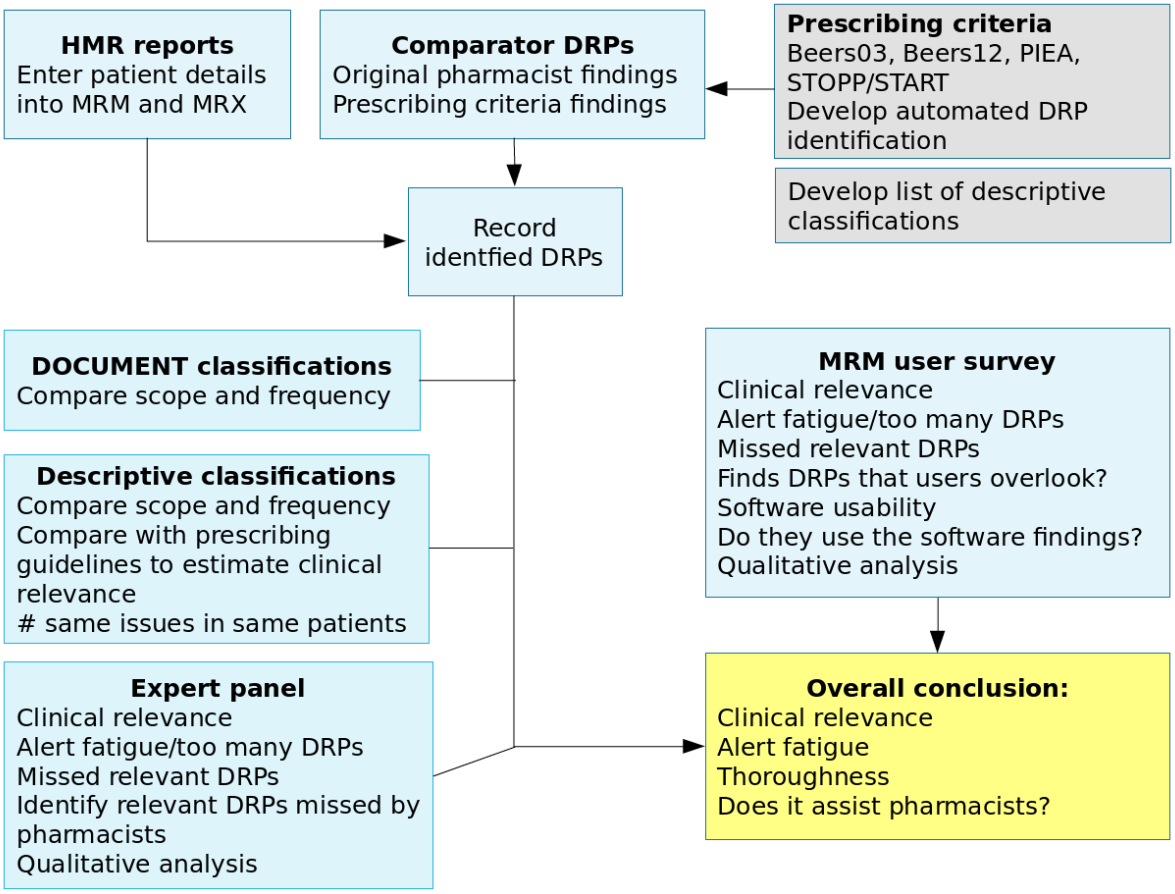


Figure 13: Schema of component projects

5.1 Methodology

5.1.1 VALMER data

The VALMER data available for this project was contained in a Microsoft Access database (Microsoft Corporation, Redmond, Washington). This database was developed by Andrew Stafford for the VALMER project.[8] The database contained the details of 661 HMR cases with review dates ranging from 28 March 2008 to 14 November 2008. Two of the cases did not contain patient birth dates, an essential requirement for software analysis leaving 659 usable cases. The 659 HMRs were performed by 149 different AACP accredited medication review pharmacists, 108 of these pharmacists each submitted five HMR reports.

The MRM software was launched in February 2009 (personal communication Dr Peter Tenni) and was not available for HMR pharmacist use at the time of VALMER data

collection. The MRX software was developed for the US market and launched during 2008.[271] A survey which recorded 117 responses of pharmacists involved in the VALMER project found twenty-two pharmacists utilised the Mediflags passive decision support product, no other products were mentioned.[272,273]

Six-hundred and fifty-nine cases were entered into MRM. MRX only analysed cases where the patient age was 60 years old or older. This resulted in 611 cases being suited for MRX. However, due to the voluminous and extremely repetitive output from MRX only 108 cases, aged 60 years old and older were actually entered into MRX. The selection of these cases was performed using Microsoft Access (Microsoft, Redmond, WA). Firstly, a randomly generated number was assigned to each case and the cases were ordered by random number from the lowest to highest values. A list of all cases aged 60 years old or older ordered by the lowest to highest random number was created. Cases aged 60 years old or older were entered one at a time into MRX until 100 cases aged 65 years old or older were entered.

The initial intention was to enter patient details regardless of patient age into MRM and patients aged 60 and older into MRX. However, prescribing criteria such as those discussed in section 2.2 were utilised in this investigation. The prescribing criteria were developed to be applicable to patients aged 65 years old and older, therefore the primary dataset used for analyses in this thesis was the cohort of 570 patients aged 65 years old and older. Four sets of prescribing criteria were automated as sets of database queries and applied to the VALMER patient data, discussed in section 5.1.4. DRPs identified through this process were recorded for comparisons with MRM, MRX and pharmacists original findings.

Patient data generally (but not always) included:

- Patient birth date, gender, height, weight
- Patient diagnoses, classified with the International Classification of Primary Care Version 2 PLUS (ICPC2-PLUS)[274]
- Medications including directions
- Laboratory test results including date of result

- Other symptoms

Drug related problems identified by the pharmacist:

- Description of the DRP
- DRP type by DOCUMENT[275] classification
- Identification of the problem drug
- Identification of the relevant related medical condition where appropriate
- Pharmacist recommendations, if any, for resolution of the DRP

The medications for each patient were stored in a *PatientDrugs* table which linked to the HMR case; each medication had a unique identifier and was assigned an ATC code. Anatomic Therapeutic Chemical (ATC) coding was used to group medications hierarchically.

Patient diagnoses and symptoms, stored in *Diagnoses*, were linked to ICPC2-PLUS terms, stored in *ICPC2Master*. ICPC2-PLUS was used to group diagnoses and symptoms in a hierarchical fashion similar to ATC coding. An example is the diagnoses of *leg oedema* and *fluid retention or swollen ankle* were grouped under the same code *K07 Swollen ankles/oedema*. These were then grouped under chapter *K Cardiovascular*. These grouping classifications were generally convenient for the development of database queries. Tables for patient blood pressure and most recent creatinine clearance were developed from data stored originally in a *Pathology* table. A schematic of the database tables is portrayed in Figure 14, the *ReviewDetail* table contained patient demographic information.

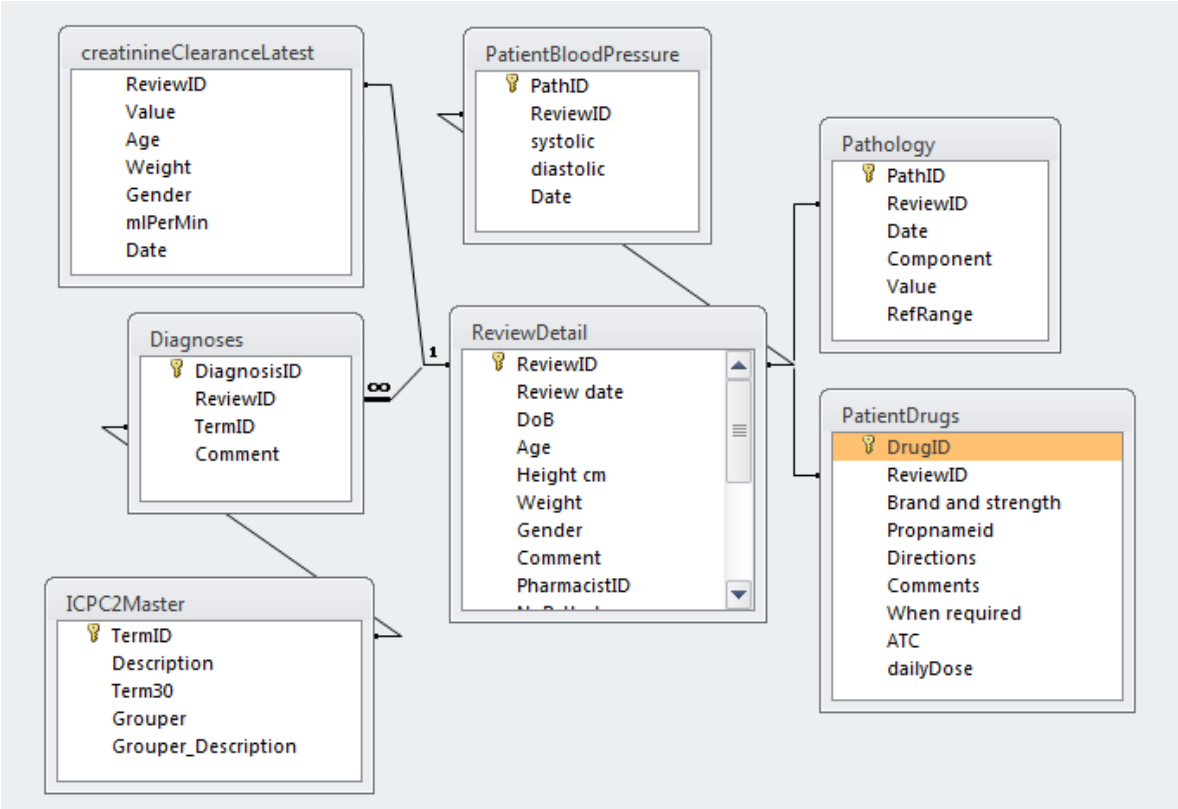


Figure 14: Database tables and relationships

5.1.2 MRM interface and data entry

The MRM software was accessed through a website. The details of each case were entered through various screens. Patient demographics, medical conditions, allergies, medications, directions, observations and laboratory test results were able to be entered. For all of these data, option lists were available to select the appropriate item. This ensured data was suitably coded for analysis by MRM. An option list for medication directions was not provided but a list of terms understood by MRM was displayed. This was used to determine the estimated daily dose for a medication.

Virtually all information stored in the VALMER cases could be entered into MRM due to the similarity of the drug names, laboratory test names, and the use by both VALMER and MRM of ICPC2-PLUS for diagnoses and symptoms. MRM accepted extra detail that was not always available in the VALMER cases.

The work flow for entering VALMER cases is shown:

1. Enter the details of a VALMER case
2. Submit the case for analysis
3. Confirm details entered accurately
4. Record the DRPs identified, rules for identifying the DRP and the associated recommendations for each case

MRM Data fields

The following patient information was able to be entered into MRM:

- Patient identifier, birth date, gender, HMR date.
- Medical conditions (using ICPC2-PLUS) and temporal history of the medical condition defined as: recent, ongoing, patient concern or past history.
- Allergies – selected by entering part or all of a medication name but not by therapeutic group.
- Medications – selected by entering part or all of name, directions, daily dose and duration of treatment. Duration was defined as: unknown, more than 12 months, 3 to 12 months or less than 3 months (recent). Medications were further classified as: taken as prescribed, not taken as prescribed, or not taken. *Pro re nata* (*PRN*) (English: as the occasion arises) dosing could be left blank or an estimate of daily use could be entered.
- Observations – height, weight, body mass index (BMI), blood pressure, heart rate, respiratory rate, temperature, mini-mental state exam (MMSE), blood sugar level (BSL), Kessler psychological distress scale (K10), blood pressure (BP) and date of observation.
- Patient laboratory test results – list of options categorised as biochemistry, haematology, lipids, thyroid, arterial blood gases, and the date of the result.

All entries showed the type of units that the software expected, e.g. haemoglobin was expected to be entered as g/L. Other information was also able to be entered, such as contact details, and reference notes but these were not directly relevant to MRM analysis of DRPs.

Entry of medications into MRM

Medications were entered into MRM as the original or generic equivalent medication via a data entry screen shown in Figure 15.

Figure 15: MRM medication data entry screen

Due to the approximately two year separation from the VALMER data collection until MRM data entry, several medication brands were not available in the MRM medication list. Close equivalents were entered; discontinued brands with frequency greater than one are shown in Table 7. A small number of medications, mostly herbal medications and topical preparations, had no equivalent and were not entered into MRM.

Table 7: Medication equivalents

VALMER medication brand	MRM equivalent brand	Active ingredient
Diamicron 30mg [2 daily]	Diamicron MR 60mg [1 daily]	Glicliazide
Ovestin vaginal cream	Ovestin vaginal pessaries	Oestriol
Nu-lax	Senokot tablet	Senna
Ducene 2mg or 5mg	Valium 2mg or 5mg	Diazepam

Some medication directions directly entered into MRM could be assessed by MRM to determine an estimated daily dose. Where it was possible to do so directions were entered into MRM in an MRM-assessable format. Many VALMER medications had *PRN* usage instructions so estimated daily doses of these medications could not be entered, except in the rare instances where the pharmacist comments indicated how frequently a patient was utilising a *PRN* medication.

Additional comments assigned to particular VALMER cases assisted with determining whether medications were being taken as directed, partially as directed, or not at all. This information was entered into MRM.

Additional comments assigned to VALMER cases indicated how long a medication had been used. MRM provided the following options: unknown, less than 3 months, 3 to 12 months or over 12 months. Very little information was available concerning the duration of use of medications. The duration for the majority of medications was entered as unknown.

Entry of medical conditions into MRM

Medical conditions were entered through a screen depicted in Figure 16. When entering the cases from VALMER, the duration for medical conditions were marked as ongoing unless the condition was clearly a unique event (e.g. hysterectomy), mentioned as a patient's concern, or annotated as past history in the VALMER case notes.

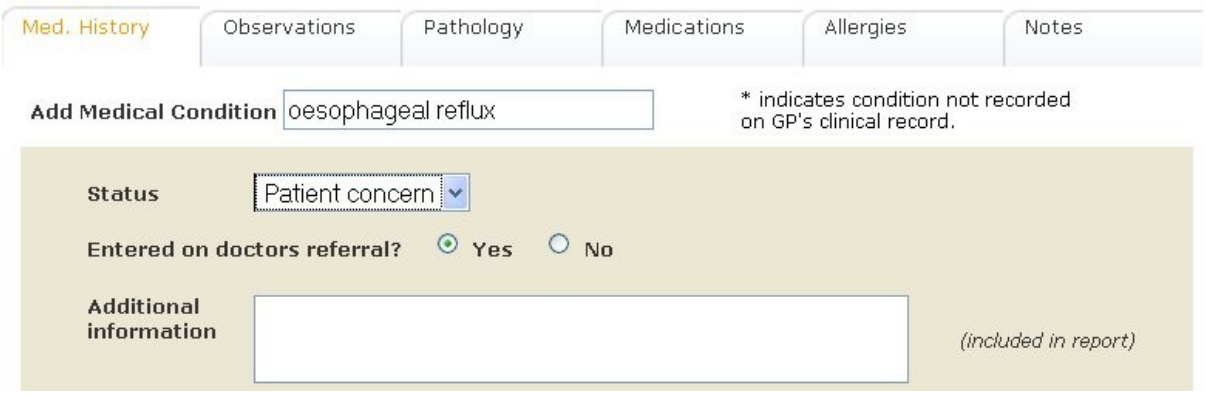


Figure 16: MRM medical history data entry screen

Entry of laboratory test results and observations into MRM

Observational information (e.g. blood pressure) and laboratory test results were stored in a pathology table in the VALMER database. Patient height and weight, where available, were stored separately. This information was entered into MRM via data entry screens, shown in Figure 17.

Figure 17: MRM observations data entry screen

Several VALMER laboratory test values required conversion into values suitable for MRM, shown in Table 8.

Table 8: Laboratory test value conversions

Item	VALMER units	Conversion factor	MRM units
Vitamin B12	ng/L	304.056	pmol/L
Folate Serum	mcg/L	10.87868	nmol/L
Transferrin	umol/L	0.208	g/L

Several VALMER laboratory test results did not have equivalents in MRM and were entered: creatinine kinase, urinary albumin and fructosamine. Also, several cases indicated ‘normal’ values for various laboratory test items rather than numeric values. These 'normal' laboratory test items were entered into MRM.

Reports created by MRM

On submitting the patient case to MRM for analysis, MRM produced a list of potential DRPs, illustrated in Figure 18. Each DRP was titled and an explanation of the potential problem and

recommendations were provided. A yellow link provided a short list of rules and values which triggered the DRP rule.

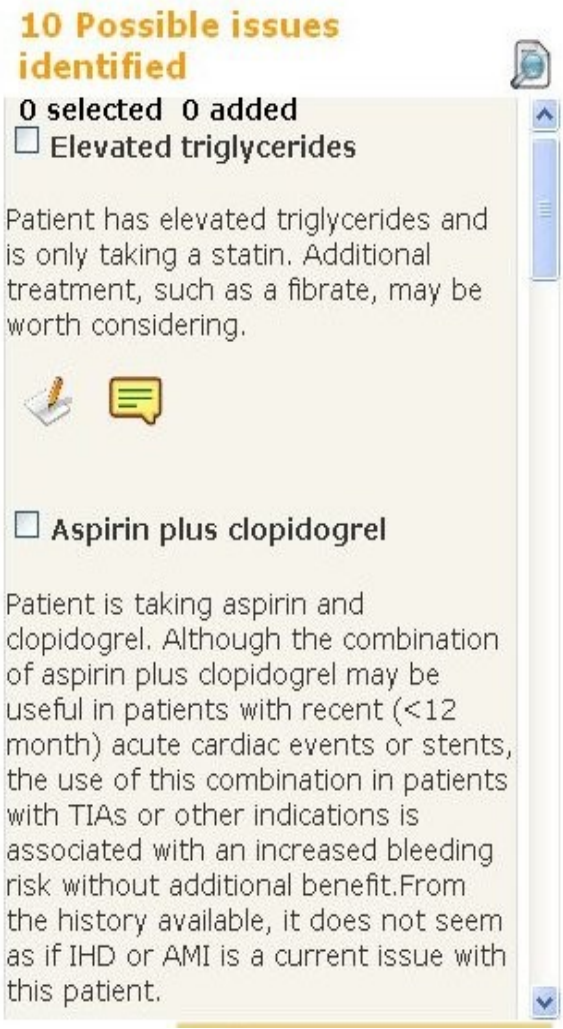


Figure 18: Example MRM-identified DRPs

MRM Data entry check

Twenty per cent of the 659 cases entered into MRM (N=132) were examined for accuracy. Data contained patient demographics, diagnoses, laboratory test results, observations and medications. The numbers of data point entry errors per case are shown in Table 31. The majority of data point errors were omissions of entry into MRM. Three errors were entry of incorrect values. Each of these errors was subsequently amended.

Table 9: Data entry errors showing count of audited cases and count of datum errors

	Number of cases		Count of data point errors		Total data points
	122		0		4064
	4		1		169
	1		2		56
	2		3		95
	1		4		23
	1		9		47
	1		23		46
Total	132	Total	42	Total	4500
Percentage of errors per case (42/4500 x 100)					0.93%

5.1.3 MRX interface and data entry

MRX software was also accessed through a website. The details of each case were entered through various screens. Patient demographics, medical conditions utilising ICD-9 codes, allergies, medications and directions were able to be entered. MRX only analysed patients who were 60 years old and older – user manual *Monitor-Rx Overview – NF 101119-1*.[276] One hundred and eight cases randomly sampled from the larger dataset of patients aged 60 years old or over were entered into MRX, of which 100 were aged 65 years old or older.

The selection of these cases was performed using Microsoft Access (Microsoft, Redmond, WA). Firstly, a randomly generated number was assigned to each case and the cases were ordered by random number from the lowest to highest values. The first 108 cases were selected for data entry into MRX.

MRX only examined the potential problems of medications used for chronic conditions, all medications were entered into the software, except those listed in the section *Entry of medications into MRX*.[260]

MRX Data fields

The following patient information was able to be entered into MRX:

- Patient identifier, birth date, gender, date.
- Diagnoses stored as free text or linked to ICD-9 codes.

- Allergies as free text entries.
- Medications – selected by entering part or all of name and directions. Medications could be marked with start dates and discontinued dates.

Entry of medications into MRX

MRX was developed for use in the USA by the American Society of Consultant Pharmacists (ASCP) Foundation so medication brand names were USA brand names. Equivalent Australian branded medications were entered using brand or generic names where possible. Prescription medications that were not listed in MRX included: lercanidipine, gliclazide, nitrazepam, betahistine, flunitrazepam. Some non-prescription medications could not be entered into MRX as the software did not have the products listed. These were: bromhexine and several herbal or vitamin supplements. The data entry screen is depicted in Figure 19, a drop down list of medications was presented on entering medication names.

Figure 19: MRX medication data entry screen

Entry of medical conditions, laboratory test results and observations into MRX

MRX was able to identify PIMs based solely on medication brand names or generic names. MRX did not utilise medical conditions nor laboratory test values for its assessments so this data was not entered into MRX (per discussion with the Director of business development ASCP, Douglas Allen).

Reports created by MRX

MRX provided three types of DRP report:

- Intervention overview
- Geriatric Problem-Med
- Med-Problem

The *intervention overview* report displayed a table of the patient's medications and a list of potential geriatric problem titles. Medications which were not screened for problems were listed as 'no problems found'.

The g*eriatric problem-med* report displayed a table divided into rows of problem areas, a description of the medication-related problem and a list of medications that could be associated with the problem area and monitoring indicators. On the website, medications identified as PIMs were highlighted in red indicating the potential for more significant problems. Monitoring indicators were a list of side effects that could result from the use of the problem medication. For each care area many monitoring indicators could be linked to an assessment test within the MDS for use within nursing homes. The purpose of the monitoring indicators was to help health care professionals identify geriatric problems that may be associated with a medication.

The *geriatric problem-med* report contained the greatest information so this was used as the basis of data collection from MRX. This report included the information available in the other tables as well as additional short comments which indicated the type of problem a medication could cause. As described in the user manual "This report is the heart and soul of Monitor-Rx. It presents the information in a helpful format for a quick and clinical evaluation."[276]

The *med-problem* report was similar to the *geriatric problem-med* report, but each row was a medication of interest followed by a list of problem titles and descriptions of medication-related problems. Each description was identical to the description shown in the *geriatric problem-med* display.

Examples of the *intervention overview* report, *geriatric problem-med* report and *med-problem* report are shown in Appendix 6. Care areas are listed in Appendix 19.

MRX Data entry check

Twenty per cent of the 108 cases, 21 cases, were examined for accuracy of entered medications. No data entry errors were found.

5.1.4 Automation of prescribing criteria

The Beers03, Beers12, STOPP/START and PIEA prescribing criteria were automated, where possible, to provide electronic reports of identified DRPs. Beers12 criteria were released during this research but the work involving the Beers03 criteria was retained. Automation was considered an appropriate action due to the large number of patient cases (570 patients aged 65 and over).

All HMR cases contained patient age, and gender. Some cases did not contain diagnoses or laboratory test results, shown in Table 10.

Table 10: HMR case information available

Case information (patients aged 65 years old and older)	Information present (number of cases)	Information absent (number of cases)
Medications	570	0
Diagnoses	566	4
Laboratory tests	455	115

Development of structured query language (SQL) queries and the application of these queries to the case data resulted in reports of cases which met specific criteria. Each criterion was assigned a DOCUMENT classification code, see section 6. Each criterion was also assigned a descriptive classification, see section 7, to assist further analysis. Lists of descriptive classifications are tabled in . A schematic of the database tables is portrayed in Figure 20, the *ReviewDetail* table contained patient demographic information.

Beers03 automation

A daily dose column was completed for medications where criteria contained dosage requirements (aspirin, lorazepam, oxazepam, alprazolam, temazepam, triazolam, digoxin,

ferrous sulphate, piroxicam, naproxen, ketoprofen, ibuprofen, indomethacin, diclofenac). This was achieved by filtering for the required medication and determining the daily dose from the medication strength and the medication directions. A limitation was lack of directions or 'when required' directions; for these medications no daily dose was entered. Individual queries were developed for 53 criteria, listed in Appendix 1.

Several medications in the Beers03 criteria were not available in Australia, and were not specifically included for the development of the automated process, although they were included if a query required the use of a higher ATC umbrella classification rather than the fifth chemical substance level. These excluded medications are listed in Appendix 4.

Fifty-one of the 68 criteria were implemented as database queries, listed in Appendix 1. Several limitations existed with the rules developed for the criteria, listed in Appendix 4.

Beers12 automation

A daily dose column was completed for medications where the criteria contained dosage requirements (aspirin, digoxin, doxepin, spironolactone). This was achieved by filtering for the required medication and determining the daily dose from the medication strength and the medication directions. A limitation was lack of directions or 'when required' directions, for these medications no daily dose was entered. Individual queries were developed for 48 of 52 criteria from Beers12 tables 2 and 3, listed in Appendix 1. Several limitations existed with the rules developed, listed in Appendix 4.

Several medications in the criteria were not available in Australia, and were not specifically included for the development of the automated process. These excluded medications are listed in Appendix 4.

PIEA automation

The PIEA tool of 48 prescribing indicators contained both PIM and potential therapeutic omissions, discussed under 2.2.4 PIEA. The SQL queries were written with the reverse intent to identify DRPs as potentially inappropriate medications or as potential therapeutic omissions. This was purposefully undertaken to allow comparisons with the STOPP/START and both Beers criteria. Generally PIEA was more explicit in stating specific conditions,

unlike the criteria defined in Beers03, Beers12 and even in STOPP/START. The advantage of this approach may be the greater sensitivity in targeting patients who met the prescribing indicators, yet the disadvantage was the greater complexity in attempting to reproduce the criteria in database queries, particularly when considering the limited data that was able to be utilised to develop the queries. This limitation may also apply to pharmacists who conduct HMRs, as they may also be hampered by lack of information to fully apply these criteria.

Thirty-seven of 48 criteria were implemented as SQL queries based on the available data. The majority of implemented criteria were assigned the following DOCUMENT codes: 14 instances *D6 – Contraindications apparent* and 12 instances *U1 – Condition undertreated*. Appendix 1 details which criteria were implemented and which were not and the DOCUMENT classification of each criterion.

There were limitations in the application of the database queries, listed in Appendix 4.

STOPP automation

Database queries were developed for the STOPP criteria utilising the patient data tables shown in Figure 45. Database queries were developed for each of the STOPP criteria, where it was possible to do so. The majority of implemented criteria were assigned DOCUMENT code *D6 – Contraindications apparent* (36 of 57 criteria), seconded by DOCUMENT code *U1 – Condition undertreated* (6 of 57 criteria). Appendix 1 tables which criteria were implemented and which were not and the DOCUMENT classification of each criterion. Fifty-seven of 65 criteria were able to be implemented as database queries.

Several limitations applied in the application of the database queries, listed in Appendix 4.

START automation

SQL queries were developed for the START criteria utilising the patient data tables shown in Figure 45 where it was possible to do so. Seventeen of 22 criteria were able to be implemented as SQL queries. All implemented criteria were assigned DOCUMENT code *U2 – Condition untreated.* Appendix 1 lists which criteria were implemented and which were not and the DOCUMENT classification of each criterion.

Several limitations applied to the application of the database queries, listed in Appendix 4.

5.1.5 Ethical approval

Minimal risk ethics approval was granted for this project through the University of Tasmania Human Research Ethics Committee to conduct this research: H0011845. The approval letter is shown in Appendix 5. The data on which this project is based, the original VALMER project, was approved by the University of Tasmania Human Research Ethics Committee ethical approval (HREC9360).

5.2 Results

Patient demographics and demographics of data subsets are shown in this section. Figure 20 Also shows the summaries of DRPs identified within the main cohort of 570 patients aged 65 years old or older. The figure also summarises the frequencies of DRPs identified by MRM, MRX and four prescribing criteria. The term case represents a patient.

5.2.1 Cases aged 65 years old and older

There were 570 cases where the patient was aged 65 years old or older, shown in Table 11.

Table 11: Demographics of patients aged 65 years old and older

Cases 65 years old and older (N = 570)	Result, count or mean ± standard deviation
Age (years)	80 ± 7
Gender	Male 234 (41.1%) : Female 336 (58.9%)
Diagnoses	With 566 (99.3%) : Without 4 (0.7%)
Laboratory test results	With 455 (79.8%) : Without 115 (20.2%)
Number of medications	12.0 ± 4.4
Number of diagnoses	9.1 ± 5.2

5.2.2 Cases entered into MRX

One hundred cases, hereafter referred to as test cases, aged 65 years old and over were entered into MRX. Statistical analyses were performed to determine whether the random sample of cases were representative of the 470 remaining cases, details shown in Table 12. Shapiro-Wilk tests for normality and quantile-quantile plots were examined to determine if age, number of medications and number of diagnoses violated normality test assumptions. Number of medications and number of diagnoses were found to be non-parametric. There were no significant differences between the 100 test cases and the remaining 470 cases.

Table 12: Demographics of patients entered into MRX

Demographic	Test cases (N = 100), count, median and range, or mean ± standard deviation	Remaining cases (N = 470), count, median and range, or mean ± standard deviation	Statistical results for representativeness
Age (years)	78 ± 6	80 ± 7	T-test, t(149.521) = 1.80, p = 0.074
Gender	Male 44 : Female 56	Male 190 : Female 280	Chi-squared test, X^2 = 0.300, df = 1, p = 0.584
Diagnoses	With 99 : Without 1	With 467 : Without 3	Fisher's Exact Test, p = 0.539
Laboratory test results	With 78 : Without 22	With 377 : Without 93	Chi-squared text, X^2 = 0.132, df = 1, p = 0.716
Number of medications	Median 11.5, range 4 - 28	Median 11.0, range 2 - 27	Wilcoxon rank sum test, W = 23923, p = 0.777
Number of diagnoses	Median 8.0, range 0 - 29	Median 8.0, range 0 - 33	Wilcoxon rank sum test, W = 24520.5, p = 0.494

5.2.3 DRP frequency

The frequency of DRPs for pharmacists, MRM, MRX and prescribing criteria are summarised in Table 13 and illustrated in Figure 20. Frequencies of DRPs for the expert panel cases are shown here and in Figure 20. Details of the expert panel assessment are described in Chapter 8.

Table 13: DRPs identified by each source.

DRP source	570 cases aged 65 plus	100 test cases	20 expert panel cases
Pharmacist	2020	346	73
MRM	3209	547	125
MRX	1265	1265	265
STOPP/START	1032	166	36
Beers03	404	55	12
PIEA	1492	245	52
Beers12	399	68	15

In the 570 cases pharmacists identified a range of 0 to 13 DRPs per patient, median 3 DRPs. MRM identified a range of 0 to 16 DRPs per patient, median DRPs.

The pharmacists, being human, and having visited patients and interviewed in their homes, can be expected to utilise more variables which would not be available to computer software.

Similarly, MRM was able to utilise more variables than MRX. Additionally, there were 256 instances where MRM repeated the presence of a DRP, although the DRP was worded slightly differently. Two examples of MRM repetition are shown:

- *GORD - Patient has a history of oesophagitis and is taking a calcium channel blocker which may exacerbate the situation. Alternative treatment of hypertension or ischaemic heart disease may be considered.*
- *Reflux with Calcium Channel Blocker - Patient is receiving a proton pump inhibitor and is taking a calcium channel blocker. CCBs may exacerbate or precipitate GORD. It may be possible to use an alternative agent with a view to reducing or ceasing the proton pump inhibitor.*
- *Potassium levels - Patient has moderately elevated potassium and is taking an angiotensin inhibitor which may be contributing to this. Dose reduction of the offending agent may be appropriate if risk of cardiac adverse events is high.*
- *Potassium levels - Patient is taking an agent affecting the angiotensin system and has an elevated potassium level. Confirmation of ongoing hyperkalaemia and evaluation of clinical risk, followed by dose adjustment of the offending agent may be appropriate.*

To make a fair and balanced comparison possible, several DRPs were excluded prior to analysis, depicted in Figure 20. Exclusions were the duplicate MRM DRPs, and pharmacist DRPs classified with DOCUMENT as *Compliance* or *Not-classifiable*.

Duplicated MRM DRPs would skew frequencies and ratios, the real interest is in the number of different DRPs found in each case. *Compliance* and *not-classifiable* DRPs were only identified by the pharmacist, since they were the only ones with the information at hand required to determine if a patient was being compliant with their medication or not. Pharmacists identified 250 *compliance* DRPs and 44 *not-classifiable* DRPs. The majority of the *compliance* DRPs (N=130) concerned patients taking too little medication and the majority of *not-classifiable* DRPs (N=36) concerned cost of therapy. Both MRM and MRX did not have the capacity to identify *compliance* or *not-classifiable* DRPs so these were

excluded. DOCUMENT classifications excluding C and N categories will be referred to as DOUMET classifications. MRX was found to present a limited set of responses centred on elderly care areas. These responses are shown in Appendix 19.

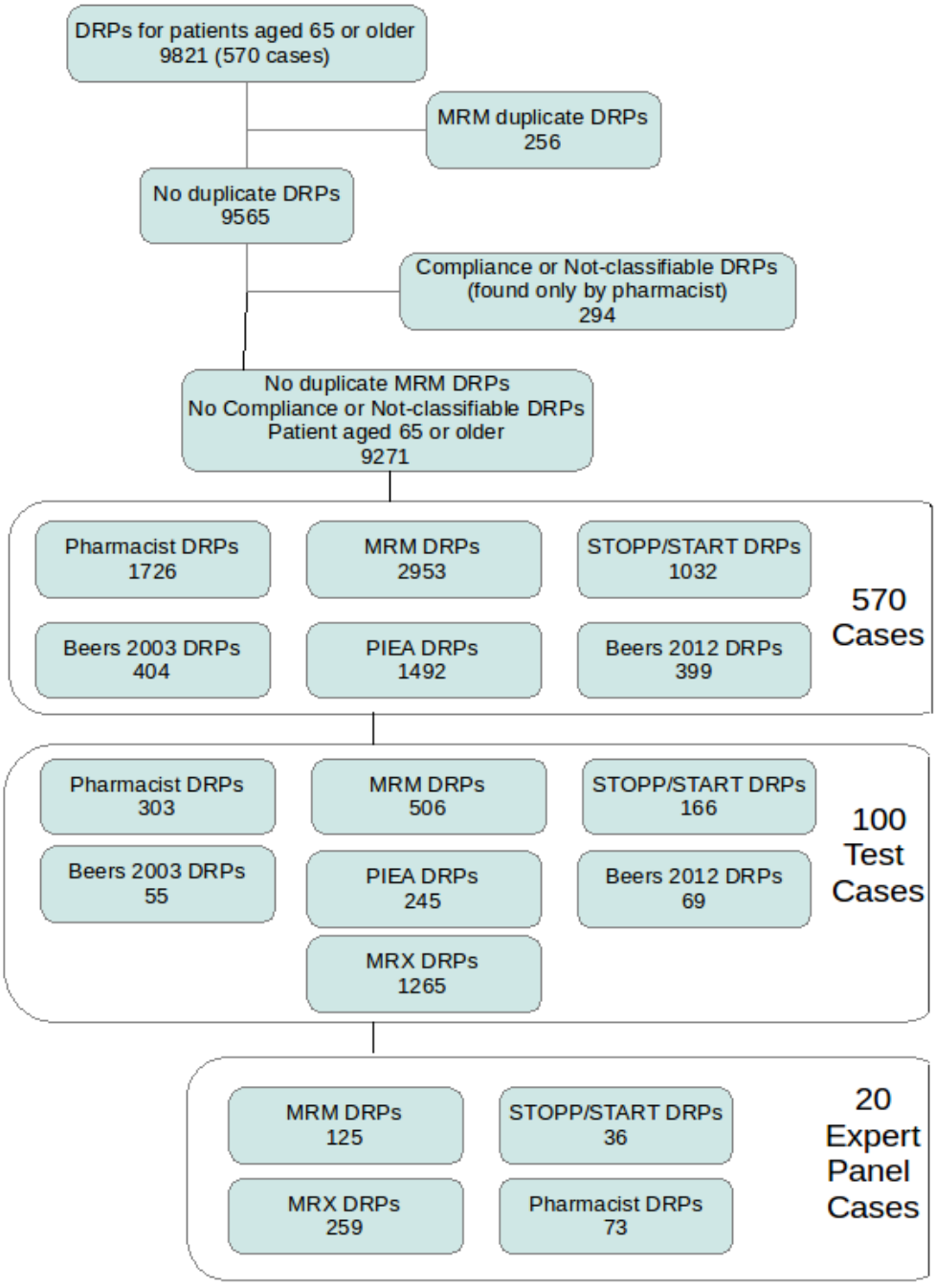


Figure 20: Frequency of DRPs identified by MRM, MRX and prescribing criteria

6 DOCUMENT classifications

The frequencies of DRPs identified by MRM, MRX, pharmacists and prescribing criteria are shown in Chapter 5. Frequencies of DRPs alone provide little information about the types of DRPs which have been identified. Classification of these DRPs using a validated DRP classification system was desirable to give greater insight into the types of problems that were able to be detected by each of these DRP-identification sources.

Each of these DRP-identifying sources may differ widely in the problem types that may be identified as each source may take a unique approach in the identification process. The original reviewing pharmacists may be anticipated to detect the broadest range of DRPs as they are most able to use a wide variety of information that may either not be available for use by software, or even if available for use by software, is not actually utilised within the software algorithms. Pharmacists may also be expected to draw upon a repository of experience and knowledge acquired from their training and practical experience in the field. MRM and MRX have been described in Chapter 5 and each utilised a different range of information. MRM incorporated a variety of information to produce lists of DRPs whereas MRX produced lists of DRPs solely based on the presence of certain medications. Apart from these commercial products, prescribing criteria also utilised various information to detect DRPs, primarily the presence of a medication of interest and often the presence of a disease state.[38,87,93,119]

The DOCUMENT classification system had been developed in Australia and has been applied in an Australian locale to categorise DRPs identified by pharmacists.[275] DOCUMENT is a two-tiered classification summarised in Table 14, with a letter denoting the main type of DRP e(.g. D - *Drug-selection*) and a number allocated to a particular problem type, (e.g. D2 *Drug-interaction*). Detail of the classifications and sub-classifications are shown in Appendix 9. Validation of the DOCUMENT system was performed and found to have moderate agreement between pharmacists (Fleiss' Kappa 0.53) and re-test concordance rate of 69%.[275]

Table 14: DOCUMENT main classifications

DOCUMENT letter code	Description	Number of sub-classifications
D	Drug selection	8
O	Over or under dose	4
C	Compliance	6
U	Undertreated	4
M	Monitoring	3
E	Education or information	3
N	Not-classifiable	1
T	Toxicity or adverse reaction	1

The DOCUMENT classifications have been utilised in several Australian studies assessing DRPs identified in HMRs and in community pharmacy practice. Williams *et al.* presented results of DRPs recorded by pharmacists during a three month trial in 185 Australian community pharmacies.[275] Stafford *et al.* examined the nature of DRPs identified from 234 HMRs and aged-care medicines reviews conducted between 1998 and 2005 in Australia.[136] The details of DRPs were examined from HMRs conducted after hospital discharge of Australian patients taking warfarin.[277] The proportions of the DOCUMENT classifications from these three studies do vary, however, *drug selection* (25% to 31%), *compliance* (3% to 11%), *monitoring* (2% to 10%) and *not-classifiable* (2% to 6%) present in similar proportions between the studies. Not surprisingly *education* issues comprised a substantial proportion of DRPs within the warfarin study.[277] *Drug selection* issues comprised a consistent and substantial proportion of DRPs in all three studies.

DOCUMENT classifications provide an appreciation of the range of DRPs that can be identified with any given approach. This may provide a greater understanding of the differences between original pharmacists, MRM, MRX as well as the four sets of prescribing criteria. Nonetheless, one important limitation is that despite the assignment of DOCUMENT classifications to any DRP, no appreciation of the severity or clinical relevance of such DRPs is possible using this approach.

6.1 Methodology

Pharmacist, MRM and MRX DRPs were classified using the validated DOCUMENT classification system.[275] The assignment of DOCUMENT classifications to DRPs were guided by the notes and examples provided in the *Standard and guidelines for pharmacists performing clinical interventions.*[278] DOCUMENT classifications were assigned by the author, who has extensive experience and has participated in training in using the DOCUMENT classification system.

All DRPs assigned C - *Compliance* or N – *Not classifiable* were excluded from analyses as these were only identifiable by the original reviewing pharmacists. Only pharmacists had access to the information required to determine these issues, see section 6.2. DOUMET denotes the DOCUMENT codes excluding *Compliance* (C) and *Not classifiable* (N). DOUMET allowed for a less pharmacist biased comparison of the types of DRPs identified by commercial software, sets of prescribing criteria and pharmacists. It is important to note that the pharmacist's ability to detect these issues as part of their medicines review process is important and valued, and the inability of other approaches to do so is an acknowledged limitation. However, these issues were excluded from this analysis so as to allow for a fair and balanced evaluation of each DRP source's ability to identify DRPs that an automated computer software solution could reasonably be expected to identify, considering the patient data available to them.

DRPs assigned DOCUMENT classifications were compared by frequency and type. Statistical analyses comparing MRM DRPs with pharmacist DRPs and MRX DRPs with pharmacists DRPs were performed using chi-square or where necessary Fisher's Exact tests. Data was split into two subsets for analysis: all 570 cases which excluded MRX and 100 test cases which included MRX DRPs. Data analysis was performed using the R statistical software, R Foundation for Statistical Computing, Vienna.[279]

6.2 Results

The results are divided into two sections: DRPs identified in all 570 cases, and DRPs identified in the 100 test cases which were entered into MRX.

6.2.1 DRPs in 570 cases (excluding MRX)

Across 570 patients, pharmacists identified a range of 0 to 13 DRPs per patient, median 3. MRM identified a range of 0 to 16 DRPs per patient, median 5. The differing medians and long tails indicating skewed data can be seen in the box-plots in Figure 21.

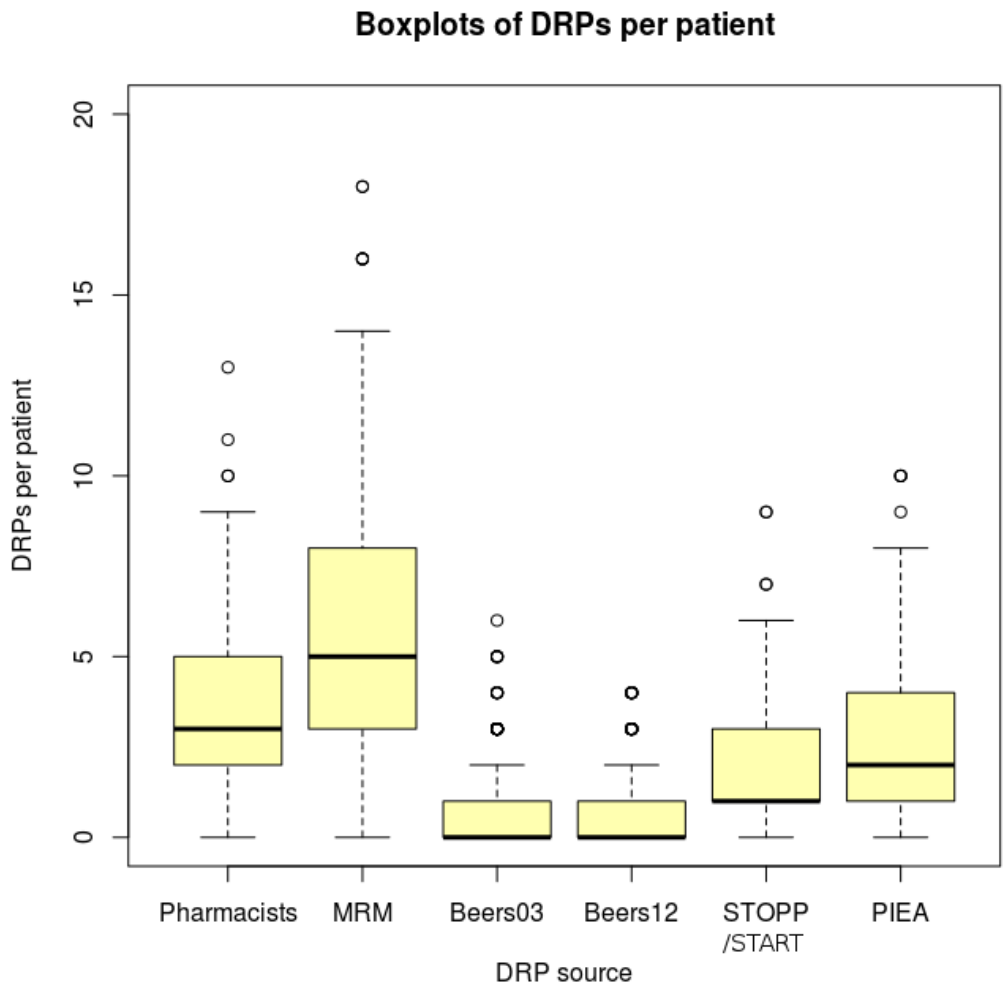


Figure 21: DRPs identified per patient, 570 cases

Table 15 summarises the DOUMET classifications of DRPs for pharmacists, MRM and prescribing criteria.

Table 15: DRPs by DOUMET

Source	D	O	U	M	E	T	Total
Pharmacist	467	170	540	213	46	290	1726
MRM	1143	206	881	504	27	192	2953
Beers03	383	21	0	0	0	0	404
Beers12	378	21	0	0	0	0	399
PIEA	868	119	500	5	0	0	1492
STOPP/ START	625	19	388	0	0	0	1032
Total	3864	556	2309	722	73	482	8006

A chi-square test showed significant difference between all six sources of DRPs, χ^2 = 2126.249, df = 25, p < 0.001. The chi-square approximation may be incorrect due to small numbers in 12 cells, Fisher's Exact Text was not able to be performed. Chi-square and Fisher's Exact Test comparisons between each source of DRPs were performed, shown in Table 16. There were significant differences in DOUMET proportions between most of the DRP sources. The exception was the Beers2003 and Beers2012 prescribing criteria in which proportions of DOUMET categories were almost identical.

Table 16: Chi-square and Fisher's Exact Test comparisons

Source	MRM	Beers03	Beers12	PIEA	STOPP/ START
Pharmacist	X^2 = 204.3801, df = 5, p < 0.001	X^2 = 639.2937, df = 5, p < 0.001	X^2 = 632.6459, df = 5, p < 0.001	X^2 = 651.8787, df = 5, p < 0.001	X^2 = 579.4555, df = 5, p < 0.001
MRM		Fishers Exact Test not able to be performed	Fishers Exact Test not able to be performed	X^2 = 441.7172, df = 5, p < 0.001	X^2 = 385.1902, df = 5, p < 0.001
Beers03			Fisher, p= 1	Fisher, p < 0.001	Fisher, p < 0.001
Beers12				Fisher, p < 0.001	Fisher, p < 0.001
PIEA					Fisher, p < 0.001

The DRPs found by each source are also shown in Figure 22. The identification of DRPs by prescribing criteria were limited to *drug selection*, *over or under-dose* and for PIEA and

START *under-treatment*. The identification of DRPs by MRM was broader and included *monitoring*, *education* and *toxicity*. Similar types and quantities of DRP were identified by both Beers03 and Beers12.

It can be seen in Figure 23 that MRM identified similar proportions of DRPs by DOUMET classification as those identified by pharmacists.

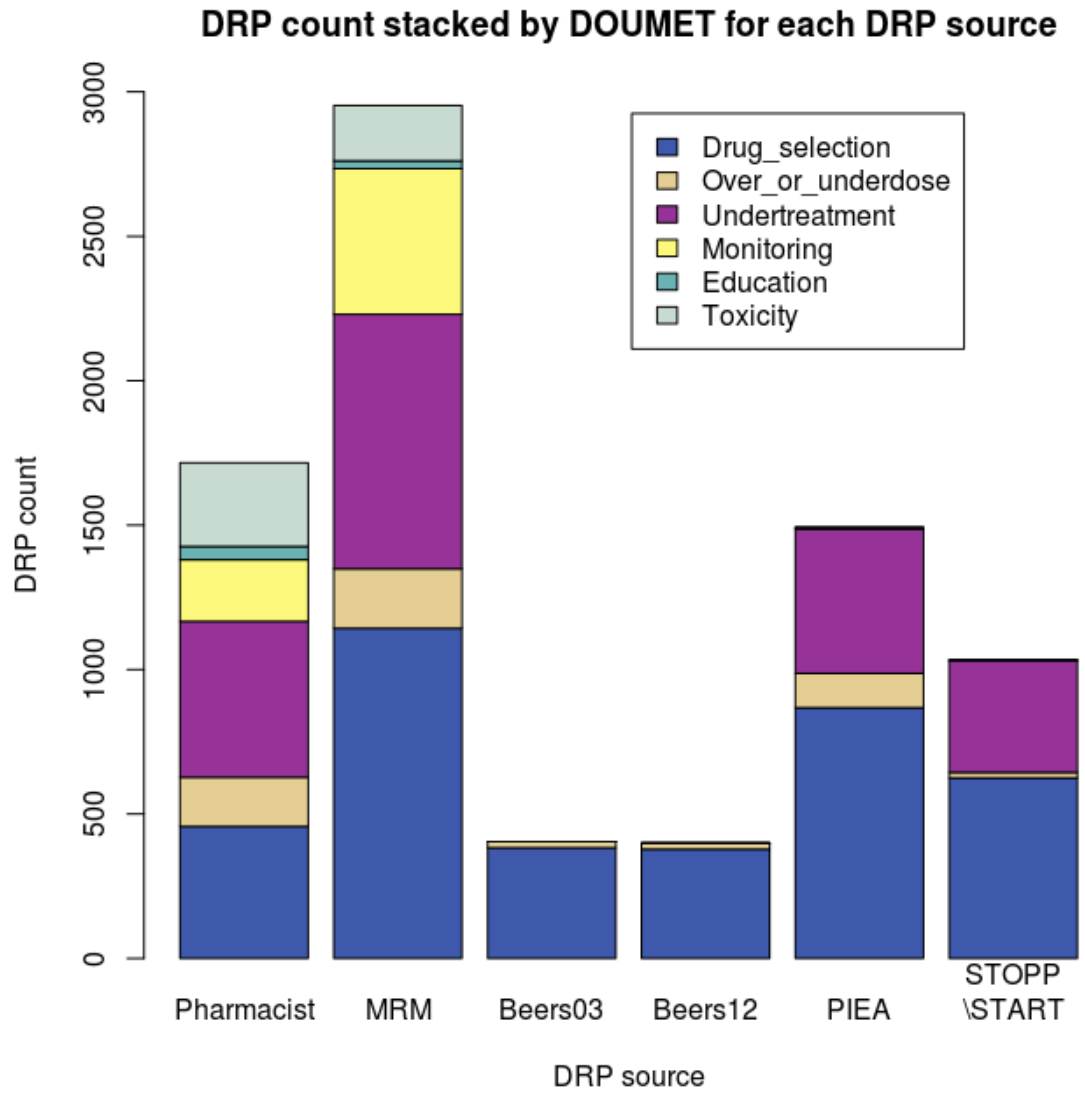


Figure 22: Count of DRPs for each source and DOUMET classification

The proportions of DRPs assigned DOUMET classifications are shown in Figure 23. The main differences between MRM and pharmacist DRPs were in the classification of *drug selection* where MRM found a greater proportion of DRPs than pharmacists, and the *toxicity* classification where pharmacists found a greater proportion of DRPs. Yet very similar proportions of DRPs were found in the categories of *over or underdose*, *undertreated* and *monitoring*.

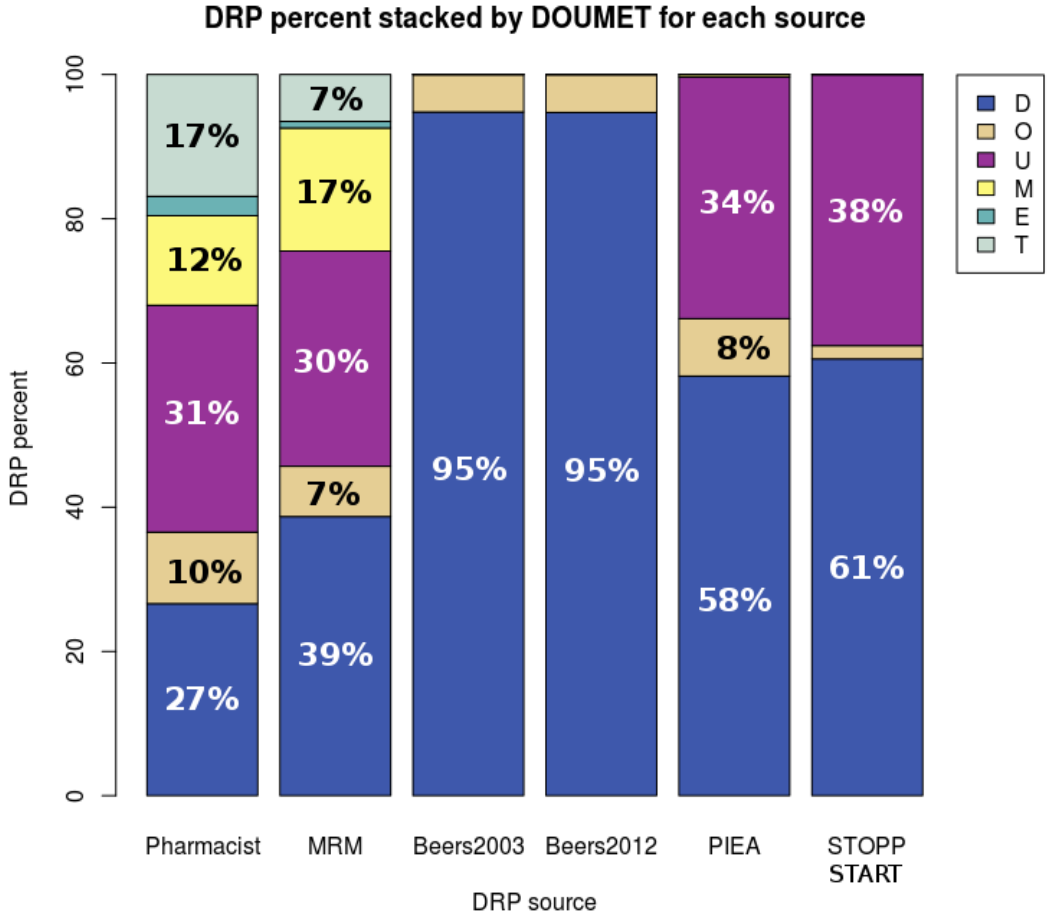


Figure 23: Proportion of DRPs from each source with DOUMET classifications

6.2.2 DRPs identified in test cases

Results of DOUMET analysis of DRPs found in the 100 test cases entered into MRX are shown in this section.

Pharmacists identified a range of 0 to 8 DRPs per patient, median 3. MRM identified a range of 1 to 12 DRPs per patient, median 5. MRX identified a range of 3 to 19 DRPs per patient, median 13, shown in Figure 24.

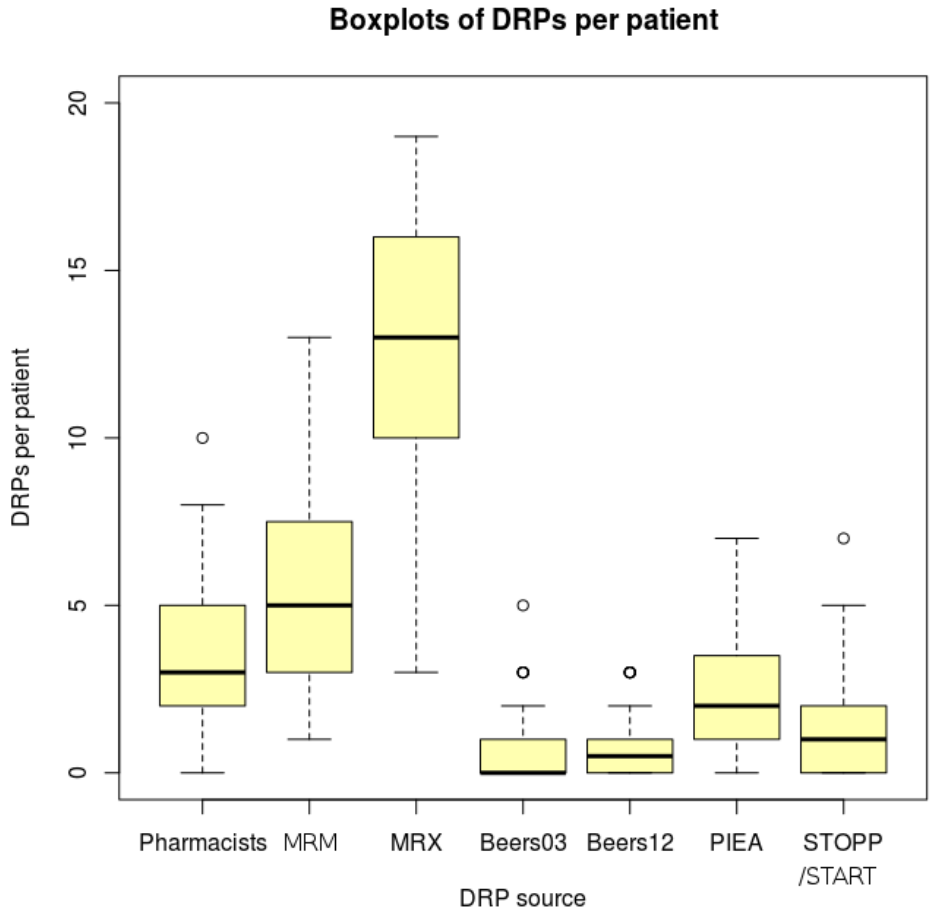


Figure 24: DRPs identified per patient, 100 cases

Table 17 shows the DOUMET classifications of DRPs of the 100 cases which had been entered into MRX.

Table 17: DRPs by DOUMET, cases entered in MRX

Source	D	O	U	M	E	T	Total
Pharmacist	77	32	86	47	7	54	303
MRM	191	42	148	91	4	30	506
MRX	0	0	0	1265	0	0	1265
Beers 2003	51	4	0	0	0	0	55
Beers 2012	61	8	0	0	0	0	69
PIEA	147	26	69	3	0	0	245
STOPP/START	105	5	56	0	0	0	166
Total	632	117	359	1406	11	84	2609

Fishers Exact Test was not able to be performed. However, an approximation using a chi-square test showed significant differences between all seven sources of DRPs, $\chi^2 = 2632.524$, df = 30, $p < 0.001$. Where Fisher's Exact Test was able to be performed there were significant differences in the proportions of DOUMET classifications between most DRP sources, shown in Table 18. The exception was the Beers2003 and Beers2012 prescribing criteria.

Table 18: Fisher's Exact Test comparisons

Source	MRX	MRM	Beers03	Beers12	PIEA	STOPP/ START
Pharmacist	Fishers Exact Test not able to be performed	Fishers Exact Test not able to be performed	Fishers Exact Test not able to be performed	Fishers Exact Test not able to be performed	Fishers Exact Test not able to be performed	Fishers Exact Test not able to be performed
MRX		Fishers Exact Test not able to be performed	Fisher, $p < 0.001$	Fisher, $p < 0.001$	Fisher, $p < 0.001$	Fisher, $p < 0.001$
MRM			Fishers Exact Test not able to be performed	Fishers Exact Test not able to be performed	Fishers Exact Test not able to be performed	Fishers Exact Test not able to be performed
Beers03				Fisher, $p = 0.546$	Fisher, $p < 0.001$	Fisher, $p < 0.001$
Beers12					Fisher, $p < 0.001$	Fisher, $p < 0.001$
PIEA						Fisher, $p = 0.008$

The frequency of DRPs found by each source is illustrated in Figure 25. This figure highlights the great quantity of DRPs found by MRX, more than twice a great as MRM, and four times as much as the pharmacists original findings. It also clearly shows the specificity of MRX for the *monitoring* classification.

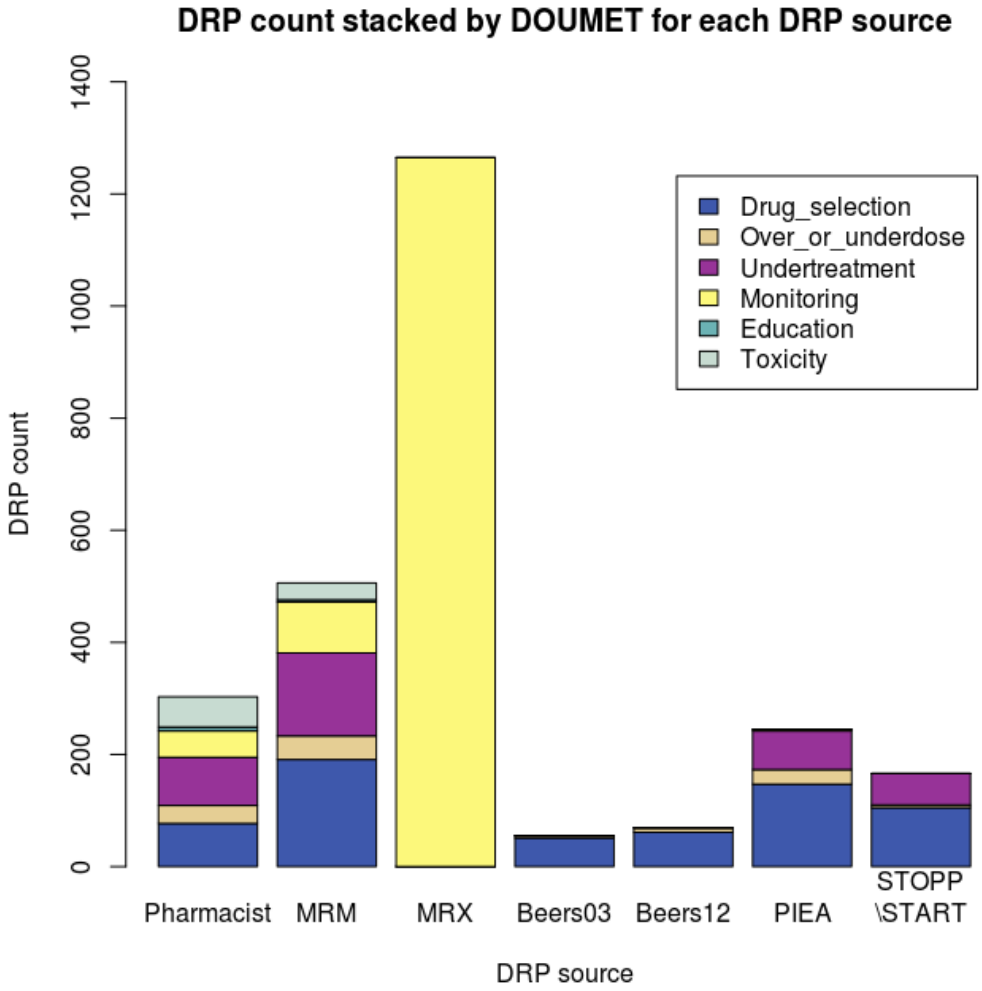


Figure 25: Count of DRPs by DOUMET classification

It can be seen in Figure 26 that MRM identified a similar type and proportion of DRPs by DOUMET classification as those identified by pharmacists.

One hundred percent of MRX DRPs involved drug *monitoring*, whereas MRM and pharmacist DRPs were spread across all of the six DOUMET classifications. The prescribing

guidelines PIEA and STOPP/START identified DRPs from d*rug selection*, o*ver or underdose* and u*ndertreated* classifications. The Beers03 and Beers12 guidelines identified *drug selection* and *over or underdose* classifications.

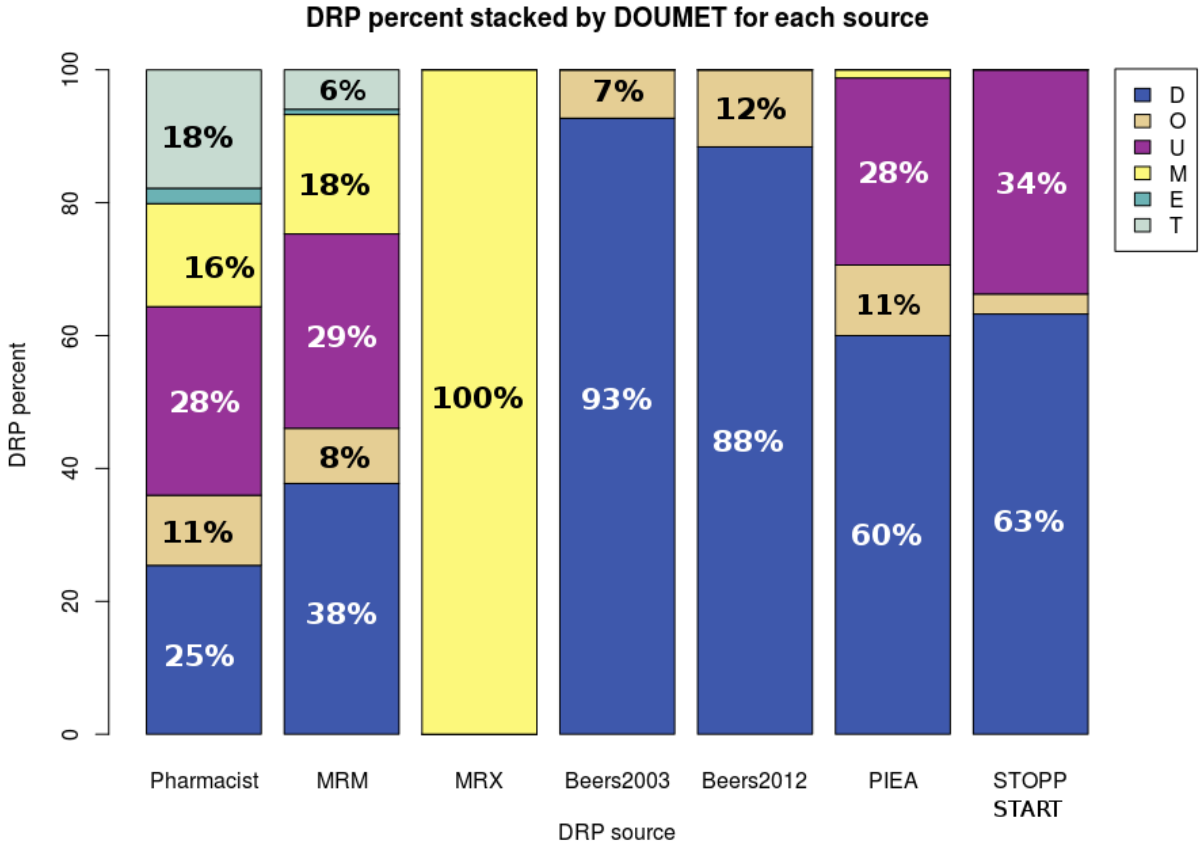


Figure 26: Proportion of DRPs by DOUMET classification

6.3 Discussion

The MRM software was able to identify DRPs that could be classified into six DOCUMENT categories. MRX was restricted to the identification of DRPs presented as *monitoring* for problems arising from medication therapy.

There were significant differences between the types and frequency of problems identified, with MRX showing the greatest extreme in the number of DRPs identified, quadruple that of pharmacist DRPs, and the narrowest range of DRP classifications. In contrast MRM identified a wide range of DRPs at double the frequency of pharmacists. MRM was

significantly different in the composition of identified DRPs, with classification of *drug selection* where MRM found a greater proportion of DRPs and *toxicity* where pharmacists found a greater proportion of DRPs.

MRX based its findings solely on the presence of medications of interest. This approach limited the range of DRPs that could be identified to only warning pharmacists of the potential for problems to occur. Essentially, the DRP text was telling pharmacists to monitor the patient for the presence of medication side effects, hence the exclusive use of the *monitoring* category for MRX. There was no incorporation of the medication strength or dosage to give identify DRPs involving of over or under-dosing. Similarly, while diagnoses were able to be entered into MRX, there was not capacity for the software to identify medications which were unsuitable in the presence of certain medical conditions. Similarly, if a medical condition existed where treatment ought to have been initialed, MRX was not able to identify the treatment omission.

The MRM software also identified a much larger number of DRPs than pharmacists, however MRM did identify a variety of DRP types, shown in Figure 26. Unlike MRX, MRM did factor in medication strength and dosing to enable it to identify potential over or under-dosing problems. MRM also was able to incorporate medical conditions allowing it to identify untreated conditions where medication was absent and to identify medications which were inappropriate in certain medical conditions.

The sets of four prescribing criteria each identified fewer DRPs overall compared to pharmacists, MRM or MRX. The scope of DRP classifications was also generally narrower, limited to *drug selection* and *overdose* and additionally *undertreatment* for PIEA and STOPP/START. Surprisingly, both PIEA and STOPP identified a larger number of *drug selection* issues than did pharmacists. The Beers2003 and Beers2012 prescribing criteria were very similar in both the frequency of findings as well as the types of DRPs.

Not unexpectedly, pharmacists were able to identify the widest range of problems with DRPs in all 8 DOCUMENT categories. Pharmacists uniquely identified *compliance* DRPs (N = 250) and *not-classifiable* DRPs (N = 44). *Not-classifiable* DRPs mainly consisted of medication cost issues.

The classification of DRPs using DOCUMENT classifications did allow for comparison between the sources of DRPs in a broad sense. It gave insight into the frequency of findings and the general type of DRPs that were identifiable. However, DOCUMENT classifications did not provide for determination of the clinical relevance of identified DRPs. Assessment of clinical relevance requires an understanding of each DRP in the context of each patient's individual circumstances. This is one of the main limitations of using the DOCUMENT classifications. A second limitation was that the clinical detail of each DRP – the medication and/or medical condition - were lost when comparing DOCUMENT classifications. Comparing the clinical detail of DRPs by frequency and type would have provided a stronger sense of the similarities and differences between MRM, MRX and pharmacists, as well as the prescribing criteria. Thus further assessments using alternative methods were performed.

7 Descriptive classifications

The DOCUMENT classifications allowed some insight into the frequency and types of DRPs that were identifiable by the various sources. However, the DOCUMENT analysis did not provide sufficient detail regarding the particular problems that were identifiable. Naturally, each source of DRPs used their own vocabulary to describe the DRPs they were identifying, making direct comparison of the specific DRPs each source identified challenging. To solve this problem we developed a set of descriptive classifications for each of the DRPs. This set of classifications provided a set of descriptive terms describing each DRP in sufficient detail to allow for comparison between DRP sources. Descriptive classifications typically included specific drugs, drug classes and/or disease states giving clinical context to aid comparison.

7.1 Methodology

All DRPs identified by each source were mapped to descriptive classifications which described the drug and/or the disease or other therapeutic problems in greater detail than DOCUMENT classifications. Descriptive classifications allowed direct and detailed comparison of the DRPs that were identified by pharmacists, MRM, MRX and prescribing criteria.

The similarities between sets of prescribing criteria, shown in Appendix 8, formed the basis of the list of classifications. The initial list of classifications was developed where at least two or more sets of prescribing criteria were in agreement concerning particular prescribing problems. Classifications described the PIM and often the associated diagnosis. An example is the classification: *NSAIDs used with (risk of) renal failure*.

DRPs identified by prescribing criteria, MRM, MRX and pharmacists were mapped to this initial list of classifications. The unmapped DRPs were then examined. Further classifications were developed where at least any two of MRM, MRX, pharmacists or prescribing criteria described the same DRP concept. Unmapped DRPs were then mapped to these additional classifications, where possible. Again, the remaining unmapped classifications were examined. Classification descriptions were broadened and included DRP classifications found in the DOCUMENT classification system.[275] Examples include: *therapeutic dose too high; other drug no indication*. Finally, remaining unmapped DRPs which did not have any

commonality with other prescribing criteria, software or pharmacists were assigned unique classifications. An example pharmacist-only classification is: *compliance – using too little medication*.

The list of descriptive classifications are tabled in Appendix 9. Distinct classifications per source are shown, that is, where two or more DRPs from the same source mapped to just one classification, that classification was counted only once, so as to eliminate duplicated findings.

Several descriptive classifications were excluded from comparisons as they were exclusively associated with pharmacists and were considered clearly out of scope of analysis that was achievable by software, given the nature of the available data. Excluded classifications involved pharmacist-only *compliance* and *not-classifiable* DRPs, specifically: *Communication breakdown, Documentation insufficient, Compliance – Confusion about therapy, Compliance – using too little medication, Compliance – using too much medication, Cost of therapy concern, Difficulty using dosage form, Eligible for DVA funded DAA, Medication expired, Medication regimen complicated, Other DRP pharmacist*.

Examples of DRPs mapped to the same classifications are presented in Table 19.

Table 19: Examples of DRPs mapped to the same classification

Classification	DRP Source	DRP Source
Hyperlipidaemia undertreated	MRM: Patient has elevated triglycerides and is only takng a statin. Additional treatment, such as a fibrate, may be worth considering.	Pharmacist: Patient's cholesterol and triglycerides remain elevated despite Lipitor. This may be due to poor compliance or an inadequate dose.
Glibenclamide prescribed	STOPP: Glibenclamide or chlorpropamide with type 2 diabetes mellitus (risk of prolonged hypoglycaemia)	Beers12: Sulphonylureas long acting: glibenclamide, chlorpropamide
Heart failure and concurrent verapamil or diltiazem	STOPP: Use of diltiazem or verapamil with NYHA class III or IV heart failure (may worsen heart failure)	Beers12: Heart failure: NSAIDS, COX2, diltiazem, verapamil, pioglitazone, rosiglitazone

Classification	DRP Source	DRP Source
Heart failure and concurrent verapamil or diltiazem	MRM: Heart failure with calcium channel blocker: Patient has a history of heart failure and is taking either verapamil or diltiazem. These agents can worsen signs and symptoms of systolic heart failure. Alternative agents should be considered if possible.	Pharmacist: Diltiazem may adversely affect patients with heart failure
Sedative long-acting or sedative long-term	MRX: Diazepam: Potentially inappropriate medications: Certain medications or medication classes should generally be avoided in older persons because they are either ineffective or they pose unnecessarily high risk for older persons and a safer alternative is available. Is there an indication for the medication?	Pharmacist: Patient has been taking diazepam and temazepam for several years, which increases the risk of adverse CNS effects

The list of classifications was validated by a second pharmacist (and supervisor) – Professor Gregory Peterson. The table of 141 classifications and the 28 groups into which they were categorised are shown in Appendix 9.

Descriptive classifications were compared by frequency and type between pharmacists, MRM, MRX and sets of prescribing criteria. Analysis of classifications was mainly descriptive, presenting classification frequencies found by one DRP source or another and by those found in common. Classifications were considered to be 'in common' if the same classifications could be identified by two DRP sources in the same patient.

The basic unit of analysis was the number of *distinct* classifications found in each case. The number of distinct classifications found in each case may differ from the number of actual DRPs found in each case. An example may be a patient using both atorvastatin and simvastatin, both statins. If statins are contraindicated due to risk of myopathy, each of these DRPs might be assigned the classification *statin myopathy risk*. These two DRPs were then collated into only one distinct classification, since the end goal was to determine if pharmacist or software was able to detect this central theme in this patient, with no extra credit being given for finding essentially the same problem multiple times.

The Jaccard index, also known as the Jaccard similarity coefficient,[280] was calculated on a per patient basis for classifications found by pharmacists and by software. The index was calculated as the number of classifications in common (set intersection) divided by the total number of classifications found by software and by pharmacists in the same patients (set union). The equation is shown in Figure 27. Potential values range from zero (no similarity) to one (complete similarity). The mean Jaccard index across all patients was calculated to determine how similar classifications were between pharmacists and MRM, pharmacists and MRX, and pharmacists and prescribing criteria.

$$\frac{Pharmacist\ classifications \cap software\ classifications}{Pharmacist\ classifications \cup software\ classifications}$$

Figure 27: Jaccard Index equation

7.2 Results

Descriptive classification results between MRM and pharmacists are shown for the larger 570 case cohort, and for the smaller 100 test case cohort which included MRX. The following subsections also show the classifications found by prescribing indicators. Bar charts highlight the unique classifications identified by software sources in dark-blue and unique classifications identified by pharmacists in light-blue. Beige highlights the classifications which were identified in common.

7.2.1 Descriptive classifications in 570 cases

The classifications from MRX DRPs were excluded from this section as only 100 of the 570 cases were entered into MRX.

MRM identified 2953 DRPs which were mapped to 2854 classifications representing 100 different types of problem. Pharmacists identified 1726 DRPs which were mapped to 1680 classifications representing 113 different types of problem.

Ten classification types were identified by MRM and not pharmacists and 23 classification types were identified by pharmacists and not MRM. Ninety of the same classification types were identified by both MRM and pharmacists. Of these, 68 were observed to be identified

concurrently by both sources on at least one patient. A table detailing the classifications and their frequencies is in Appendix 14.

Descriptive classifications identified by pharmacists, MRM and by prescribing criteria were summed and compared, shown in Table 20 and Table 21. Comparison with published prescribing criteria was performed. The details of descriptive classifications identified by each of the prescribing criteria are shown in Appendix 14.

As a percentage of the pharmacist classifications, MRM found 23%, PIEA 9%, STOPP/START 8%, Beers12 5% and Beers03 4%. Compared to pharmacists, greater proportions of DRPs identifiable by each of the prescribing criteria were identified by MRM.

Table 20: Classifications found by each source and classifications in common with MRM

	Beers03	Beers12	Pharmacist	PIEA	STOPP/START
Total classifications found	374	387	1680	1460	977
Number of different classification types identified by each source	23	21	113	33	42
Classifications in common with MRM	119	108	389	314	314
Total MRM classifications	2854	2854	2854	2854	2854
Percent of classifications in common with MRM classifications	4%	4%	14%	11%	11%
Percent of prescribing criteria classifications found in common by MRM	32%	28%		22%	32%

Table 21: Classifications found by each source and classifications in common with pharmacists

	Beers03	Beers12	MRM	PIEA	STOPP/START
Total classifications found	374	387	2854	1460	977
Number of different classification types identified by each source	23	21	100	33	42
Classifications in common with pharmacists	66	77	389	158	126
Total pharmacist classifications	1680	1680	1680	1680	1680
Percent of classifications in common with pharmacist classifications	4%	5%	23%	9%	8%
Percent of prescribing criteria classifications found in common by pharmacists	18%	20%		11%	13%
Jaccard Index, mean ± standard deviation	0.03 ± 0.09	0.04 ± 0.12	0.09 ± 0.12	0.05 ± 0.10	0.04 ± 0.10
Jaccard Index Range	0 – 0.67	0 – 1	0 - 1	0 – 0.67	0 – 0.67

Figure 28 also highlights the overlap of classifications identified by software sources with pharmacist classification findings. There was low overlap (identification of the same types of problems in the same patients) between pharmacists and all software or prescribing criteria using the Jaccard Index, shown in Table 21. The highest albeit low overlap was shown between MRM and pharmacists with a mean Jaccard index of 0.09 ± 0.12 across the 570 patients.

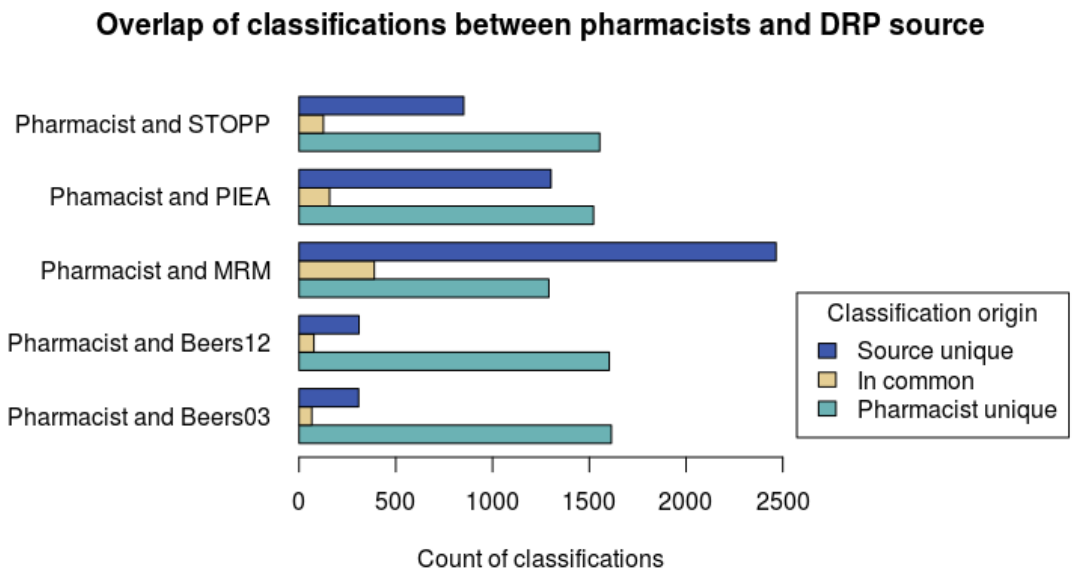


Figure 28: Classifications unique to pharmacists or computer source and classifications in common

Classification categories found by MRM and pharmacists and those found in common in the same patient cases are shown in Table 22 and Figure 29, ordered by most to least common findings.

Table 22: Classification groups found by MRM and pharmacists (570 cases)

Classification category	Total cases MRM found	Total cases pharmacist found	Total number of cases found in common	Total cases	Overlap percent of total cases
GORD	304	44	15	333	4.5%
Coagulation/platelet	208	96	39	265	14.7%
Renal impairment	211	74	39	246	15.9%
Lipidaemia	191	75	33	233	14.2%
Analgesia	147	103	24	226	10.6%
Osteoporosis	144	118	50	212	23.6%
Other cardiovascular	144	66	23	187	12.3%
Mineral/vitamin supplementation	95	74	18	151	11.9%
Respiratory	113	27	10	130	7.7%
Diabetes	104	39	18	125	14.4%
Interaction	62	59	5	116	4.3%
Toxicity	39	81	11	109	10.1%
NSAID	81	52	26	107	24.3%
Neurologic (Epilepsy / parkinsons / other)	95	14	7	102	6.9%
Undertreatment	61	34	4	91	4.4%
Anticholinergic	59	40	11	88	12.5%
Gout	76	13	11	78	14.1%
Sedative	55	31	18	68	26.5%
No indication	35	34	1	68	1.5%
Digoxin	55	20	10	65	15.4%
Other	28	19	2	45	4.4%
Constipation	36	11	4	43	9.3%
Monitoring	22	19	5	36	13.9%
Heart failure	23	6	4	25	16.0%
Dose or duration of therapy	2	3	1	4	25.0%

The classification categories with the most in common between MRM and pharmacists were *Osteoporosis* (50), *Renal impairment* (39), *Coagulation/antiplatelet* (39), *Lipidaemia* (33) and *NSAID* (26). The majority of classification categories were dominated by findings from MRM with the exception of *Toxicity*. Findings in the classification categories of *GORD* (304

vs. 44), *Gout* (76 vs. 13), *Neurological* (95 vs. 14*)* and *Heart failure* (23 vs. 6) were heavily weighted toward MRM.

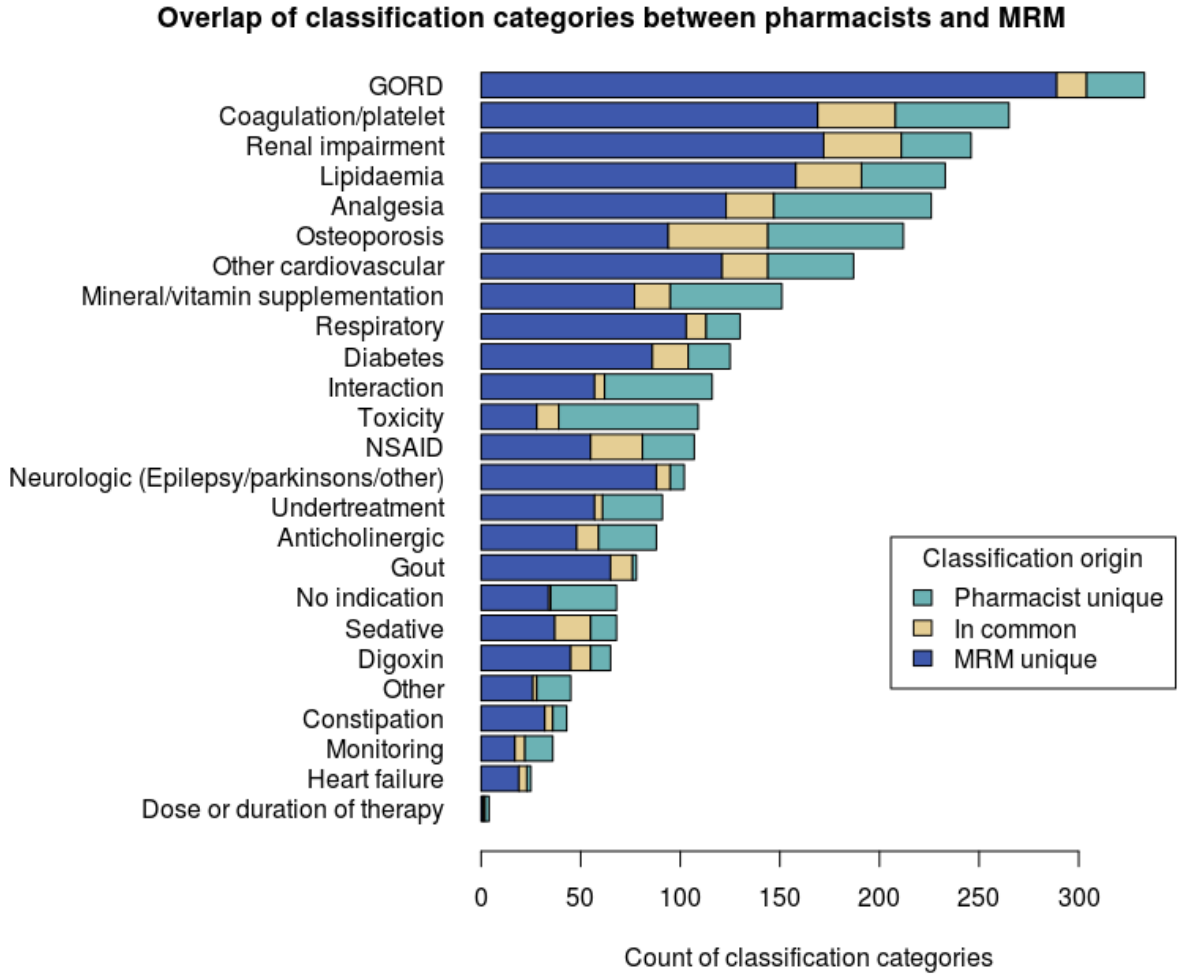


Figure 29: Classification categories in common or unique to MRM or pharmacists

Classifications in common between MRM and pharmacists are shown in Appendix 15 and in Figure 30 and Figure 31. Of 90 classification types found by both MRM and pharmacists, 68 of these had at least one patient in common.

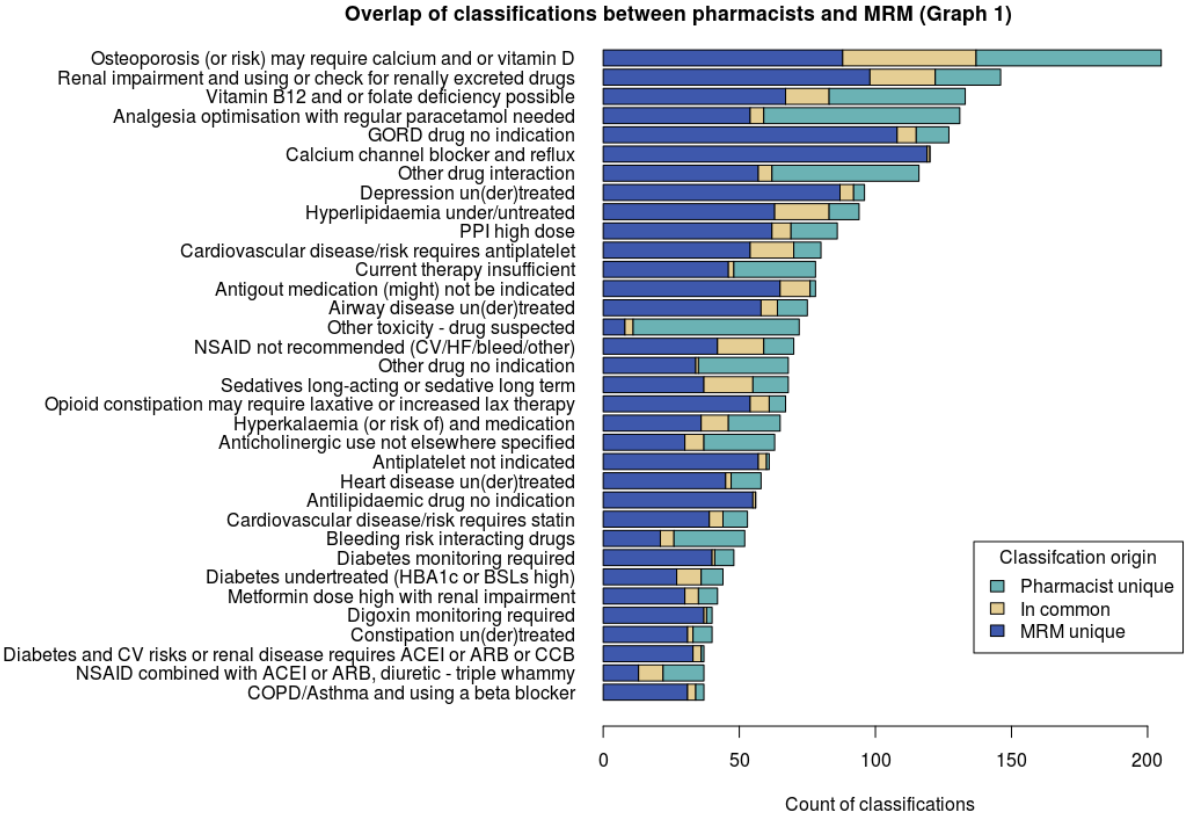


Figure 30: Overlap of common classifications between MRM and pharmacists (first 34 of 68), count of classifications equals the number of patients

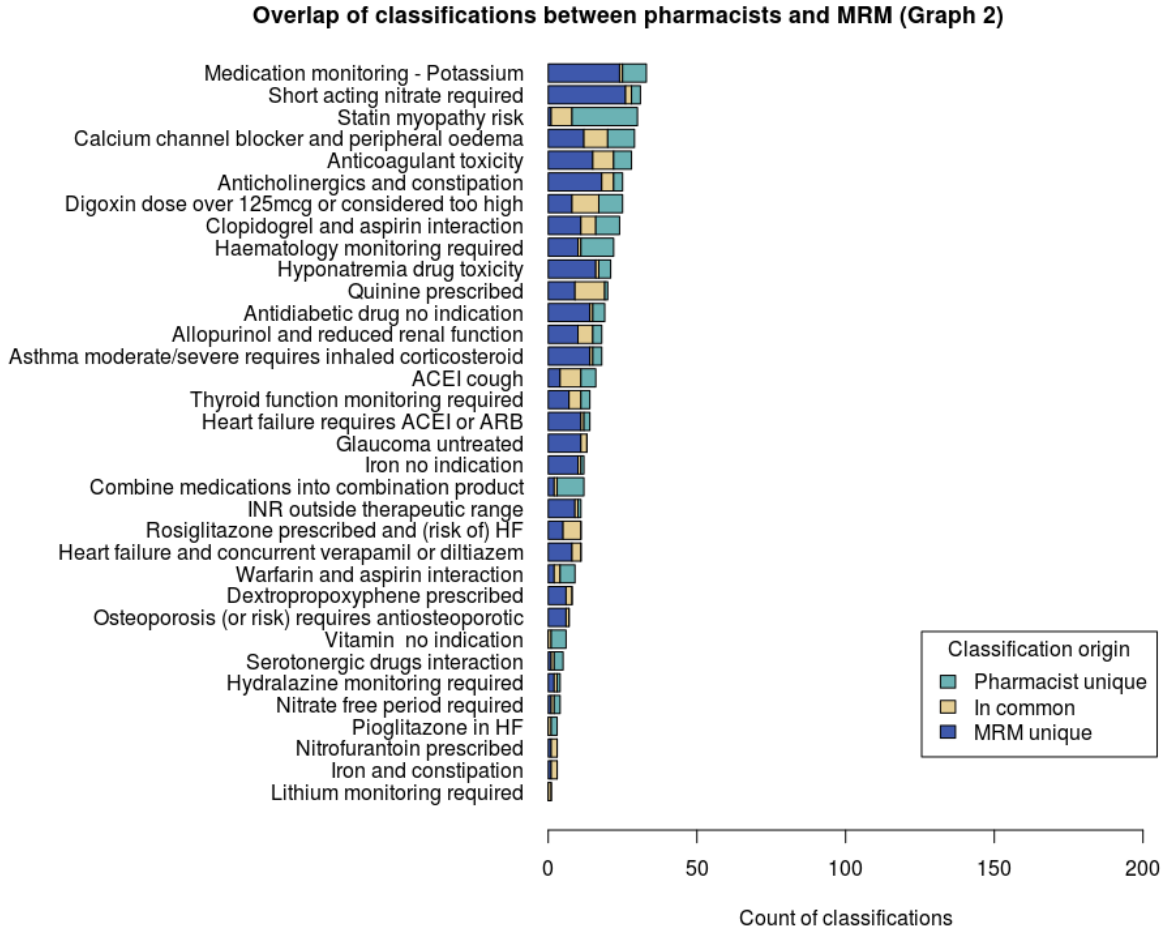


Figure 31: Overlap of common classifications between MRM and pharmacists (second 34 of 68), count of classifications equals the number of patients

The most frequent 'in common' classifications identified were: *osteoporosis (or risk) may require calcium or vitamin D* - 49, *renal impairment and using or check for renally excreted drugs* - 24, *hyperlipidaemia under/untreated* - 20, *sedatives long-acting or sedative long-term* - 18, *NSAID not recommended (CV/HF/bleed/other)* – 17, *cardiovascular disease/risk requires antiplatelet* – 16, and *vitamin B12 and or folate deficiency possible* – 16.

MRM found fifty percent or more of pharmacist findings for twenty classifications: *Digoxin dose over 125mcg or considered too high* (53%), *COPD/Asthma and using a beta blocker* (50%), A*ntiplatelet not indicated* (75%), *Sedatives long-acting or sedative long term* (58%), *Anticholinergics and constipation* (57%), *NSAID not recommended (CV/HF/bleed/other)* (61%), *Opioid constipation may require laxative or increased lax therapy* (54%),

Cardiovascular disease/risk requires antiplatelet (62%), *Diabetes and CV risks or renal disease requires ACEI or ARB or CCB* (75%), *Renal impairment and using or check for renally excreted drugs* (50%), *Antigout medication (might) not indicated* (85%), *ACEI cough* (58%), *Quinine prescribed* (91%), *Hyperlipidaemia under/untreated* (65%), *Diabetes undertreated (HBA1c or BSLs high)* (53%), *Depression un(der)treated* (56%), *Iron no indication* (50%), *Thyroid function monitoring required* (57%), *Anticoagulant toxicity* (54%), *Allopurinol with reduced renal function* (63%).

MRM found all of the pharmacists findings for ten classifications: *Heart failure and concurrent verapamil or diltiazem, Dextropropoxyphene prescribed, Rosiglitazone prescribed and (risk of) HF, Iron and constipation, Nitrofurantoin prescribed, Osteoporosis (or risk) requires antiosteoporotic, Calcium channel blocker and reflux, Glaucoma untreated, Antilipidaemic drug no indication, Lithium monitoring required*.

The scope of DRP detection is shown in Figure 32. It can be seen MRM identified a wide range of problems approaching the range of problems detectable by pharmacists, yet MRM identified a far greater frequency of problems. The various prescribing criteria identified a small variety of problem types and in smaller volume. Interestingly, the two sets of Beers criteria identified the least number of problems by both volume and problem type.

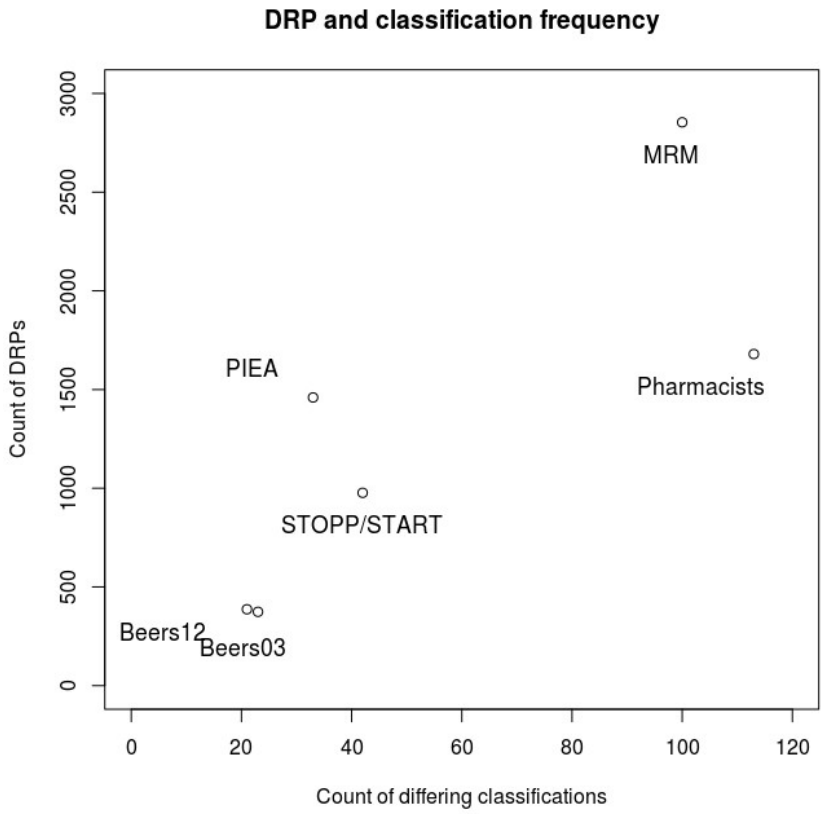


Figure 32: Frequency and variety of classifications for each DRP source

7.2.2 Descriptive classifications in 100 test cases

MRM identified 506 DRPs which were mapped to 492 classifications representing 80 different types of classification. MRX identified 1265 DRPs which were mapped to 880 classifications representing 17 different types of classification. Pharmacists identified 303 DRPs which were mapped to 297 classifications representing 79 different types of classification.

All 100 cases which were entered into MRX and aged 65 years old or over were used in this section. Classifications were summed and compared with pharmacist and MRM classifications, shown in Tables 23, 24 and 25.

Sixty of the same types of classifications were identified by both MRM and pharmacists. Five of the same types of classifications were identified by both MRX and pharmacists.

Table 23: Classifications found by each source and classifications in common with MRM findings (test cases)

	Beers03	Beers12	MRX	Pharmacist	PIEA	STOPP/START
Total other source classifications	53	68	880	297	241	156
Number of different classification types identified by each source	10	16	17	79	27	32
Classifications in common with MRM	19	21	22	69	51	54
Total MRM classifications	492	492	492	492	492	492
Percent in common MRM classifications	4%	4%	4%	14%	10%	11%
Percent of prescribing criteria classifications found in common by MRM	36%	31%			21%	35%

Table 24: Classifications found by each source and classifications in common with pharmacists findings (test cases)

	Beers03	Beers12	MRM	MRX	PIEA	STOPP/START
Total other source classifications	53	68	492	880	241	156
Number of different classification types identified by each source	10	16	80	17	27	32
Classifications in common with pharmacists	9	15	69	11	24	20
Total Pharmacist classifications	297	297	297	297	297	297
Percent in common with pharmacist classifications	3%	5%	23%	4%	8%	7%
Percent of prescribing criteria classifications found in common by pharmacists	17%	22%			10%	13%

Table 25: Classifications found by each source and classifications found in common with MRX findings (test cases)

	Beers03	Beers12	MRM	Pharmacist	PIEA	STOPP/START
Total other source classifications	53	68	492	297	241	156
Number of different classification types identified by each source	10	16	80	79	27	32
Classifications in common with MRX	25	28	22	11	18	14
Total MRX classifications	880	880	880	880	880	880
Percent in common with MRX classifications	3%	3%	3%	1%	2%	2%
Percent of prescribing criteria classifications found in common by MRX	47%	41%			7%	9%

As a percentage of the pharmacist classifications, MRM found 23%, PIEA 8%, STOPP 7%, Beers12 5%, MRX 4%, Beers03 3%. MRX identified the greatest number of classifications overall with minimal overlap of pharmacist classifications. Unlike MRX, MRM identified a smaller number of classifications yet a much greater proportion of classifications overlapped with pharmacist classifications. MRX identified the largest proportions of classifications identified by both sets of Beers criteria and the smallest proportions of PIEA and STOPP/START. MRM identified the largest proportions of the classifications found by PIEA and STOPP/START. The proportions of Beers03 and Beers12 classifications identified by pharmacists were lower than MRX and similar to MRM. Pharmacists identified more PIEA and STOPP/START classifications than MRX but less than MRM. Figure 33 displays the overlap of classifications identified by software and prescribing criteria with pharmacist classification findings.

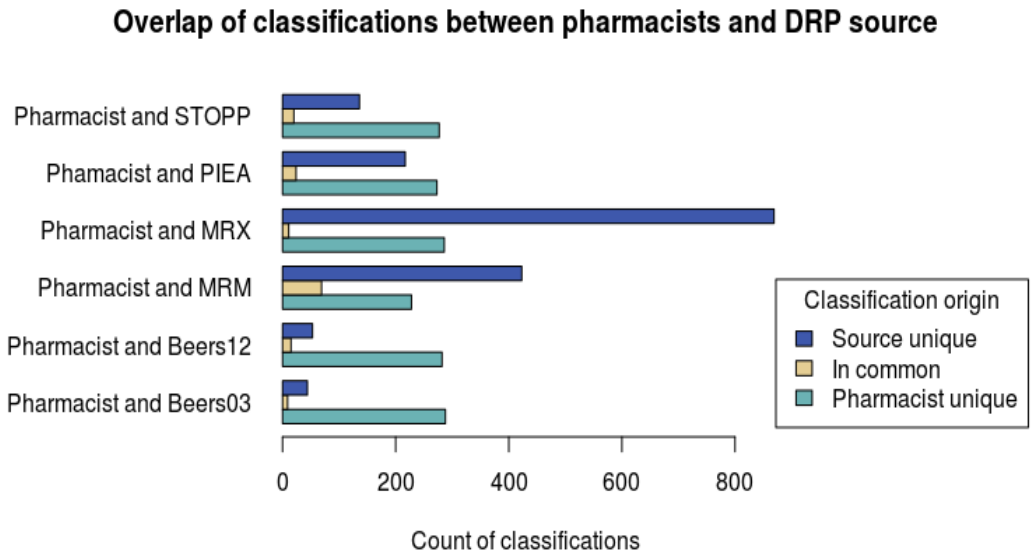


Figure 33: Classifications unique to the pharmacist or computer source and classification in common (100 test cases)

There was a low similarity between MRM and pharmacists with the identification of the same types of problems in the same patients calculated using the Jaccard index. The Jaccard index ranged from 0 (no similarity) to 0.375 (partial similarity) with a mean of 0.09 ± 0.11 across the 100 patients indicating low overlap overall. There was very low similarity between MRX and pharmacists with the identification of the same types of problems in the same patients calculated using the Jaccard index. The Jaccard index ranged from 0 (no similarity) to 0.125 (partial similarity) with a mean of 0.008 ± 0.03 across the 100 patients indicating very low overlap overall.

Classification categories in common and unique to MRX or pharmacists are shown in Table 26 and Figure 34, ordered by most to least findings. MRX identified a small scope of 20 types of potential DRP found in the elderly, these are listed in Appendix 19. However, only a small number of DRP types overlapped with pharmacist findings.

Table 26: Overlap of common classification categories between MRX and pharmacists (100 test cases)

Classification category	Total cases MRM found	Total cases pharmacists found	Total cases found in common	Total cases	Overlap percent of total cases
Other	160	3	3	160	1.9%
Anticholinergic	75	6	6	75	8.0%
Sedative	6	2	2	6	33.3%

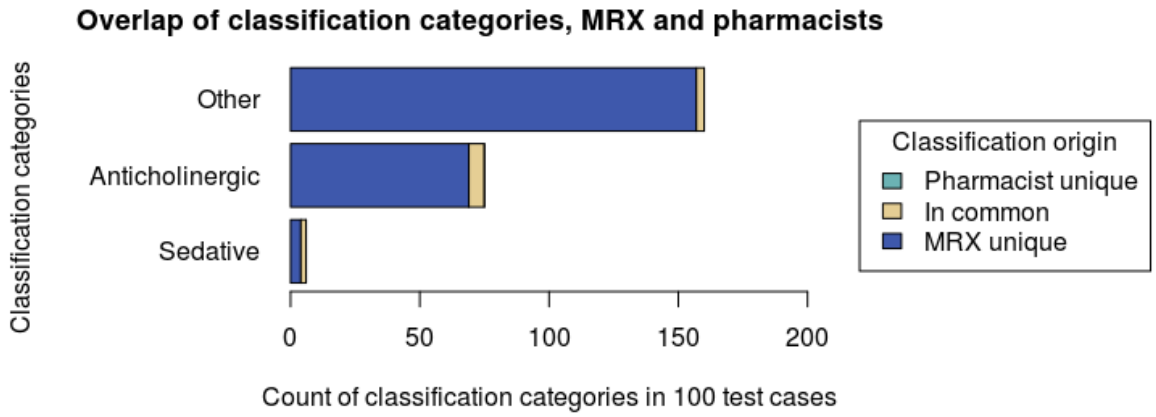


Figure 34: Overlap of theme groups between MRX and pharmacists (100 test cases)

Classifications in common between MRX and pharmacists are shown in Table 27 and Figure 35. The most common classification identified was: *Anticholinergic use not elsewhere specified* (6). This is perhaps not surprising, since anticholinergic and sedative classifications were the predominant findings by MRX. These classifications are prominent in the Beers03 criteria which were incorporated into MRX. MRX overlapped with every instance of a descriptive classifications pharmacists found in the four classifications listed in Table 27, as it based DRP detection solely on presence of specific medications. However, MRX appeared to be unrefined, or excessive, in the frequency of descriptive classifications found.

Table 27: Overlap of common classifications between MRX and pharmacists (100 test cases)

Classification	Total cases MRX found	Total cases pharmacists found	Total cases found in common	Total cases	Overlap percent of total cases
Falls risk/history and sedatives/antihypertensives/ other	100	1	1	100	1.0%
Anticholinergic use not elsewhere specified	75	6	6	75	8.0%
Other drug disease contraindication	60	2	2	60	3.3%
Sedatives long-acting or sedative long term	6	2	2	6	33.3%

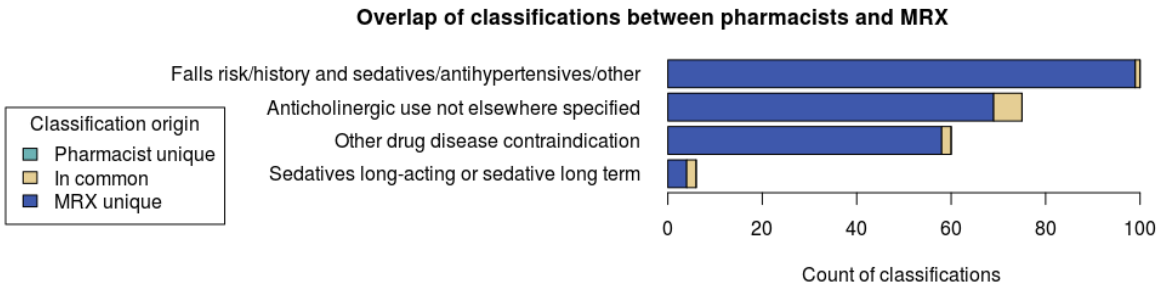


Figure 35: Overlap of classification between pharmacists and MRX, count of classifications equals the number of patients (100 test cases)

The scope of DRP detection is shown in Figure 36. It can be seen that MRM identified a wide range of problems approaching the range of problems detectable by pharmacists, yet MRM identified a far greater frequency of problems, but surprisingly still failed to identify many of the problems that pharmacists identified. MRX identified the greatest number of problems yet only identified a narrow range of problem types.

Among this reduced set of cases, the prescribing criteria again identified a smaller variety of problems and in smaller volume. Again, the two sets of Beers criteria identified the least number of problems by both volume and problem type.

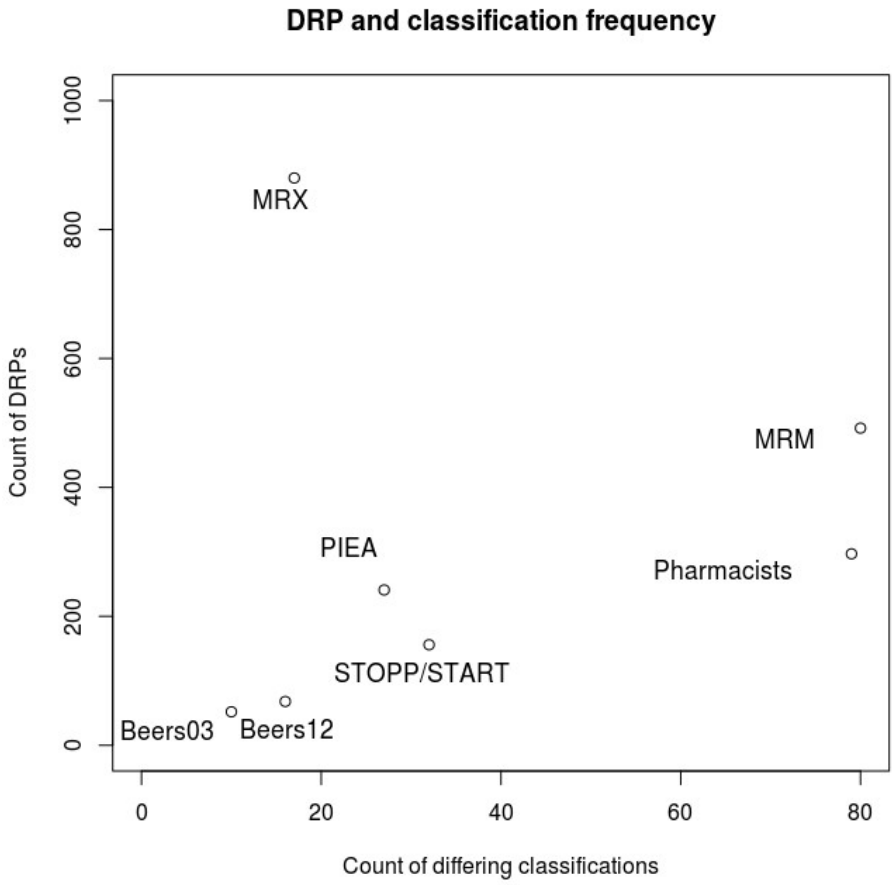


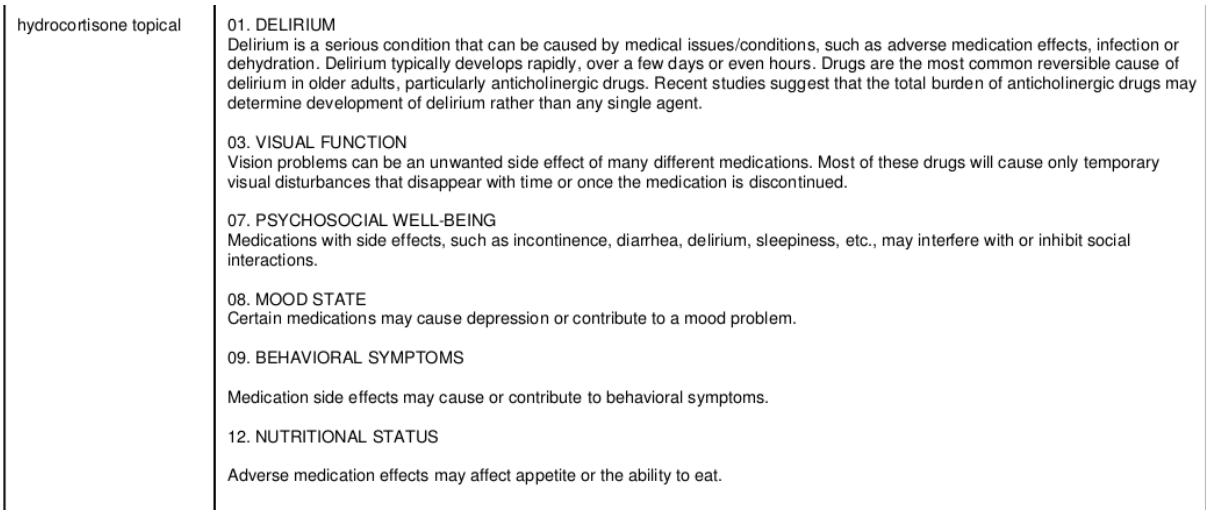
Figure 36: Number of classifications identified by type of classification for each DRP source

7.3 Discussion

Two main classification approaches were used to compare MRM, MRX and the various prescribing criteria alongside the original reviewing pharmacists' findings. The DOCUMENT classification system was a fairly straightforward although generic approach to classifying the DRPs. The development of a list of descriptive classifications that described the DRPs in greater clinical detail was more complex, requiring several iterations to come to the final version. Unlike DOCUMENT the themes provided greater insight into the similarities and differences of the DRPs associated with drug classes and medical conditions.

MRX was designed to highlight monitoring recommendations for medications, particularly sedatives and anticholinergics that may lead to problems in older people. MRX was limited to

only taking the presence of a medication into consideration, so it was only able to highlight the need to monitor for potential negative medication outcomes. Such negative outcomes were presented regardless of whether actual patient symptoms occurred and without consideration of other mitigating factors recorded in the patient's details. MRX was also deficient concerning realistic medication side effects. An extreme example was the need to monitor for delirium among patients using dermal hydrocortisone therapy, see Figure 37. This is an extremely unlikely scenario and is not even mentioned in the product information for various brands of hydrocortisone creams: e.g. Cortic-DS Cream®, DermAid Cream®, in MIMs.[281]



hydrocortisone topical	01. DELIRIUM Delirium is a serious condition that can be caused by medical issues/conditions, such as adverse medication effects, infection or dehydration. Delirium typically develops rapidly, over a few days or even hours. Drugs are the most common reversible cause of delirium in older adults, particularly anticholinergic drugs. Recent studies suggest that the total burden of anticholinergic drugs may determine development of delirium rather than any single agent. 03. VISUAL FUNCTION Vision problems can be an unwanted side effect of many different medications. Most of these drugs will cause only temporary visual disturbances that disappear with time or once the medication is discontinued. 07. PSYCHOSOCIAL WELL-BEING Medications with side effects, such as incontinence, diarrhea, delirium, sleepiness, etc., may interfere with or inhibit social interactions. 08. MOOD STATE Certain medications may cause depression or contribute to a mood problem. 09. BEHAVIORAL SYMPTOMS Medication side effects may cause or contribute to behavioral symptoms. 12. NUTRITIONAL STATUS Adverse medication effects may affect appetite or the ability to eat.

Figure 37: Problems associated with topical hydrocortisone, from MRX report

The presentation of every instance of a potential problem no matter how unlikely led to MRX having the highest frequency of DRP identification. This is evidenced by looking at those themes that overlapped with pharmacist findings. Of the few types of DRPs identifiable by MRX, MRX never failed to identify the problem when the pharmacist also identified it, however, MRX also identified the problem in a vast number of patients where the pharmacist did not agree. As an example, the descriptive classification *falls risk/history and sedatives/antihypertensives/other* was identified only once by a pharmacist. Yet, the same issue was identified in every single patient by MRX. This suggests MRX's findings tended to lack clinical relevance.

MRM identified DRPs with a much greater frequency, about double, than pharmacists (Figure 22) although MRM's findings were still quite few when compared to MRX's findings (Figure 25). Unlike MRX, MRM was able to find a broad variety of different types of problems. While the proportions of DOCUMENT category types were generally similar to the proportions found by pharmacists (Figures 23 and 26) there were some differences. Pharmacists identified more *toxicity* problems, likely due to information obtained from patient discussions. MRM was more likely to detect *drug selection* problems which may be due to more consistency and reliability in identifying DRPs, or perhaps MRM may have identified problems that lacked clinical relevance.

The scope of problem types detected by MRM was also demonstrated by the broad range of one hundred different themes assigned to MRM DRPs. Ninety of these themes were problem types similarly found by pharmacists and ten were only identifiable by MRM. Sixty-eight of these problem types were identified in the same patients by both MRM and by pharmacists. For a range of these, MRM found the same problems that pharmacists found in half to all of the patients who were identified with particular problems by pharmacists, examples are: *cardiovascular disease/risk requires antiplatelet, heart failure and concurrent verapamil or diltiazem.* This high overlap for several types of DRP suggests MRM has the capacity to identify clinically relevant problems. There were also instances where MRM identified many or all pharmacist-identified problems *and* MRM additionally identified many, more instances of the same types of problem. A good example is: *calcium channel blocker and reflux*. MRM identified the one instance where a pharmacist identified this problem, yet MRM also found this same problem in 120 more instances.

However, many of the descriptive classifications had minimal overlap, with MRM identifying many problems that pharmacists did not, and pharmacists identifying many problems that MRM did not. There are a range of reasons behind this lack of overlap. Some reasons are related to potential software limitations. An example is the descriptive classification *NSAID combined with ACEI or ARB, diuretic - triple whammy*. On examination of the instances where only pharmacists identified this problem, the root cause was that pharmacist were able to understand that a combination medication product contained two of the three dug classes with the potential for a triple whammy, whereas the MRM software did

not detect the two ingredients within the combination medication product. This was also likely the reason *therapy duplication* which was identified far more frequently by pharmacists than by MRM, however without any overlap, see Appendix 14.

Another reason pharmacist-identified DRPs did not overlap with MRM was the lack of specific detail written in several of the pharmacists' DRP descriptions. One pharmacist example was a "patient may have low vitamin D", however no reason supporting this potential problem was provided. Another vague example in a patient using both antihypertensive medication and sedating medication was "[patient] unsteady on feet and has frequent falls" which as assigned to *Other DRP pharmacist*. However MRM provided specific potential DRPs for this patient which were assigned *sedatives long-acting or long term* and *falls risk/history and sedatives/antihypertensives/other*. An additional reason was pharmacists had knowledge of complementary medicines and vitamins that seemed to be out of scope of MRM. An example was a pharmacist suggesting "concurrent use of glucosamine and metformin may reduce the efficacy of metformin".

The results so far suggest MRX identified an excessive quantity of DRPs with perhaps insufficient clinical relevance whereas MRM was less excessive in quantity, had a broad scope of problem detection and may be more clinically relevant. The Jaccard index, comparing software to pharmacist similarity, although small for each of the software products was the greatest for MRM, ten times greater than for MRX, also suggesting greater relevance.

The lack of overlap between MRM or MRX and pharmacists strongly shows that they used different approaches to identify DRPs than did pharmacists. However, this main issue is whether the DRPs that there only found by the software were important clinically relevant problems that the pharmacists were overlooking in their patient reviews. If this is ascertained to be the case then the software has a strong role to complement pharmacists reviews by adding consistency and thoroughness to the detection of DRPs in each patient.

Since the sets of prescribing criteria used in this assessment were generally developed by expert consensus and generally had references supporting the included criteria, it is not entirely unreasonable to treat them as a crude measure of clinical relevance.

However the various sets of criteria were limited in the range of identifiable DRPs. The identifiable types of problems involved *drug selection*, *over or underdose* and *undertreatment* and it was interesting to see these criteria identified drug selection problems with similar or greater frequency than did pharmacists (Figures 22 and 25). The main limitation of using prescribing criteria as a guide to clinical relevance was the inability to contextualise each criterion to the circumstances of individual patients. This may make using prescribing criteria a less than ideal surrogate for clinical relevance.

MRX identified the largest proportions of Beers03 and Beers12 findings and the smallest proportions of PIEA and STOPP/START findings. In contrast, MRM identified small proportions of Beers03 and Beers12 (as did the pharmacists) and the greatest proportions of PIEA and STOPP/START.

Several descriptive classifications identified by prescribing criteria such as: *drugs causing dyspepsia with PPI* (PIEA) - were overly sensitive to triggering conditions, see Appendix 14. When compared to other guidelines and pharmacists findings this criterion appeared to lack clinical relevance as it was not only too sensitive but too non-specific. Several criteria were unique to particular sets of criteria, example themes are: *amiodarone or other antiarrhythmic prescribed* (Beers only) and *HF or HTN and using high sodium or salt retaining drugs* (PIEA only). These criteria likely lack relevance as even pharmacists did not identify these issues. A revised and validated PIEA was published September 2012 from which the high sodium criterion was removed.[94]

As such, using prescribing criteria as an indicator for clinical relevance is not ideal and is dependent on which set of prescribing criteria are chosen. If either of the sets of Beers criteria are considered the ideal standard for clinical relevance then MRX was the best performer followed by MRM then pharmacists. This seems counter-intuitive if one considers pharmacists the most capable of identifying clinically relevant DRPs. If PIEA or STOPP/START are considered the best standards for clinical relevance then MRM is the clear winner followed by pharmacists and MRX last. Previous studies have suggested preference for STOPP/START over Beers03 in which case MRM may be the preferred software for identifying clinical relevant DRPs.[118,119] Ultimately, this approach to determine clinical relevance may be limited when considering pharmacists may be the best marker for

clinical relevance and yet pharmacists performed the worst compared to Beers guidelines findings and middling compared to PIEA and STOPP/START findings.

Limitations

There were limitations in mapping DRPs to common classifications. The most important potential limitation is the classifications may sometimes be too broad, with classifications perhaps describing differing albeit similar concepts. DRPs from differing sources may be mapped to the same concept, yet the two DRPs may differ in key factors, such as to the actual cause of the DRP. To minimise this occurrence, overlapping classifications were checked to determine if substantial differences occurred between DRPs from different sources. Iterative adjustments were made by increasing both the number and specificity of classifications to lessen the potential of conceptually different DRPs being mapped to the same classification.

8 Expert panel assessment

8.1 Introduction

Prescribing criteria were used as a surrogate for clinical relevance, but they were considered to be inferior to experts who may assess the patient's medication regimen in the full context of the available patient demographic, diagnoses and laboratory test results. To more accurately determine whether the DRPs identified by the various sources were clinically relevant, an expert panel assessment of the problems identified by MRM, MRX and STOPP/START was undertaken.

8.2 Methodology

DRP assessment by a panel of experts for all cases would not have been cost effective, so a subset of 20 cases were validated by an expert panel for clinical relevance of any identified DRPs and for appropriateness of any recommendations made. Similarly, it was necessary to reduce the number of DRPs that the experts were required to assess, so as to reduce the amount of time they would be required to spend on the task. It had already been determined through earlier analysis that STOPP/START was likely to be the most effective of the various prescribing criteria evaluated, so both Beers criteria and PIEA were removed from consideration for the purposes of this evaluation.

8.2.1 Recruitment of experts

A panel of ten experts in pharmacology was sought. The experts were to be drawn from accredited pharmacists, general practitioners and clinical pharmacologists. The intention was to have a panel made up of five accredited pharmacists and five general practitioners or clinical pharmacologists to give a mixture of professional insight. A list of experts who provided assessments for a previous project (PROMISe[282]) was used as a contact list for this project. In addition, expert recruitment was undertaken through networking and word of mouth. Each of these contacts were emailed an offer of interest to participate in this study, along with an information sheet, shown in Appendix 10. Those contacts who expressed interest were mailed consent forms to participate in the study.

8.2.2 Selection of patients

A random selection of 20 patients who were aged 65 years old or older were selected from the VALMER dataset. The STOPP/START criteria were designed for patients in this age bracket and the MRX software determined findings based on a minimum patient age of 60 years.

The selection of these cases was performed using Microsoft Access (Microsoft, Redmond, WA). For each of the cases aged 65 years old or older which had been entered into MRX a randomly generated number was assigned. The cases were ordered by random number from the lowest to highest values. From the lowest random number value every second case was selected until 20 cases were obtained. Using every case in order rather than every second case resulted in a set of cases which were not representative of the larger cohort.

8.2.3 Costs and funding

The time involved was estimated to be between 10 and 30 minutes per case, approximately 6 to 8 hours for all cases. The experts were reimbursed $500 for the time involved for completing an assessment of all 20 cases. The total cost associated with expert reimbursement was anticipated to be $5,000. Funding was obtained through Pharmacy, School of Medicine, University of Tasmania.

8.2.4 Expert Panel Survey

The 20 cases were presented via a website to be readily accessible by the experts. The website was developed by the author. Website coding was checked for potential security problems by Dr Ivan Bindoff, and the website was tested in-house for content and usability prior to being utilised by expert panel members. Appendix 11 shows illustrations of the website.

On logging in to the website, each expert was shown a list of twenty cases, numbered 1 to 20. To prevent skewing of results due to human factors such as initial enthusiasm and subsequent wane, the cases were presented in a different, randomised order for each expert.

A separate page showed each case and its associated DRP findings. All of the available information for each case was displayed for assessment: patient gender, age, date of review,

diagnoses and symptoms, laboratory test results with reference ranges, observations and medications by brand name. Where comments were available relating to diagnosis, symptoms and drug usage these were included to assist in providing a more complete picture of the case. Hovering the mouse pointer over medication brand names displayed ingredient names.

All DRPs identified by each source (HMR pharmacist, MRM, Monitor-Rx, STOPP/START) were displayed for each patient. The text was presented as accurately as possible for all sources. Pharmacist DRPs texts were obtained from transcribed summaries stored in the VALMER database. DRPs identified by pharmacists and MRM also contained recommendations to resolve DRPs. The recommendations were also assessed by the expert panel.

Each source was numbered to blind the expert assessor to the true nature of the source:

- 1 – Pharmacist DRPs
- 2 – MRM DRPs
- 3 – MRX DRPs
- 4 – STOPP/START DRPs

The blinding of the assessor to the source of each set of DRPs, whether pharmacist or computer-originated, is known as a Turing test.[283,284] An important point made by O'Keefe and O'Leary is "... there is no assumption that the human expert is correct: the third-party expert can compare, rank or criticise as deemed appropriate."[283] In practice experts may have been able to determine the identity of each source based on DRP wording, particularly in situations where software repetitively presented identically worded DRPs across cases.

The experts had two main assessment sections for each case: assessment of individual DRPs from each source and an overall assessment of the capability of each source to present relevant DRPs. The assessment items are shown in Appendix 11.

8.2.5 Assessment items for each DRP from each source in each patient

Each DRP was assessed for clinical relevance, and if recommendations were made, each DRP recommendation was assessed for appropriateness.

DRP clinical relevance was defined as: "If unresolved would have resulted in suboptimal outcome for this patient"

Appropriate was defined as "Quality expected in practice from a competent accredited pharmacist"

These definitions were displayed when the expert hovered the mouse pointer over each term.

The assessment statements were:

- "The DRP is clinically relevant in this case, i.e. if unresolved the DRP would have resulted in a suboptimal outcome (e.g. under treatment, patient harm)" Experts indicated agreement with this statement on a 5 point Likert response.
- General comment.

For pharmacist and MRM DRPs assessment of recommendations was required.

- "The recommendation for resolving this DRP was appropriate" Experts indicated agreement with this statement on a 5 point Likert response.
- If you believe there is a better recommendation to resolve this DRP, please comment.

8.2.6 Assessment items for overall opinion of each source in each patient

Expert opinion of the overall impression of each source of DRPs was sought. The experts were asked to determine the clinical relevance of each source for identifying DRPs, and where recommendations were made, the overall appropriateness of these. In addition, the experts were asked to determine whether the source displayed an excessive number of DRPs. Finally experts were asked to rate whether each source missed any DRPs that would have been relevant to each patient and to provide details of any missed relevant DRPs.

The assessment statements were:

- "Overall, this source identified clinically relevant DRPs" Experts indicated agreement to this statement using a 5 point Likert response.
- "The number of DRPs identified was excessive" Experts indicated agreement to this statement using a 5 point Likert response.
- "Clinically relevant DRPs were not identified" Experts indicated agreement to this statement using a 5 point Likert response.

- If any clinically relevant DRPs were not identified, please comment.
- General comment.

For both the pharmacist and MRM sources an overall opinion of the recommendations made was required. This statement did not apply to the STOPP/START nor to MRX as these sources only identified DRPs and did not make recommendations to resolve identified DRPs.

- "Overall, this source offered appropriate recommendations" Experts indicated agreement to this statement using a 5 point Likert response.

8.2.7 Data analysis

Expert panel responses for each of the four sources of DRPs were obtained mainly using 5 point Likert items. Normality was assessed using Shapiro-Wilk tests and Bartlett's test for homogeneity of variance. Between group Likert item responses were analysed by comparing medians and non-parametric statistical techniques, Kruskall-Wallis Tests followed *post hoc* with pairwise Wilcoxon Rank-Sum Tests using the Bonferroni correction. Inter-rater agreement was measured using Kendall's coefficient of concordance (Kendall's W) corrected for ties, where 0 is no agreement and 1 is complete agreement. Strength of rater agreement was worded according to Landis and Koch.[285] Kendall's W values can be interpreted as *poor*, *slight*, *fair*, *moderate*, *substantial* and *almost perfect* agreement, shown in Table 28.[285]

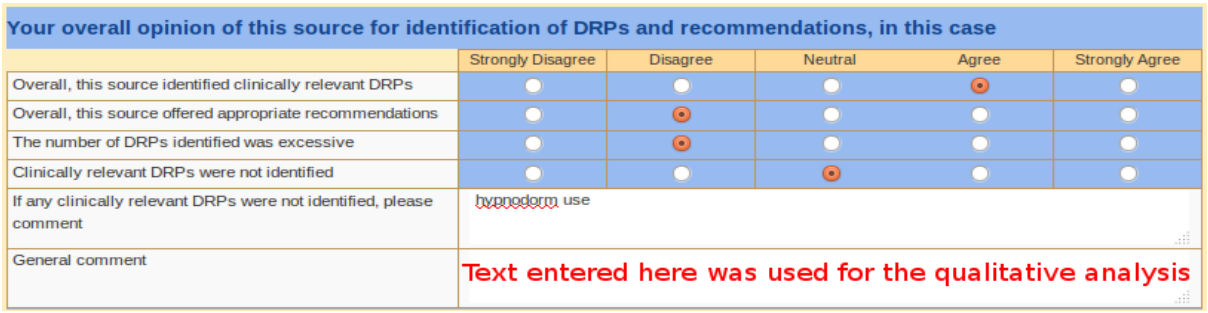
Table 28: Interpretation of Kendall's coefficient of concordance

Kendall's W	Strength of Agreement
< 0.00	poor
0.00 – 0.20	slight
0.21 – 0.40	fair
0.41 – 0.60	moderate
0.61 – 0.80	substantial
0.80 – 1.00	Almost perfect

Quantitative data analysis was performed using R, R Foundation for Statistical Computing, Vienna.[279]

Experts were able to provide narrative of their opinions for each source in each of the 20 cases. The data entry screen is depicted in Figure 38. Qualitative analysis of the expert

narratives was performed to increase understanding of the findings resulting from the quantitative data.



Your overall opinion of this source for identification of DRPs and recommendations, in this case					
	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Overall, this source identified clinically relevant DRPs	○	○	○	◉	○
Overall, this source offered appropriate recommendations	○	◉	○	○	○
The number of DRPs identified was excessive	○	◉	○	○	○
Clinically relevant DRPs were not identified	○	○	◉	○	○
If any clinically relevant DRPs were not identified, please comment	hypnodorm use				
General comment	Text entered here was used for the qualitative analysis				

Figure 38: Optional general comment text box for overall opinion

The intention of qualitative research is to find answers to questions that cannot be easily measured. Rather than finding answers based on counts or other measurements, the qualitative approach attempts to answer questions of why or how through exploring personal experiences, feelings and opinions.[286] Grounded theory is a term that describes a commonly used qualitative methodology.[287] The aim of grounded theory is to develop theory 'grounded' in the data, systematically gathered and analysed.[288]

The systematic examination of the narratives followed the basic grounded theory methodology by reading and reviewing the narratives to identify personal perspectives and assign or re-assign codes to text that reflected the meaning in the narrative.[286,287] Codes describing common concepts were grouped into categories. Revisiting and reviewing the data was undertaken to confirm assigned codes and categories were appropriate or if they needed to be changed. The intent of the review process was also to ensure the data was exhausted of new ideas and concepts, a position known as saturation.[287] The coding process was undertaken only by the author. Review and reflection of the assigned codes and code categories was undertaken to clarify and finalise the accuracy of coding. The RQDA package was used to manage and organise the data and codes.[289]

Experts were able to provide comments for each individual DRP. True qualitative analysis was not undertaken for the assessment of expert comments involving individual DRPs. On examination, comments were very specific to each individual DRP so thematic analysis was not possible.

Minimal risk ethics approval was granted through the University of Tasmania Human Research Ethics Committee to conduct this research, reference H12269. The approval letter is presented in Appendix 5.

8.3 Results

Emails were sent to 41 GPs, accredited pharmacists and specialist physicians. Fourteen experts consented to participate – two specialist physicians, two GPs and 10 accredited pharmacists. Twelve experts completed the assessment of 20 cases and two did not complete any cases, detailed in Table 29.

Table 29: Completion of cases by expert

Expert ID	Expert field	Cases completed
21	Medicine, Specialist - pharmacologist	20
22	Pharmacy	20
23	Medicine, GP and lecturer in medicine	20
24	Pharmacy	20
25	Medicine, Specialist – pharmacologist and endocrinologist	20
26	Pharmacy	20
27	Pharmacy	0
28	Pharmacy	20
29	Pharmacy	20
30	Medicine, GP	0
31	Pharmacy	20
32	Pharmacy	20
33	Pharmacy	20
35	Pharmacy	20

Table 30 shows the breakdown of the 493 DRPs for each case and DRP source. Unfortunately due to refinement of database queries to automate the STOPP/START criteria, one STOPP/START DRP concerning hypertension remained in one case, this should have been removed prior to the website going live. Secondly due to inappropriate labelling of DRPs by the author, one MRX DRP was missed from 6 cases which concerned *Psychotropic Medication Use – Anxiolytics*. However, as can be seen in Table 30, the effects of these errors were quite minor.

Table 30: DRPs shown to experts by case and DRP source, * MRX anxiolytic DRP missed, ** STOPP hypertension DRP

Case ID	Pharmacist	MRM	MRX	STOPP/START	Total
51	4	6	11	2	23
138	4	10	16*	0	30
140	6	10	15*	3	34
145	5	11	16	2	34
185	4	1	10	0	15
221	3	3	16*	0	22
297	4	13	14	5	36
312	3	2	5	1	11
313	3	3	14	4	24
323	6	5	16*	2	29
373	4	5	8	3	20
415	2	8	12	1	23
418	3	9	16*	0	28
443	2	9	14	0	25
473	5	4	17	0	26
499	4	5	15*	4	28
522	1	2	6	3	12
573	5	4	9	4**	22
615	2	7	12	0	21
639	3	8	17	2	30
Total	**73**	**125**	**259**	**36**	**493**

8.3.1 Representativeness of randomly selected cases

Twenty cases were used for the expert panel analysis, demographics, detailed in Table 31. Statistical analysis was performed to determine whether the random sample of cases for expert assessment were representative of all remaining 550 cases where patients were aged 65 or older. There were no significant differences between the two groups, shown in Table 31.

Table 31: Demographics of patients for expert panel

Demographic	Panel cases (N = 20), count or mean ± standard deviation	VALMER dataset (N = 550), count or mean ± standard deviation	Statistical analysis for representativeness
Age (years)	79 ± 8	80 ± 7	T-test, t(20.024) = 0.474, p = 0.641
Gender	Male 9 (45%) : Female 11 (55%)	Male 225 (41%) : Female 325 (59%)	Chi-squared test, X^2 = 0.018, df = 1, p = 0.893
Diagnoses	With 20 (100%) : Without 0 (0%)	With 546 (99%) : Without 4 (1%)	Fisher's Exact test, p = 1
Laboratory tests	With 13 (65%) : Without 7 (35%)	With 442 (80%) : Without 108 (20%)	Chi-squared text, X^2 = 1.955, df = 1, p = 0.162
Number of medications	13.6 ± 6.0	12.0 ± 4.3	T-test, t(19.727) = -1.241, p = 0.229
Number of diagnoses	10.0 ± 6.2	9.1 ± 5.2	T-test, t(19.984) = -0.643, p = 0.527

8.3.2 Opinion of individual DRPs identified in each case

Each of the 12 experts who completed the assessment provided responses to each of the 493 DRPs presented to them.

Clinically relevant DRPs

Likert responses to the statement "The DRP is clinically relevant in this case, i.e. if unresolved the DRP would have resulted in a suboptimal outcome (e.g. under treatment, patient harm)" were recorded for each of the 493 DRPs across the 20 cases by 12 experts. A summary is shown in Table 32.

Table 32: Opinions of clinically relevant DRPs identified by each DRP source, total (percent)

Likert response	Pharmacists	MRM	MRX	STOPP/START
Strongly agree	116 (13%)	165 (11%)	36 (1%)	59 (14%)
Agree	529 (60%)	927 (62%)	600 (19%)	253 (59%)
Neutral	162 (18%)	272 (18%)	471 (15%)	64 (15%)
Disagree	67 (8%)	121 (8%)	1112 (36%)	52 (12%)
Strongly disagree	2 (0%)	15 (1%)	889 (29%)	4 (1%)

Shapiro-Wilk tests for normality were significant for each group (each group, $p < 0.001$) and Bartlett's test for homogeneity of variance was significant ($p < 0.001$) indicating non-parametric data.

A Kruskal-Wallis Test revealed statistically significant difference across the four DRP sources (Pharmacists, N = 876, median = 4; MRM, N = 1500, median = 4; MRX, N = 3108, median = 2; STOPP, N = 432, median = 4) $\chi^2 = 2116.239$, df = 3, $p < 0.001$.

Inter-rater agreement was assessed using Kendall's coefficient of concordance (Kendall's W) corrected for ties, where 0 is no agreement and 1 is complete agreement. Agreement among experts was Kendall's W 0.59, $p < 0.001$, suggesting moderate agreement.

Wilcoxon rank-sum tests between pharmacists and software sources were performed, Bonferroni correction required $p < 0.017$ for significance. There were no significant differences between pharmacists and MRM ($W = 674591$, $p = 0.212$) and pharmacists and STOPP/START ($W = 193358.5$, $p = 0.465$). There was a significant difference between pharmacists and MRX ($W = 2284845$, $p < 0.001$).

Although MRX identified the most DRPs (259 DRPs), most of the DRPs it identified were not considered clinically relevant. In contrast, experts were of the opinion that pharmacists, MRM and STOPP found clinically relevant DRPs in a majority of cases, shown in Figure 39.

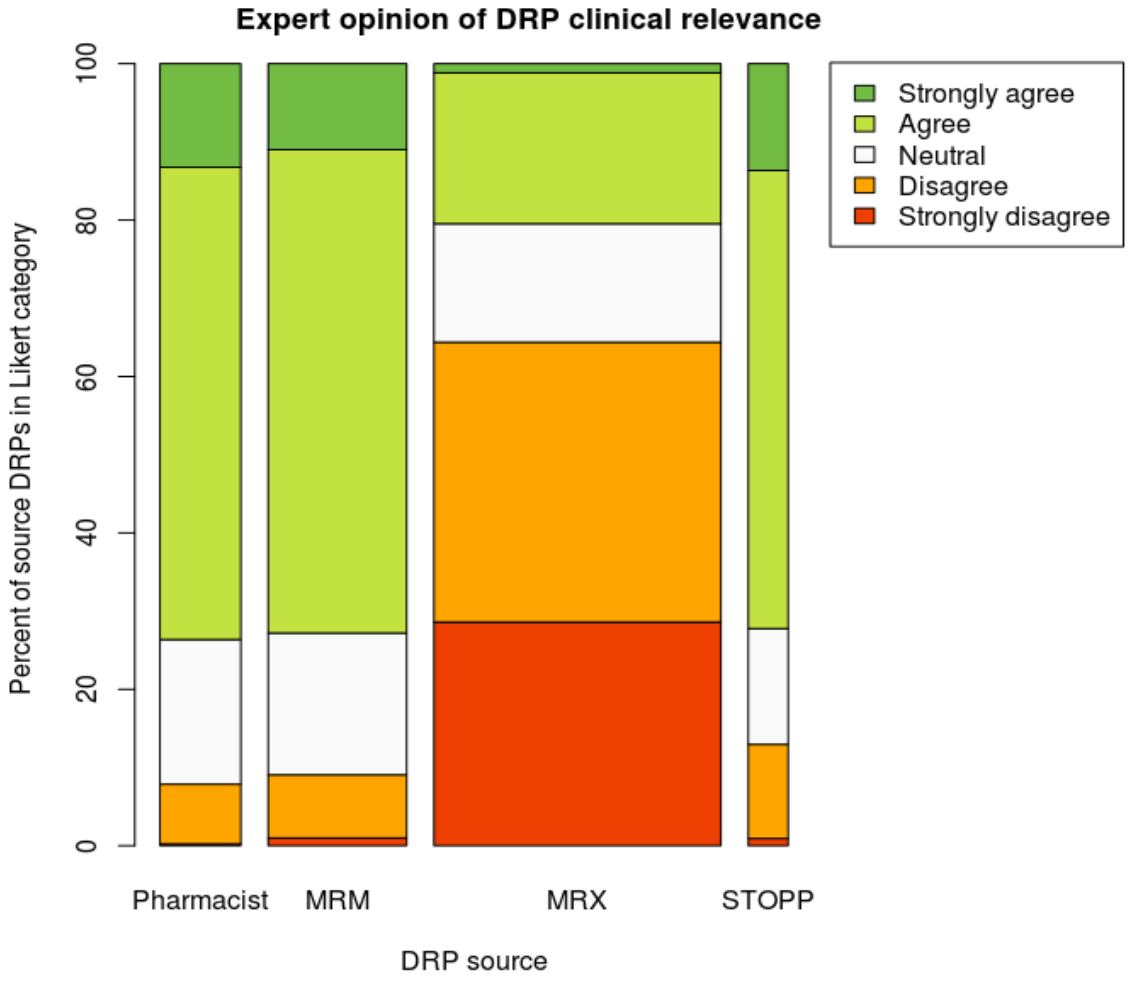


Figure 39: Expert responses of source identified clinically relevant DRPs, bar width proportional to the number of DRPs

Appropriateness of recommendations

Each of the 12 experts were presented with 73 pharmacist DRPs and with 125 MRM DRPs. For each of these DRPs responses to the statement "The recommendation for resolving this DRP was appropriate" were obtained. Responses are shown in Table 33.

Table 33: Opinions of appropriateness of recommendations for each source, total (percent)

Likert response	Pharmacists		MRM	
Strongly agree	82	(9%)	141	(9%)
Agree	380	(43%)	853	(57%)
Neutral	244	(28%)	335	(22%)
Disagree	146	(17%)	151	(10%)
Strongly disagree	24	(3%)	20	(1%)

The Shapiro-Wilk test for normality was significant for each group (each group, $p < 0.001$) and Bartlett's test for homogeneity of variance was significant ($p < 0.001$) indicating non-parametric data. A Wilcoxon rank-sum test between pharmacists and MRM was performed. There was significant difference between pharmacists and MRM ($W = 568346$, $p < 0.001$)

Experts were of the opinion both pharmacist and MRM recommendations were appropriate in the majority of DRPs. Despite this positive finding a greater proportion of MRM recommendations were considered to be appropriate whereas a greater proportion of pharmacist findings were considered to be neutral or not appropriate. There was fair agreement among experts (Kendall's W 0.29, $p < 0.001$).

The differences in proportions of findings can be seen in Figure 40. It is interesting to note not only did MRM identify more DRPs than pharmacists, but experts were of the opinion a greater proportion of MRM recommendations were appropriate.

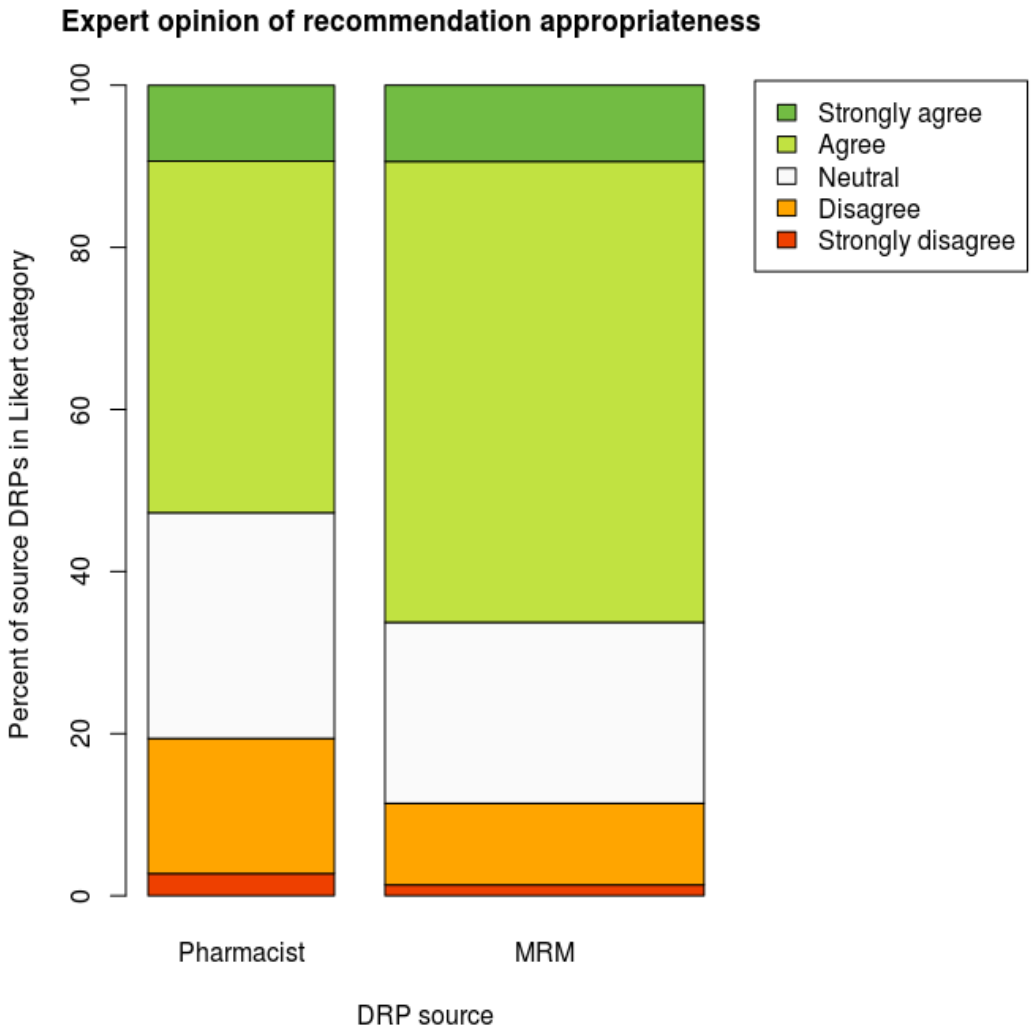


Figure 40: Expert responses of source provided appropriate recommendations, bar width proportional to the number of DRPs

Summary of individual DRP comments

There were 969 comments made for 441 of 493 DRPs. All experts provided comments, ranging from 1 comment to 186 comments (average of 81 ± 61 comments per expert). Many DRPs (N = 277) were assigned comments made by more than one expert, ranging from 2 to 8 comments (average 3 ± 1).

There were too many varied opinions concerning a wide range of DRPs to easily summarise. One DRP produced by the automation of the STOPP criteria resulted in uniform criticism from five experts – *E05 Warfarin and NSAID together (risk of gastrointestinal bleeding)* – was associated with a patient's concomitant use of warfarin and glucosamine. The comments are shown:

> "Glucosamine is not an NSAID" (by three experts)
>
> "Patient is not taking an NSAID"
>
> "Hmmm, not sure about describing glucosamine as NSAID but agree with the DRP, Could also mention fish oil"

Glucosamine is not a NSAID but is classified through the ATC classification system under classification M01AX - *Other antiinflammatory and antirheumatic agents, non-steroids*. The classification is correct, but the database query developed for this STOPP criterion did not exclude M01AX from its result set. The author was aware of the potential interactions between glucosamine and warfarin and chose not to exclude M01AX from the result set. Three case reports have identified an interaction between glucosamine and warfarin resulting in changed INR.[290]

DRPs found by MRM but missed by pharmacists

This section evaluates the DRPs that were found by MRM but were not found by pharmacists. It attempts to answer the question – did MRM identify clinically relevant DRPs that were missed by pharmacists?

A subset of DRPs were identified for this evaluation. Where MRM identified duplicate DRPs, only the 'second' DRPs were excluded (N = 9). MRM DRPs in common with pharmacist DRPs, based on the descriptive classifications described earlier, were also excluded (N = 17).

This subset resulted in 1188 opinions of 99 MRM DRPs with a range of 1 (strongly disagree) to 5 (strongly agree) and a median of 4 (agree), shown in Table 34. This shows the potential of this software to add clinical value to medication review reports.

MRM did miss the identification of 56 DRPs found only by pharmacists. This resulted in 672 opinions of 56 pharmacist DRPs, range of 1 (strongly disagree) to 5 (strongly agree) and a median of 4 (agree), details also shown in Table 34. These included pharmacist only *compliance* and *not-classifiable* DRPs.

Table 34: Opinions of clinical relevance of pharmacist DRPs missed by MRM and vice versa, total (percent)

Likert response	Pharmacists DRPs missed by MRM		MRM DRPs missed by pharmacists	
Strongly agree	80	(12%)	120	(10%)
Agree	397	(59%)	716	(60%)
Neutral	142	(21%)	230	(19%)
Disagree	51	(8%)	108	(9%)
Strongly disagree	2	(0%)	14	(1%)

A Wilcoxon rank-sum test showed no significant difference between the clinical relevance of pharmacist DRPs missed by MRM and of MRM DRPs missed by pharmacists, W = 409246, p = 0.304.

Subsetting resulted in 672 opinions of 56 recommendations from pharmacist DRPs, range of 1 to 5 and a median of 4 and 1188 opinions of 99 recommendations from MRM DRPs with a range of 1 to 5 and a median of 4. The breakdown of opinion is shown in Table 35.

Table 35: Opinions of appropriateness of recommendations arising from missed DRPs, total (percent)

Likert response	Recommendations from pharmacists DRPs missed by MRM		Recommendations from MRM DRPs missed by pharmacists	
Strongly agree	62	(9%)	108	(9%)
Agree	294	(44%)	674	(57%)
Neutral	186	(28%)	261	(22%)
Disagree	112	(17%)	128	(11%)
Strongly disagree	18	(3%)	17	(1%)

A Wilcoxon rank-sum test showed a significant difference between the clinical relevance of pharmacist recommendations from DRPs missed by MRM and of MRM recommendations

from DRPs missed by pharmacists, W = 349218, p < 0.001. There was a preference for recommendations made by MRM.

8.3.3 Overall opinion of each source in each case

For each of the 20 cases presented the experts provided opinions to three statements concerning their overall impression of each of the four DRP sources within each case. An additional statement concerning recommendation appropriateness was presented for pharmacists and MRM.

Identification of clinically relevant DRPs

Responses to the statement "Overall, this source identified clinically relevant DRPs" are shown in Table 36. The Shapiro-Wilk test for normality of each group was significant (each group p < 0.001) and the Bartlett test for homogeneity of variance was also significant (p < 0.001) indicating non-parametric data.

Table 36: Opinions of clinical relevance of each source in each case, total (percent)

Likert response	Pharmacists	MRM	MRX	STOPP/START
Strongly agree	13 (5%)	17 (7%)	0 (0%)	13 (5%)
Agree	169 (70%)	176 (73%)	30 (13%)	103 (43%)
Neutral	47 (20%)	34 (14%)	34 (14%)	72 (30%)
Disagree	10 (4%)	12 (5%)	93 (39%)	30 (13%)
Strongly disagree	1 (0%)	1 (0%)	83 (35%)	22 (9%)

A Kruskal-Wallis Test revealed a statistically significant difference between the four DRP sources (Pharmacists, N = 240, median = 4; MRM, N = 240, median = 4; MRX, N = 240, median = 2; STOPP/START, N = 240, median = 3) $\chi^2 = 368.9353$, df = 3, p < 0.001. There was substantial agreement among experts (Kendall's W 0.612 p < 0.001).

Wilcoxon rank-sum tests between pharmacists and each of the software sources were performed, Bonferroni correction required p < 0.0167 for significance. There was no significant difference between pharmacists and MRM (W = 27305, p = 0.213). There was significant difference between pharmacists and MRX (W = 51552.5, p < 0.001) with a more positive opinion of pharmacists. Similarly there was a significant difference between

pharmacists and STOPP/START (W = 37212, p < 0.001) with a more positive opinion of pharmacists.

Expert opinion of clinical relevance of DRPs produced by each source is shown in Figure 41. It can be seen experts were in agreement that pharmacists and MRM identified clinically relevant DRPs. The experts generally had an *agree* or *neutral* position regarding STOPP/START identifying clinically relevant DRPs. The experts generally disagreed that MRX identified clinically relevant DRPs.

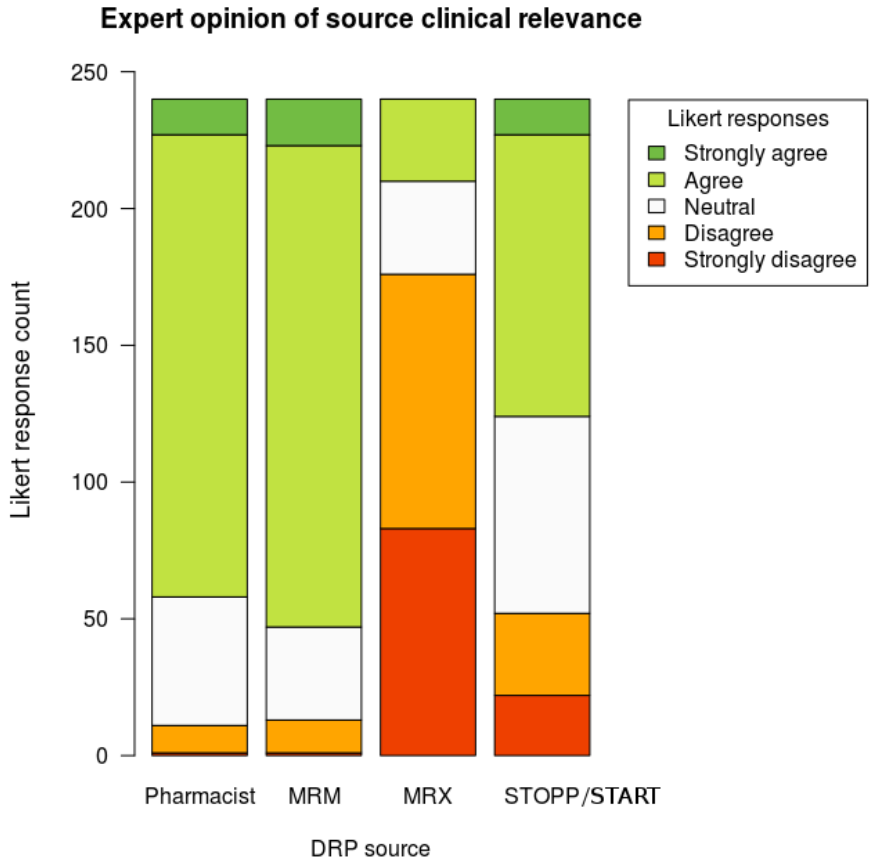


Figure 41: Expert opinion per case, source identified clinically relevant DRPs

Clinically relevant DRPs not identified

Responses to the statement "Clinically relevant DRPs were not identified" are shown in Table 37. The Bartlett test for homogeneity of variance was not significant ($p = 0.298$). The Shapiro-Wilk test for normality of each group was significant (each group $p < 0.001$) indicating non-parametric data.

Table 37: Opinions of clinical relevant DRPs missed for each source in each case, total (percent)

Likert response	Pharmacists	MRM	MRX	STOPP/START
Strongly agree	11 (5%)	8 (3%)	55 (23%)	42 (18%)
Agree	154 (64%)	108 (45%)	127 (53%)	111 (46%)
Neutral	35 (15%)	54 (23%)	37 (15%)	66 (28%)
Disagree	40 (17%)	68 (28%)	19 (8%)	21 (9%)
Strongly disagree	0 (0%)	2 (1%)	2 (1%)	0 (0%)

A Kruskal-Wallis Test revealed statistically significant difference across the four DRP sources (Pharmacists, N = 240, median = 4; MRM, N = 240, median = 3; MRX, N = 240, median = 4; STOPP/START, N = 240, median = 4) $\chi^2 = 70.5388$, df = 3, $p < 0.001$. There was fair agreement among experts (Kendall's W 0.255, $p < 0.001$).

Wilcoxon rank-sum tests between pharmacists and each of the software sources were performed, Bonferroni correction required $p < 0.0167$ for significance. There was significant difference between pharmacists and MRM ($W = 34843$, $p < 0.001$) with pharmacists missing more clinically relevant DRPs. There was significant difference between pharmacists and MRX ($W = 22891$, $p < 0.001$) with MRX missing more clinically relevant DRPs (despite finding more DRPs). No significant difference was found between pharmacists and STOPP/START ($W = 26664$, $p = 0.1204$).

Opinion of missed clinically relevant DRPs for each source can be seen in Figure 42. Across all four sources experts generally agreed clinically relevant DRPs were missed. The responses of *agree* and *strongly agree* were larger for pharmacists, MRX and STOPP/START. The responses that disagreed with the statement were larger for MRM. The STOPP/START source had a significant *neutral* response.

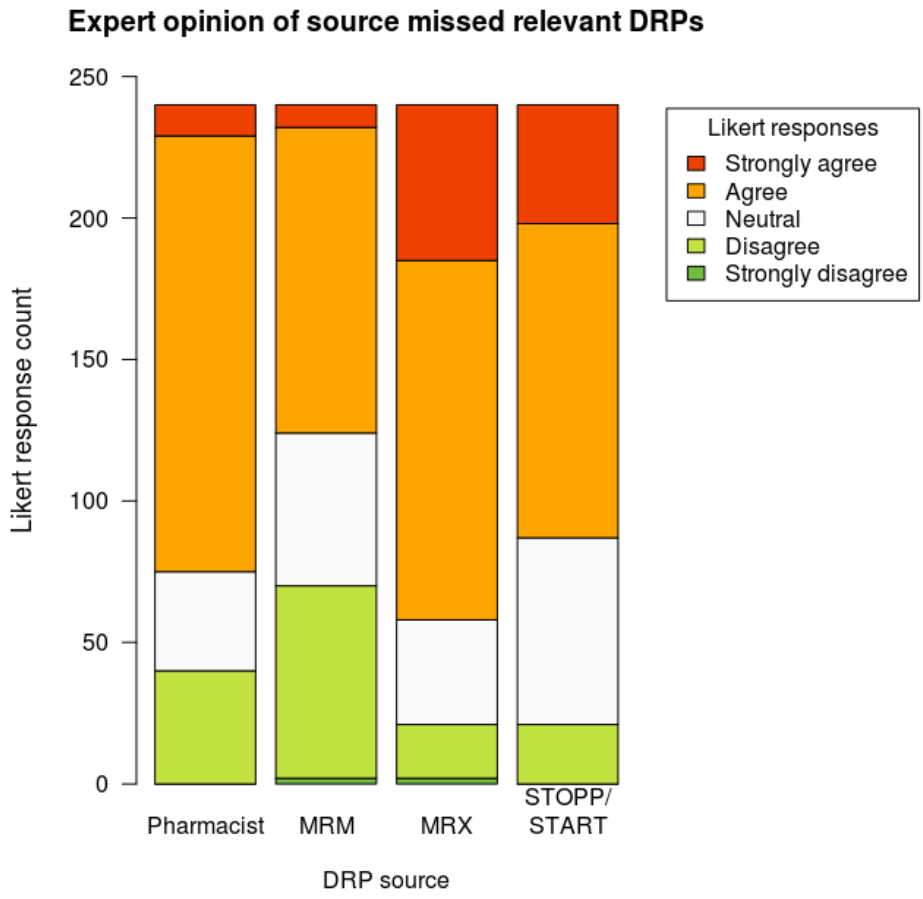


Figure 42: Expert opinion per case, source missed clinically relevant DRPs

Excessive DRPs identified

Responses to the statement "The number of DRPs identified was excessive" are shown in Table 38. The Shapiro-Wilk test for normality of each group was significant (each group $p < 0.001$) and the Bartlett test for homogeneity of variance was also significant ($p < 0.001$) indicating non-parametric data.

Table 38: Opinions of excessive findings for each source in each case, total (percent)

Likert response	Pharmacists	MRM	MRX	STOPP/START
Strongly agree	0 (0%)	8 (3%)	108 (45%)	1 (0%)
Agree	7 (3%)	39 (16%)	116 (48%)	13 (5%)
Neutral	22 (9%)	38 (16%)	8 (3%)	55 (23%)
Disagree	180 (75%)	141 (59%)	6 (3%)	118 (49%)
Strongly disagree	31 (13%)	14 (6%)	2 (1%)	53 (22%)

A Kruskal-Wallis Test revealed statistically significant difference across the four DRP sources (Pharmacists, N = 240, median = 2; MRM, N = 240, median = 2; MRX, N = 240, median = 4; STOPP/START, N = 240, median = 2) $\chi^2 = 503.3437$, df = 3, $p < 0.001$. Expert agreement was substantial (Kendall's W 0.649, $p < 0.001$).

Wilcoxon rank-sum tests between pharmacists and each of the software sources were performed, Bonferroni correction required $p < 0.0167$ for significance. There was significant difference between pharmacists and MRM (W = 20742.5, $p < 0.001$) with greater agreement MRM was excessive. There was significant difference between pharmacists and MRX (W = 1713, $p < 0.001$) with greater agreement MRX was excessive. There was no significant difference between and pharmacists and STOPP/START (W = 26976, $p = 0.166$).

Opinion about the identification of excessive DRPs produced by each source is displayed in Figure 43. Experts disagreed that pharmacists, MRM and STOPP/START presented an excessive number of DRPs. In stark contrast, opinion concerning MRX showed agreement or strong agreement that MRX presented an excessive number of DRPs, which may be associated with expert opinion of the lack of clinical relevance of this source (see above).

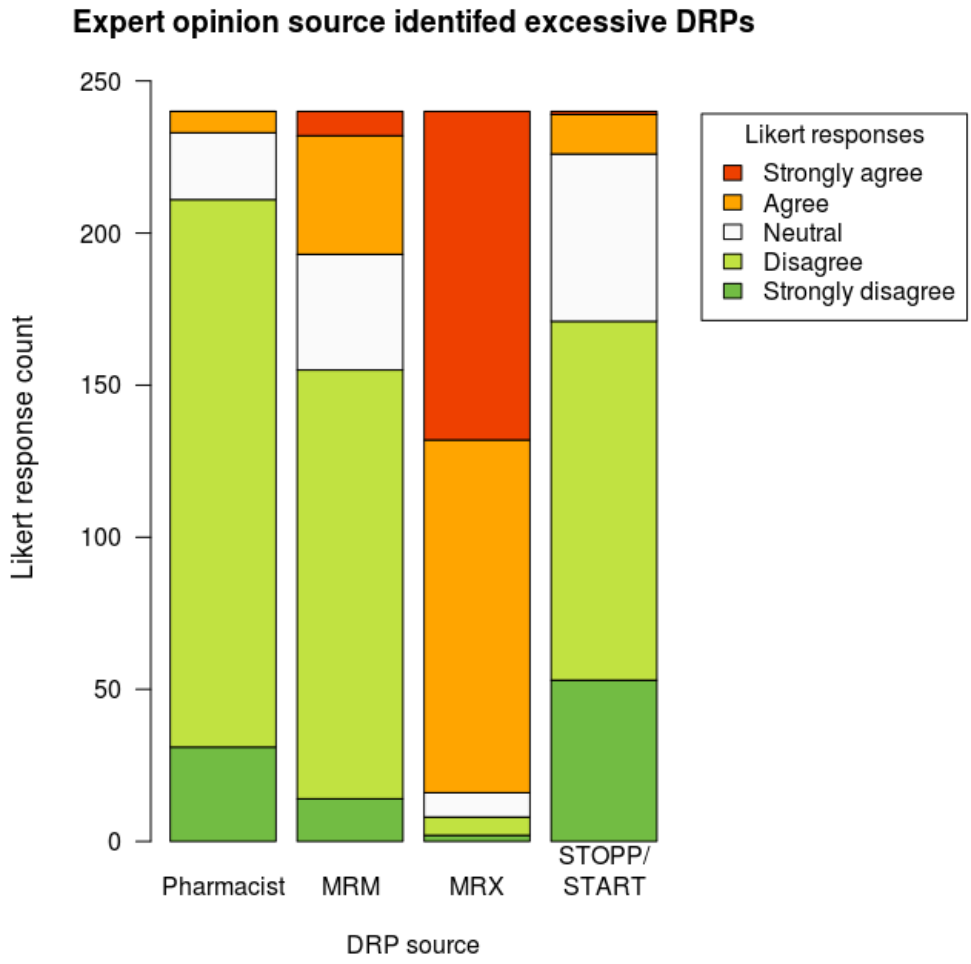


Figure 43: Expert opinion per case, source identified excessive number of DRPs

Appropriateness of recommendations

Responses to the statement "Overall, this source offered appropriate recommendations" are shown in Table 39.

Table 39: Opinions of clinical relevant DRPs missed for each source in each case, total (percent)

Likert response	Pharmacists	MRM
Strongly agree	9 (4%)	16 (7%)
Agree	130 (54%)	165 (69%)
Neutral	75 (31%)	48 (20%)
Disagree	26 (11%)	10 (4%)
Strongly disagree	0 (0%)	1 (0%)

This statement was only displayed for the pharmacist and MRM sources. The Shapiro-Wilk test for normality was significant for each group (each group, $p < 0.001$) and the Bartlett test for homogeneity of variance was also significant ($p < 0.001$) indicating non-parametric data. A Wilcoxon rank-sum test between pharmacists and MRM was performed. There was significant difference between pharmacists and MRM ($W = 23264$, $p < 0.001$). Expert agreement was fair (Kendall's W 0.285, $p < 0.001$).

Expert opinion concerning the appropriateness of recommendations provided by pharmacists and MRM are displayed in Figure 44. A majority of responses indicated agreement that each source provided appropriate recommendations, yet there was a significant difference between groups which may reflect the greater proportion of agreement with MRM recommendations compared to pharmacist recommendations. This finding is corroborated by analysis of individual DRP recommendations, see section 8.3.2.

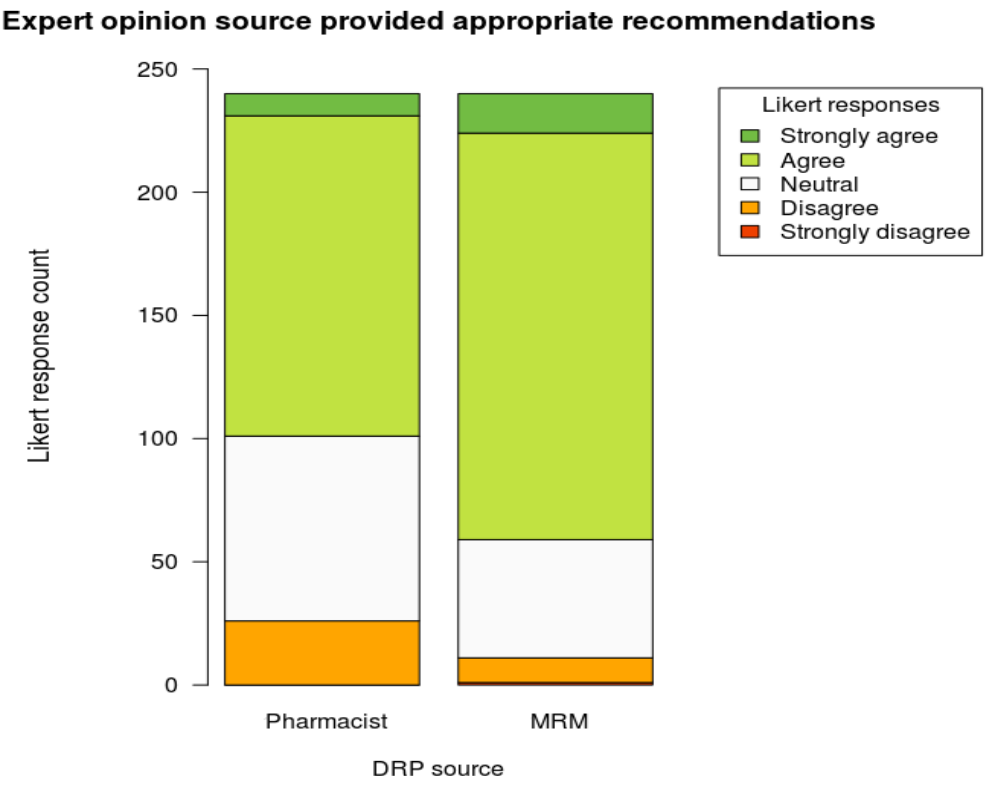


Figure 44: Expert opinions per case, source provided appropriate recommendations

8.3.4 Qualitative analysis – Overall opinion of each source

Narrative recorded by panel experts in text boxes allocated to each DRP source in each case was analysed to draw out issues surrounding each source to supplement the quantitative research.

One hundred and fifty-six comments were entered by 10 of 12 experts. Codes were assigned to the majority of the text and where possible codes were grouped under one or more code categories. Codes, code frequencies and code categories are tabled in Appendix 15. One comment appeared to relate to the wrong DRP source – a source which displayed no DRPs for the particular case had a comment relating to display of generic DRPs which appeared to follow on from comments of a previous source. Various themes emerged and are discussed below.

Clinical relevance of DRPs

Experts commented on lack of relevance of DRPs identified by each software source and possibly also pharmacist DRPs.

> "Not excessive number [of DRPs] - but I would probably have swapped some in for others!" Pharmacist, ID 31 re pharmacist

> "Many of the above identified problems were not specifically patient related but more general in nature" Pharmacist, ID 32 re MRM

> "This source did not relate issues to the specific patient" Pharmacist, ID 32 re STOPP/START

> "Golly gosh, it raised a lot of things which were likely to be completely irrelevant for this patient" Pharmacist, ID 33 re MRX

The number of comments about the lack of relevance of MRX greatly exceeded those of any other source and may be indicative of the strength of expert opinion of MRX. In addition, only MRX elicited vehement emotional responses.

> "More crap" Clinical pharmacologist, ID 25 re MRX

> "I really hate this source...." Pharmacist, ID 33 re MRX

The capacity of MRX to identify DRPs was summed up by experts in the following quotes.

> "This is not medication review but just textbook information" Pharmacist, ID 32 re MRX

> "Source is a mere regurg [*sic*] of facts, hence useless" General practitioner, ID 23 re MRX

One clinical pharmacologist identified the patient's treatment goals as an important characteristic of clinical relevance.

> "The context is not considered. This is a patient with months to live. Most of this was irrelevant to this case" Clinical pharmacologist, ID 25 re MRM (This patient was an 80

year old female with a history of congestive heart failure and multiple cerebrovascular accidents)

In contrast experts also considered each source's DRPs to be relevant in various cases. Two comments were about pharmacists.

"This source dealt with specific issues identified for the specific patient" Pharmacist, ID 32 re pharmacist

Nine comments stated MRM produced a good review of patients' DRPs, these were written mostly by a pharmacologist and a general practitioner.

"Most important clinical DRPs identified" Pharmacist, ID 29 re MRM

"Perfect assessment" Clinical pharmacologist, ID 21 re MRM

Only one comment indicated STOPP had identified relevant DRPs.

"Yes, NSAID is a problem..." Pharmacist, ID 33 re STOPP/START

Considering the strongly negative opinions of MRX, three comments disparagingly indicated this source was sometimes relevant.

"Some relevant DRP's identified - majority not relevant" Pharmacist, ID 31 re MRX

Repetition of DRPs

Experts commented on the repetitive nature of DRPs presented to them by each of the software sources. No commentary identified pharmacists being repetitious. In particular MRM elicited fifteen such comments. Experts proffered suggestions of combining repeated DRPs into single DRPs by collating similar issues into drug-specific or disease-specific DRPs.

"There were a number of DRPs that were duplicates or were different facets of a larger issue." Pharmacist, ID 28 re MRM

"Please avoid repetitive recommendation and try to combine recommendations under each disease state if possible" General practitioner, ID 23 re MRM

> "Number of DPRs excessive but if the issues about digoxin were grouped into one then the number of DPRs is not excessive" Pharmacist, ID 29 re MRM

One general practitioner commented on several occasions MRX was repetitive. Two pharmacists found STOPP/START repetitive, referring to NSAID use and benzodiazepine use. Inappropriate prescribing with these medications is listed multiple times in different contexts within the STOPP/START criteria.

> "Yes, NSAID is a problem but it's not necessary to state it in 3 problems" Pharmacist, ID 33 re STOPP/START

Preparation for an HMR interview

Two pharmacists identified the potential benefit of MRX as a preparatory list to prompt the HMR pharmacist to check for potential DRPs during an HMR interview.

> "This would be more helpful prior to conducting the HMR, as a reminder to ask about incontinence, anticholinergic side effects, assess cognition etc" Pharmacist, ID 28 re MRX

Lack of thoroughness

Pharmacists and STOPP/START identified the least number of DRPs of the four sources, 73 and 36 respectively. The STOPP/START criteria consisted of 74 implemented criteria and in 7 of the 12 cases did not identify any DRPs leading to some confusion.

> "No comments to review ???" Pharmacist, ID 32 re STOPP/START

An extension of this limited capacity to identify DRPs involved opinion of lack of thoroughness.

> "Does not identify very much at all" Pharmacist, ID 31 re STOPP/START

Similarly, comments suggested pharmacists were not thorough in identifying DRPs.

> "Significant issues with patients management of cardiovascular issues not addressed in the review. Anticoagulant issues not addressed." Pharmacist, ID 32 re pharmacist

Interestingly, lack of thoroughness was not associated with MRM or MRX.

8.4 Discussion

Discussion of the expert panel results is broken into several distinct yet overlapping sections: clinical relevance of identified DRPs, missed relevant DRPs and excessive number of identified DRPs.

8.4.1 Clinical relevance of identified DRPs

The assessment of DRPs was determined through two main methods: by expert opinion of the overall DRP findings made in each case and by expert opinion of each individual DRP in the context of each case. This assessment was corroborated by general comments made by experts concerning each DRP source.

Experts agreed on a 'case by case' assessment that pharmacists and MRM were able to identify clinically relevant DRPs. Experts also agreed to a lesser extent that STOPP/START identified clinically relevant DRPs although a pronounced portion of opinions were neutral. This neutrality likely reflected the uncertainty of how to respond in several cases in which STOPP/START did not identify any DRPs. MRX however, elicited contrary views from the expert panel. Whilst experts wrote comments about both relevance and lack of relevance of each source, the majority of comments related to the lack of relevance of MRX. Presence of potentially inappropriate medicines without considering any other variables, that is without patient, context produced excessive findings with minimal clinical relevance, in other words alert fatigue.

Interestingly, MRM found a larger number of DRPs (125 DRPs) than pharmacists (73 DRPs) and MRM's findings were considered to be as relevant as the findings by pharmacists. The implication is MRM is finding DRPs that are missed by pharmacists. There were only 17 DRPs that overlapped between pharmacist and MRM – that is the same issue identified in the same patients by both. This left a substantial number of problems detected by pharmacists and by MRM which were not able to be detected by the other. However, not only did both identify different DRPs from the other, but both MRM and pharmacists did identify clinically relevant DRPs. This is strong evidence for MRM to add consistency and thoroughness to the pharmacist's work through supplementing pharmacist findings. MRM being an automated

tool, is likely to be more consistent at finding DRPs, using the artificial intelligence case-based reasoning approach. Such consistency mirrors the results of other studies using knowledge based systems[167,178,239], including two which use similar case-based implementation as the MRM software.[167,178]

There are good reasons behind why the experts having the opinion that MRX lacked clinical relevance. MRX did not identify a wide range of issues, primarily potential problems in the elderly, such as use of anticholinergics or PIMs or areas of concern for elderly patients (falls, incontinence, visual function, etc.). The main difference of MRX was it associated many medications, no matter how unlikely, to these few issues. MRX was really nagging the pharmacist to check in every instance that the patient was actually suffering these side-effects from the medications. MRX lacked the ability to state that due to the presence of a medical condition or observation, such as frequent falling, that relevant medications were to be scrutinised for the potential to cause the observed effect. The implications of clinical relevance are strong – it is likely pharmacists will ignore software warnings when the software by and large presents irrelevant findings.

8.4.2 Missed identification of relevant DRPs

On assessment of each case, experts agreed each source failed to identify all potentially relevant DRPs. Interestingly, MRM was considered the source least likely to miss the identification of relevant DRPs. This supports the concept that MRM may be more consistent at identifying DRPs. This consistency was identified in earlier experimental prototypes.[167,178]

Experts did comment on the lack of DRPs identified by STOPP/START. This is not surprising as in 7 of the cases STOPP/START did not identify any DRPs. STOPP/START was limited to 74 specific criteria unlike the wider array of DRPs that could be identified by pharmacists or MRM, or the narrow range but copious quantity of DRPs associated with MRX. Comments were not made regarding the missed identification of DRPs for MRM or MRX.

8.4.3 Excessive number of identified DRPs

The excessiveness of findings directly links to the perception of clinical relevance. As discussed in section 8.4.1 MRM was considered to be clinically relevant however the experts perception of excessive findings was low. At the opposite end of the spectrum, MRX was not

considered to be clinically relevant, and expectantly, experts were of the opinion MRM presented an excessive number of findings.

Several experts commented on the repetition of DRPs identified by MRM, STOPP/START and particularly MRX. Pharmacists being human are most likely to be able to collate DRPs into core issues or simply present core issues and may ignore minor problems. This is not an ability that appears to have been programmed into any of the software applications.

MRM as discussed in section 5.2.3 did present 'duplicate' DRPs which were identical in concept but worded only marginally differently. MRX was repetitive due to the narrow scope of problems identified (20 problem areas were observed, see Appendix 19). Also MRX DRPs overlapped, for example, a medication may have been assigned to several of the 20 problems: *Potentially Inappropriate Medications (PIMs)* and *Anticholinergic* and *Delirium* and *Falls*. STOPP was implemented as listed in the guidelines and no attempt was made to combine similar DRP problems such as those noted by a pharmacist expert (ID 33) – "Yes, NSAID is a problem but it's not necessary to state it in 3 problems" – referring to NSAID-specific STOPP/START criteria E03, E04 and E06.

It should be noted that the MRM and MRX products, and also the prescribing criteria, are not designed to be stand-alone systems. The reviewing pharmacist is the arbiter of MRM DRPs and free to choose those DRPs considered relevant to include in GP reports, and to add DRPs of their own. Similarly, MRX and the various sets of prescribing criteria were to be used judiciously by reviewing pharmacists, to identify those patients at high risk of actual or potential DRPs.

8.4.4 DRP recommendations for resolution

Experts agreed both pharmacists and MRM provided appropriate recommendations to resolve identified DRPs. However, the recommendations provided by MRM were rated as more appropriate than the pharmacists own recommendations. There may be good reasons for the preference for MRM's recommendations to resolve DRPs. A team of medication review pharmacists develop the wording for each recommendation. This collaboration along with any feedback from pharmacist users of the system provides for a more detailed and considered recommendation than perhaps an individual medication review pharmacist may be

able to write. The advantage of the input of a team of experts is that the end user can directly draw on the expertise of the team by using the written recommendations in their own medication review reports. Individual pharmacists, particularly those who are new to writing medication review reports, may need to develop the writing skills needed for quality reports, so a tool such as MRM may be particularly beneficial to these pharmacists.

8.4.5 Qualitative analysis

Several points of interest appeared from the qualitative analysis. There appeared to be a divide between pharmacists and software sources over DRP repetition and relevance.

Each software source displayed DRPs surrounding similar concepts but did not collate and display these DRPs as consolidated problems. The STOPP/START criteria as with the MRX software simply presented any findings which were triggered by specific rules. MRM also presented repetitious findings which may be unavoidable, perhaps the AI routines may be able to be modified to minimise this effect. Pharmacists, being human, may have been able to collate aspects of DRPs into one central issue and likely ignored lesser facets, perhaps in the knowledge that when the main issue was resolved related facets would also naturally resolve.

Lack of clinical relevance or patient context was associated with each software source, although the majority of comments were related to MRX. Lack of relevance was suggested but not directly commented upon concerning pharmacists. Lack of relevance may not be surprising with simpler software implementations for identification of DRPs such as STOPP/START with the implementation of 74 criteria, or MRX triggered only by presence of specific drugs. MRM utilised a large number of rules in conjunction with patient-specific information, but still lack of relevance was commented upon. Contrarily, clinical relevance was also associated with each software source. In particular MRM was considered in particularly favourable light with numerous comments, particularly from one clinical pharmacologist, indicating both the identification of DRPs and recommendations for resolving DRPs were good.

Experts did express the lack of thoroughness of pharmacists in several reviews, suggesting pharmacists did not identify all the relevant DRPs in cases and (or) more pertinent DRPs

could have been identified. Lack of thoroughness was also an issue for STOPP/START. This is not surprising considering the limited set of criteria which could be applied to the cases.

8.4.6 Summary

The DRP findings and recommendations by pharmacists were the baseline against which software was measured. It is reassuring the experts agreed that pharmacists did identify relevant DRPs in the majority of cases and that they did provide appropriate recommendations.

Pharmacists were not considered to have found an excessive number of DRPs, indeed they were thought to have missed some relevant DRPs. This was similar to a finding in a study by Martins *et al.* in which the CDSS was considered to be more thorough.[239] Between pharmacists and MRM there were only a few instances where the same DRPs were identified in the same patients. Even so, both MRM and pharmacists were each considered to have identified clinically relevant DRPs. This finding sheds light on the lack of overlap uncovered in the analysis in Chapter 7 using descriptive classifications. Both pharmacists and MRM are finding important but different problems in the patients under examination. This is a key finding as it shows that MRM is a tool that can complement the work of pharmacists. It also highlights the fact that software such as MRM cannot replace a pharmacist's knowledge as there are many factors and nuances outside MRM's ambit.

MRX was not favoured by the experts. MRX was thought to lack clinical relevance and was described as "... not medication reviews but just textbook information". The potential for preparing questions for an HMR interview was noted "This would be more helpful prior to conducting the HMR, as a reminder to ask about incontinence, anticholinergic side effects, assess cognition etc".

Unlike MRX, he experts thought MRM and STOPP/START were also able to identify relevant DRPs. The main difference when compared to pharmacists was the number of DRPs identified. STOPP/START found a much smaller number of DRPs whereas MRM found a much greater number of DRPs than pharmacists.

STOPP/START have a small set of criteria, essentially a small scope for problem identification, yet it has been shown the criteria can be successfully automated for detection

of relevant DRPs. MRM on the other hand has a wide scope for problem identification, identifying a larger number of DRPs than STOPP/START or pharmacists. The results suggest MRM may be more consistent than pharmacists at identifying relevant DRPs. Such results concur with previous investigations involving the prototype artificial intelligence software.[167,178]

The combination of the identification of a wide range of clinically relevant DRPs and provision of appropriate recommendations rendered a satisfactory measure of confidence in the decision support output of MRM. Additionally, whilst MRM did identify more DRPs than pharmacists its did not appear to do so at the expense of causing alert fatigue, in fact the identification of a larger number of relevant DRPs per patient highlighted the support such a tool can provide to pharmacists conducting HMRs.

9 MRM user survey

9.1 Introduction

Other assessments undertaken within this thesis examined the type, frequency and clinical relevance of DRPs identified by software. An important complementary factor is the acceptance, or trust, placed in the software by the end user – the medication review pharmacist. Pharmacist acceptance of such software may be closely associated with the capacity of the software to identify a suitable number of clinically relevant DRPs. Pharmacist acceptance of software may likely also affect the inclusion of software identified DRPs in the medication review report that is ultimately sent to the GP.

The Technology Acceptance Model (TAM) – a model based on the theory of reasoned action to explain actual acceptance and use of technology is made up of two central and measurable components – usability and perceived usefulness, see section 3.6.

Several general purpose scales have been developed to assess technology usability including: Software Usability Measurement Inventory (SUMI)[291], System Usability Scale (SUS)[292], Summated Usability Metric[293], Usability Magnitude Estimation.[294] Perceived usefulness is the second core constituent of the TAM, helping to predict acceptance and use of technology. Perceived usefulness has been defined as "...the degree to which a person believes that using a particular system would enhance his or her job performance."[195]

9.2 Methodology

Pharmacist opinion of the decision support capabilities of the MRM software was sought. This company was locally based and readily approachable. The MRX software company was not approached as the company was located in the USA and the company was superseded by MedOptz during February 2013, see Appendix 3.

9.2.1 Recruitment of pharmacists

Staff from Medscope Pty. Ltd. were approached to send emails to subscribers. An email was prepared which presented the details of the study, an attached information sheet (see Appendix 12) and a link to the online survey.

9.2.2 Survey development

A survey was developed to obtain pharmacist opinion of factors associated with the use of MRM. Several sections addressed various software use factors, screen-shots of all the survey questions are shown in Appendix 13. The survey was prepared using LimeSurvey version 2.00+ (www.limesurvey.org). Survey items are discussed under the following subheadings.

Pharmacist background and intended use of software

This section covered pharmacist medication review experience, use of the software to prepare patient interview questions and use of software to include software-identified DRPs in medication review reports presented to GPs.

Data entry into MRM

The ability of MRM to identify DRPs is linked to the availability of information to assess. One question asked the pharmacists whether patient data was entered manually or through an automated process. For manual data entry questions were asked of the completeness of data that was available to be entered for patient medications, medical conditions, laboratory test results and observations.

System usability scale

Software must be relatively easy to use if people are likely to make use of it, see section 3.6. Several scales have been developed to assess product usability including: Software Usability Measurement Inventory (SUMI)[291], System Usability Scale (SUS)[292], Summated Usability Metric[293], Usability Magnitude Estimation.[294]

The SUS was chosen because it was freely available and quick to complete with only 10 statements producing a Likert scale score ranging from 0 to 100.[292] Questions are shown in Appendix 13. How to score the SUS is quoted:

> 'To calculate the SUS score, first sum the score contributions from each item. Each item's score contribution will range from 0 to 4. For items 1,3,5,7,and 9 the score contribution is the scale position minus 1. For items 2,4,6,8 and 10, the contribution is 5 minus the scale position. Multiply the sum of the scores by 2.5 to obtain the overall value...'[292]

The SUS has been applied to a variety of technology including software[295] and has been shown to correlate closely with the SUMI.[296] A score of 70 or more indicates good usability, illustrated in Figure 45.[295]

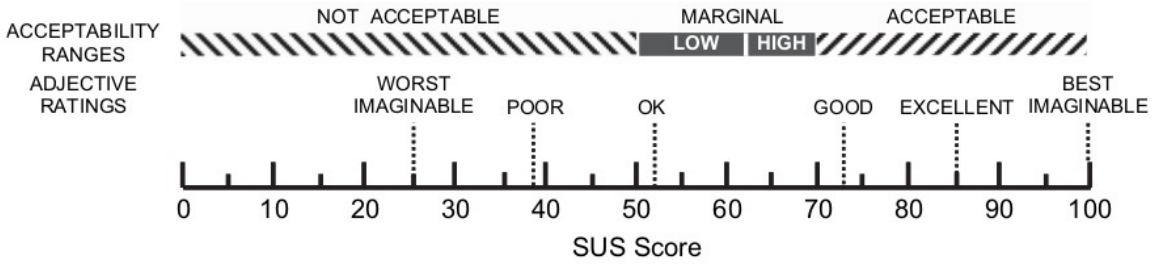


Figure 45: Interpretation of SUS score reproduced from Bangor *et al*.[295]

The original SUS used the word "cumbersome" in statement 8. This word was replaced with the suggested word "awkward".[295,297] Testing undertaken by Finstad and by Bangor *et al*. found some participants were unclear of the meaning of "cumbersome".[295,297] The statements are shown in Appendix 13.

Perceived usefulness score

The MRM software organises and stores patient and medication review details as well as being CDSS. The objective of this assessment was to examine the perceived usefulness of the CDSS component of this product rather than the product overall. A short Likert scale for perceived usefulness, scored using a mean of statement scores, was developed by Davis.[195] Higher mean scores indicate greater perceived usefulness.[195]

Brinkman *et al.* applied the perceived usefulness scale to components within software as opposed to the software overall and found the scale was able to be used to assess individual components that make up software.[298] Mean scores of more than 3.5 imply positive opinion of perceived usefulness whereas mean scores below 3.5 indicate negative opinion.

The original "CHART-MASTER" wording was replaced with "MRM decision support" shown in Appendix 13.

Pharmacist opinion of decision support

Five statements were presented to pharmacists requiring responses of *strongly disagree* to *strongly agree* using 5 point Likert items. Four of these statements matched the statements presented to the expert panel, see section 8.2.6. The intention was to compare the pharmacist MRM user responses with the responses from the expert panel.

The matching statements were:

- "Overall, this source identified clinically relevant DRPs" Pharmacists indicated agreement to this statement using a 5 point Likert item response.
- "The number of DRPs identified was excessive" Pharmacists indicated agreement to this statement using a 5 point Likert item response.
- "Clinically relevant DRPs were not identified" Pharmacists indicated agreement to this statement using a 5 point Likert item response.
- "Overall, this source offered appropriate recommendations" Pharmacists indicated agreement to this statement using a 5 point Likert item response.

An additional statement was:

- "MRM identifies clinically relevant drug-related problems which you may have overlooked" Pharmacists indicated agreement to this statement using a 5 point Likert response.

User satisfaction with MRM

Pharmacists' satisfaction with the software was assessed based on questions from a frequently cited article by McDougall and Levesque.[299] The authors examined the relations between core service quality, relational service quality and perceived value, and customer satisfaction. Core service quality was defined by the authors as "the basic service, 'contracted for' or promised" and relational service quality was defined as "the way in which the service was delivered". Core service quality and perceived value were the main factors associated with satisfaction. Satisfaction in turn led to loyalty to a service (or product) and non-intention to switch to another service (or product), illustrated in Figure 46.

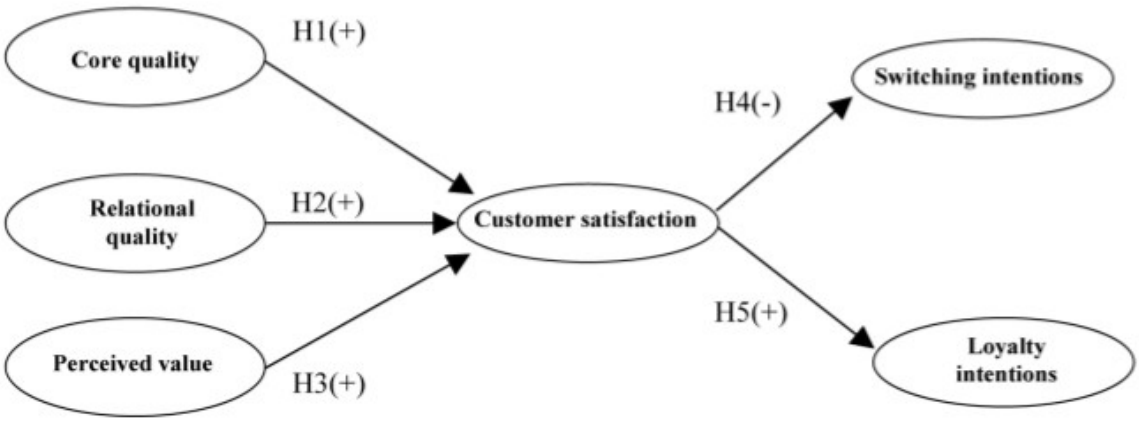


Figure 46: Proposed drivers of customer satisfaction and future intentions, McDougall and Levesque[299]

Core service quality was assessed as "How would you rate the assistance MRM software provides for managing your medication reviews, 1:terrible to 100:best" based on an example from McDougall and Levesque "If an ideal rating was 100 percent, how would you rate the dentist on: technical ability?". Perceived value was assessed using a 7 point Likert item as "Overall MRM offers good value for money" based on the example "The dentist offered good value for money". Satisfaction was assessed using a 7 point Likert item as "MRM meets my expectations" based on the example "The dentist met my expectations". Questions are shown in Appendix 13.

9.2.3 Data analysis and ethics

Results from the SUS, perceived usefulness and core service quality were presented as histograms. Opinions of the decision support were presented as tables and results were compared with expert panel results using either chi-square or Fisher's Exact Test. Five point Likert item responses were presented as median and range. Shapiro-Wilk tests for normality were performed for the SUS, perceived usefulness and core service quality. Various factors such as years of pharmacy practice and years accredited for medication review, gender, SUS, perceived usefulness, opinions of decision support and software satisfaction were examined for correlations using either Kendall's tau-b (for one or two ordinal variables taking tied ranks into account) or Spearman's rho, (for interval and continuous variables which are not normally distributed).[300]

Correlation tests were performed using Spearman's correlation test for non-parametric continuous variables and Kendall's tau-b correlation test for ordinal data with many tied values.[300] Correlation coefficients were interpreted according to Swinscow[301] shown in Table 41. Plots of correlation tests are shown in Appendix 20.

Table 40: Interpretation of correlation coefficient

Correlation coefficient range	Correlation strength
0.00 – 0.19	Very weak
0.20 – 0.39	Weak
0.40 – 0.59	Moderate
0.60 – 0.79	Strong
0.80 – 1.00	Very strong

Text entry was provided to obtain user comments regarding data entry and a *final comments* text entry was provided for any additional comments. True qualitative analysis was not undertaken for the assessment of data entry comments as too few comments were received.

Qualitative analysis of the *final comments* narrative was performed to ascertain additional facets of information to add support or refute results acquired though quantitative analyses. This was conducted in the same manner as described in section 8.2.7. The RQDA package was used to assist with this activity.[289]

Ethics approval was obtained for the MRM user survey. Minimal risk ethics approval was granted through the University of Tasmania Human Research Ethics Committee to conduct this research, reference H13161. The approval letter is presented in Appendix 5.

9.3 Results

Emails were sent on Friday 12th April 2013 to 335 present and past pharmacist subscribers of MRM software. The pharmacists were asked to complete an online survey of the MRM software by the end of May 2013. Thirteen email addresses were invalid providing a pool of 322 potential participants. After 10 incomplete responses were excluded, 60 fully completed responses were received, a response rate of 19 percent.

9.3.1 Pharmacist Background

The majority of respondents were female with a mean of 22 years of pharmacy practice and a mean of 8 years medication review practice, shown in Table 41. One respondent provided percentage responses exceeding 100 percent for two questions involving the proportion of HMRs and the proportion of residential medication management reviews (RMMRs)[302] performed using MRM. The same respondent also provided the highest response for the number of HMRs performed over the last 12 months (900). These specific responses were excluded from analyses. This respondent otherwise provided responses that were not exceptional.

Table 41: Pharmacist background

Demographic variable	Result, count, median and range or mean ± standard deviation
Gender	Female: 41 Male: 19
Number of years of pharmacy practice	22 ± 12 years
Number of years accredited for medication reviews	8 ± 5 years
HMRs conducted over the last 12 months	Median 50, range 0 to 900
Percent of HMRs completed using MRM	86 ± 27
RMMRs conducted over the last 12 months	Median 0, range 0 to 1000
Percent of RMMRs completed using MRM	64 ± 44 (excluding 32 pharmacists who did not do any RMMRs)
Include MRM-identifed DRPs in report	Median: Often (range Always to Rarely)
Include MRM-identified DRPs to prepare interview	Median: Sometimes (range Always to Never)

Pharmacists performed a median of 50 HMRs with the majority using MRM for HMRs, shown in Table 41 and Figure 47. Only one pharmacist indicated no HMRs were performed. Pharmacists performed a median of zero RMMRs over the last 12 months, over half of the respondents (N = 32) indicated no RMMRs were performed. These pharmacists exclusively performed HMRs. The 28 pharmacists who did perform RMMRs used MRM for the majority of their reports, shown in Table 41 and Figure 48.

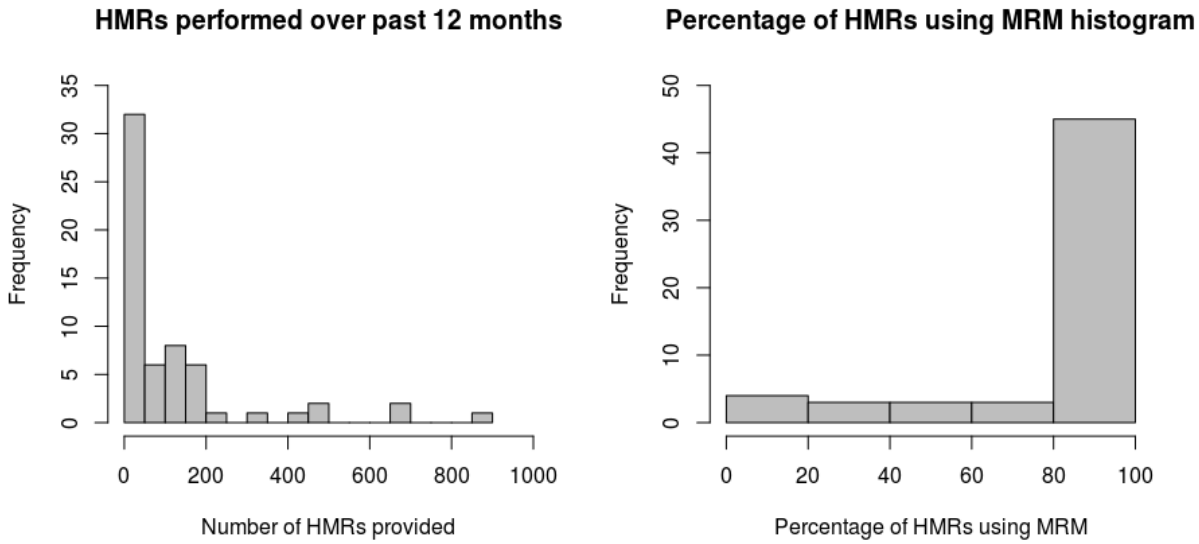


Figure 47: Histograms of HMRs performed over the last 12 months and the proportion performed using MRM

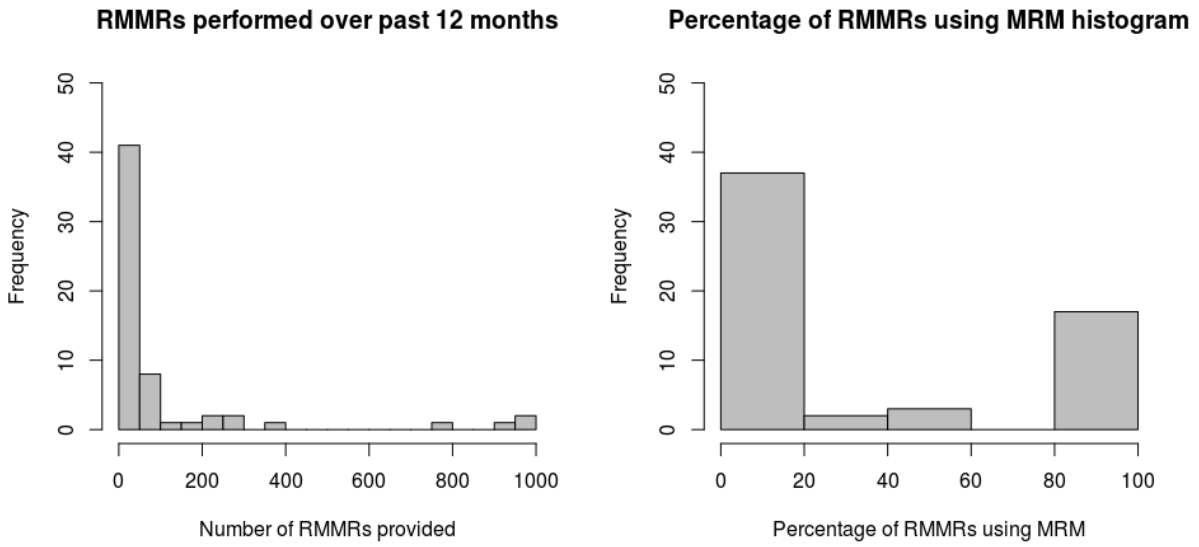


Figure 48: Histograms of RMMRs performed over the last 12 months and performed using MRM

High numbers of HMRs and RMMRs were entered by several pharmacists, the validity of these could not be confirmed. Pharmacists who provided higher numbers of HMRs generally focussed on HMR services and similarly pharmacists who provided higher numbers of RMMRs generally focussed on RMMR services shown in Figure 49.

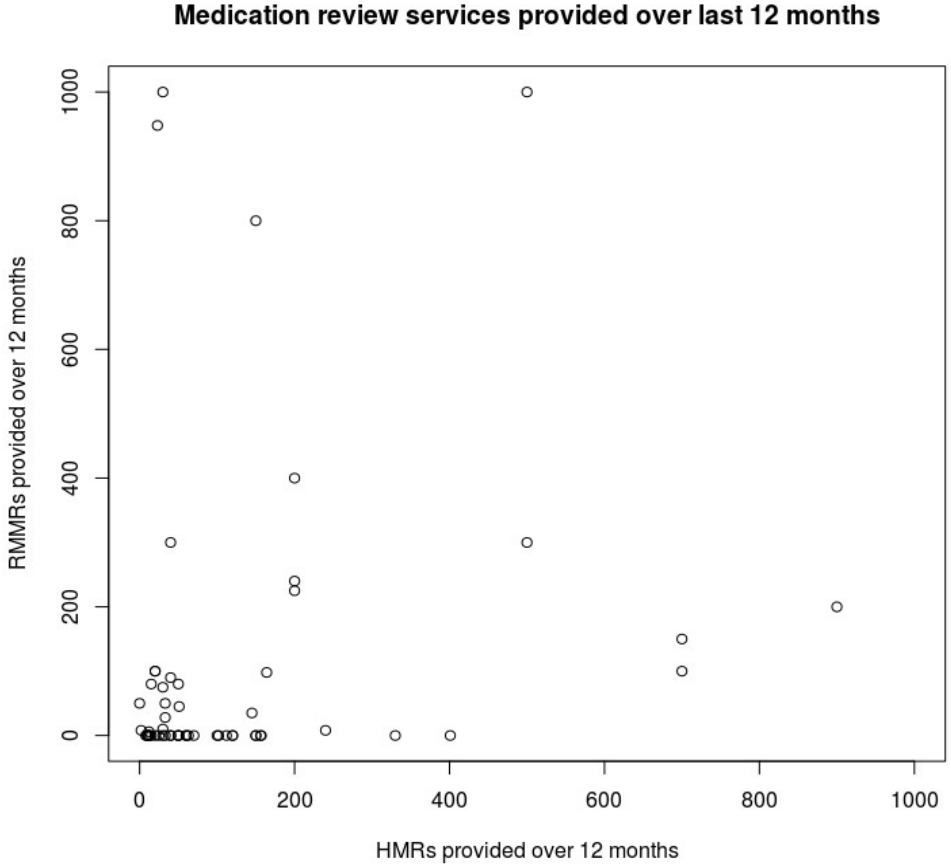


Figure 49: Medication review services provided over the last 12 months

A larger proportion of pharmacists (45%) always or often used MRM DRPs to prepare for a patient interview. A smaller proportion (24%) sometimes used MRM DRPs. A third of pharmacists (32%) used MRM DRPs rarely or never to prepare for patient interviews. Results are shown in Figure 50 and Table 41.

The use of MRM DRPs for reports was different to the use of MRM DRPs for preparing patient interviews. The majority of pharmacists (65%) included MRM DRPs always or often

in their medication review reports. Another 30% sometimes included MRM DRPs in their reports. Results are shown in Figure 50 and Table 41.

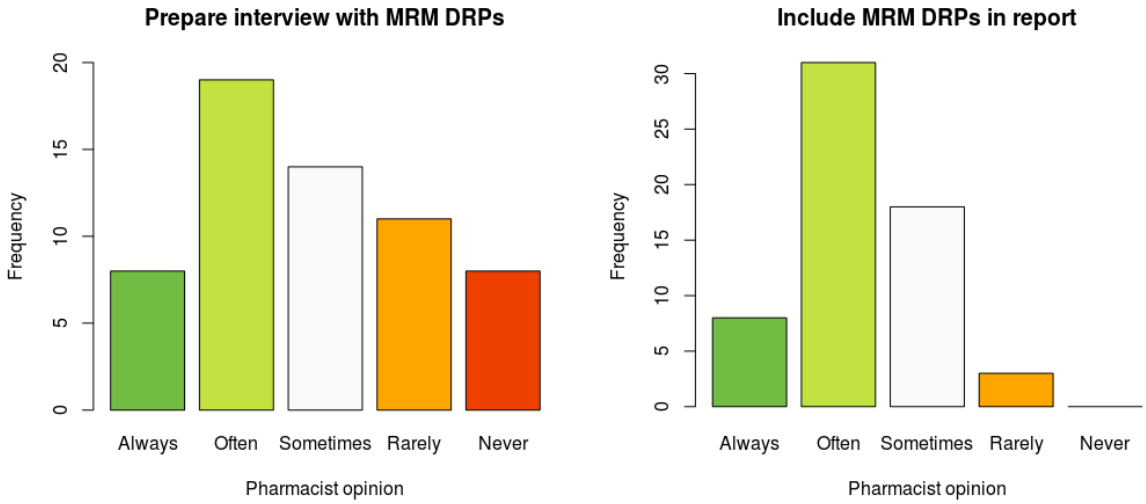


Figure 50: Use of MRM-identified DRPs for patient interview preparation and for medication review reports

A range of guidelines were used by pharmacists to aid detection of DRPs and provide recommendations to resolve DRPs. The published prescribing guidelines in the elderly consisting of Beers, STOPP/START and PIEA were infrequently used, shown in Figure 51. Guidelines frequently used were the Therapeutic Guidelines,[303] Diabetes Australia,[304] Heart Foundation[305] and NPS[306] guidelines, shown in Figure 51. Several other guidelines, references and software were also used: Australian Medicines Handbook (https://shop.amh.net.au/), Australian Medicines Handbook Aged Care (https://shop.amh.net.au/), MIMs (www.mims.com.au/), AusDi Advanced (http://www.phoenixmedical.com.au/ausdi_advanced.php), Medscape Drug Interaction Checker (http://reference.medscape.com/drug-interactionchecker), Drugs.com Drug Interactions Checker (http://www.drugs.com/drug_interactions.html), NICE (www.nice.org.uk/), tripdatabase (www.tripdatabase.com), CKD guidelines (may be the CKD Management Guideline Booklet produced by Kidney Health Australia), Veterans Mates (www.veteransmates.net.au).

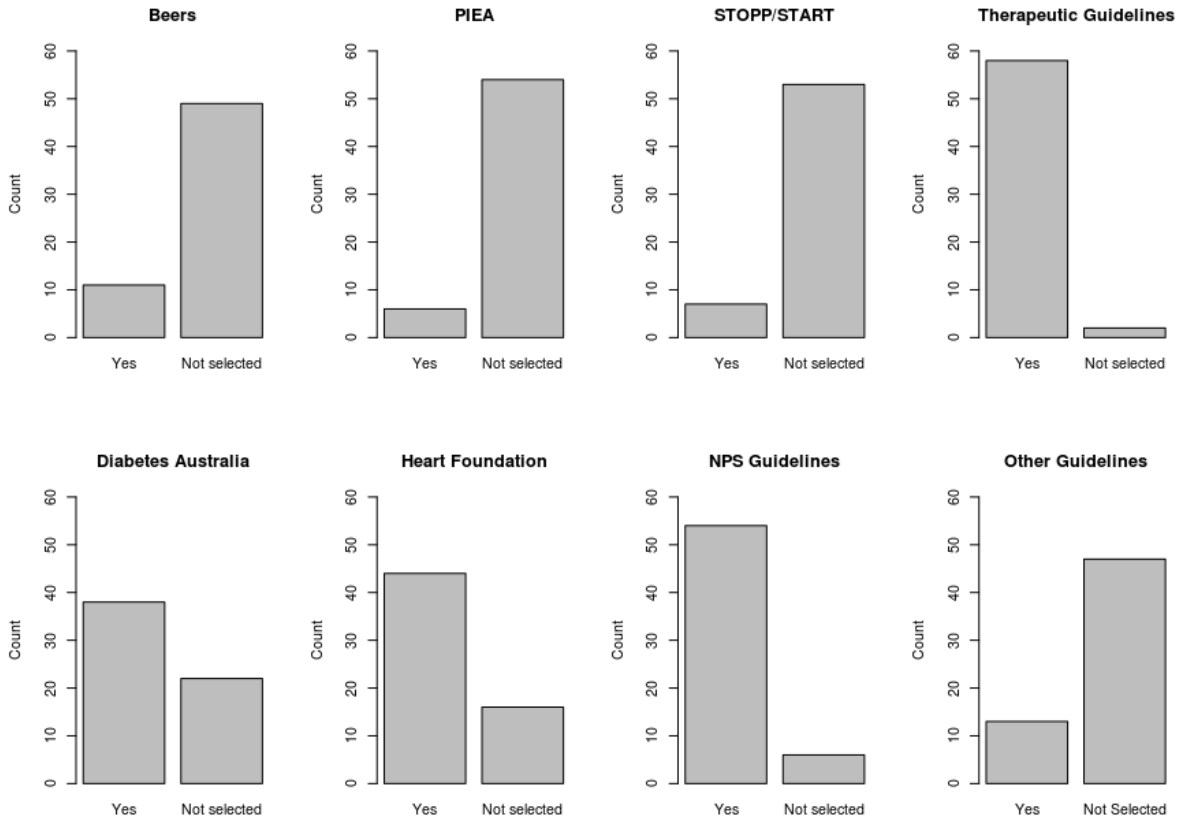


Figure 51: Pharmacist use of prescribing guidelines

9.3.2 Data Entry into MRM

The majority of pharmacists did manually enter all patient medications, diagnoses, observations and pathology results, shown in Table 42. A smaller majority of pharmacists also entered all patient observations and laboratory test results. These questions were not mandatory so totals do not add to 60. One pharmacist who consistently chose *never* may have been a past, but not current, subscriber of MRM.

Table 42: Pharmacist manual data entry

	Always	Often	Sometimes	Rarely	Never	Total
Medications	57				2	59
Diagnoses	55	3			1	59
Observations	40	6	10	1	1	58
Pathology results	37	11	8	2	1	59

A data entry score was calculated by adding the responses to the four questions. *Always* was assigned the value of 1 and *Never* was assigned the value of 5. The minimum score attainable was 4 indicating all patient data was entered and the maximum score attainable was 20 indicating no patient data was entered. Scores for two pharmacists were not calculated as not all four questions were completed. The median score was 4 with scores ranging from 4 to 20, shown as a histogram in Figure 52.

Correlation tests using the data entry score and various factors were performed using Kendall's tau-b correlation test. No correlations were identified.

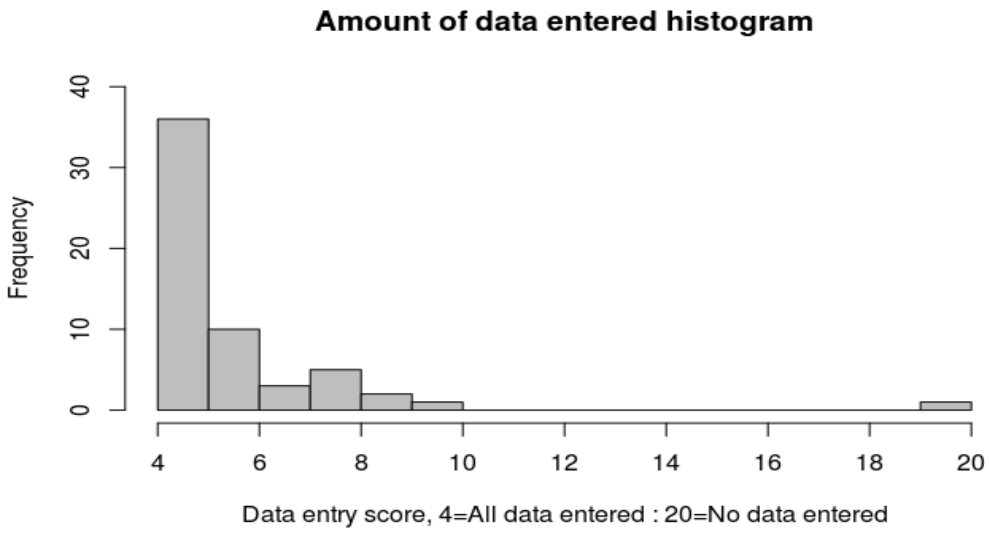


Figure 52: Histogram of data entry scores

There were 25 comments concerning data entry. Thirteen of these were grouped into categories of *time consuming* and *cumbersome*. A related category was *interest in direct downloading from GP surgeries*. Another category mentioned several times was the software contained *limited diagnoses to select from*.

9.3.3 System Usability Scale

An objective measure of software usability was determined through the SUS with a median of 77.5 and range 2.5 to 100. The majority of pharmacists scored 70 or more indicating the

MRM software was easy to use, shown in Figure 53. Eleven pharmacists found the software had acceptable usability. Four pharmacists indicated the software was not easy to use.

An independent samples t-test was performed to compare SUS score in males and females. There was a significant difference in the scores for males (mean 67) and females (mean 79); t = 2.11, p = 0.045. The result suggests females found MRM easier to use.

A Shapiro-Wilk test for normality showed the SUS was not normally distributed, W = 0.9069, p < 0.001. Correlation tests between SUS and various factors were performed using, where appropriate, Spearman's correlation or Kendall's tau-b (for tied ordinal values). Results using Spearman's correlation tests of the SUS score with years accredited, years of pharmacy practice, HMRs per year, RMMRs per year, inclusion of MRM DRPs in medication reports interview were very weak and not significant. Results using Kendall's tau-b of the SUS score with *including MRM DRPs in medication review reports*, and with *using MRM DRPs to prepare for a patient interview* were also very weak and not significant.

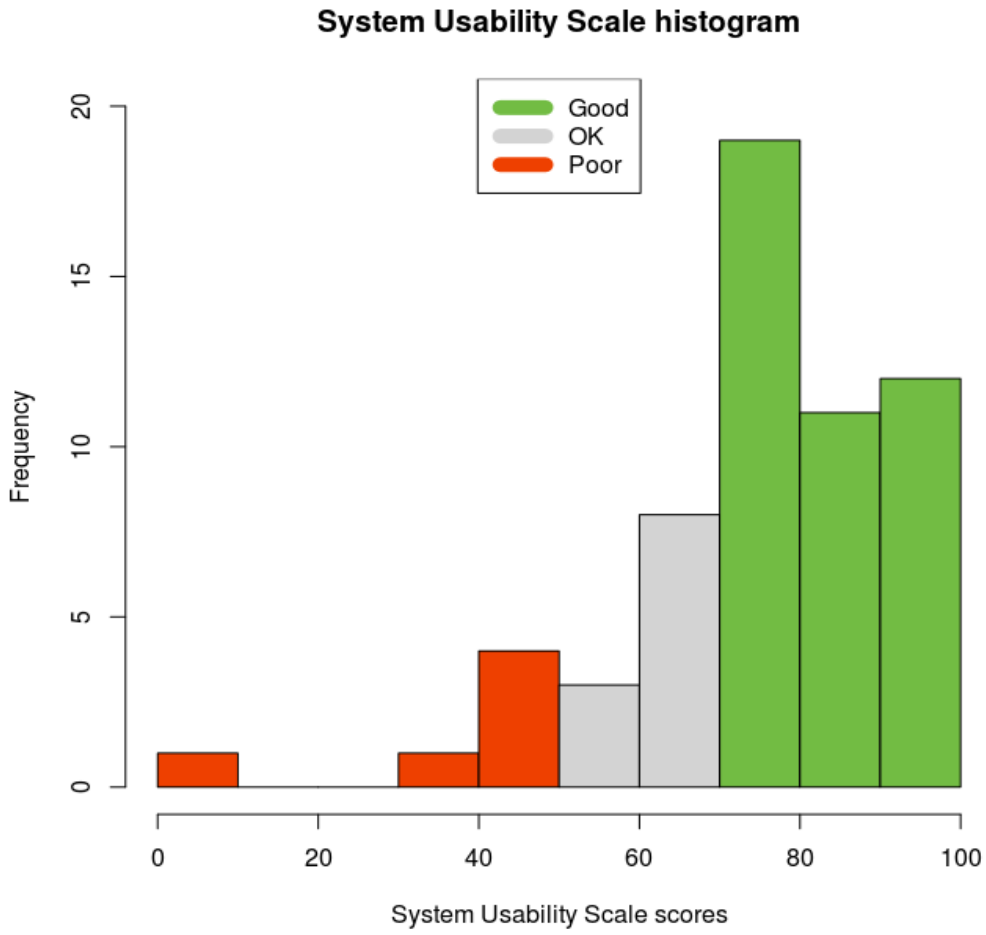


Figure 53: SUS histogram

Correlations were found with clinical relevance of MRM DRPs, MRM providing appropriate recommendations (see section 9.3.5); core service quality, value for money and satisfaction with the software (see section 9.3.6).

9.3.4 Perceived usefulness of MRM

Perceived usefulness was calculated as the mean score for all six items in the perceived usefulness scale, the lowest attainable score was 1, a neutral score was 4 and the highest attainable score was 7. Perceived usefulness of MRM's decision support ranged from 2 (quite unlikely to be useful) to 7 (extremely likely to be useful) with a median of 5.8. Two pharmacists indicated the decision support was unlikely to be useful (scores: 2.0, 2.2). Five pharmacists indicated a neutral opinion of the decision support (scores: as 4.0, 4.0, 4.0, 4.3, 4.5). The majority of pharmacists (N=53) indicated MRM's decision support was useful. The range of responses is shown in Figure 54.

A Shapiro-Wilk test for normality showed perceived usefulness was not normally distributed, $W = 0.8786$, $p < 0.001$. Correlation tests between perceived usefulness of the decision support and various factors were performed, using where appropriate, Spearmans correlation or Kendall's tau-b (for tied ordinal values). Correlation with years accredited, years of pharmacy practice, HMRs per year, RMMRs per year, using MRM DRPs to prepare for a patient interview were very weak and not significant.

There was a weak negative correlation between perceived usefulness and inclusion of MRM DRPs in medication review reports, Kendall's tau-b = -0.36, $p < 0.001$, with greater perceived usefulness associated with increased inclusion of MRM DRPs in medication review reports. The direction was negative because *always include MRM DRPs* was assigned the value 1 and *never include MRM DRPs* was assigned the value 5. There was a weak positive correlation with the SUS, Spearman's rho = 0.27, $p = 0.035$. Correlations were also found with MRM finding clinically relevant DRPs, MRM not missing the identification of DRPs, MRM not finding excess DRPs, MRM providing appropriate recommendations, MRM finding DRPs pharmacists overlook (see section 9.3.5); core service quality, value for money and satisfaction (see section 9.3.6). Figure 55 illustrates the main factors correlating with perceived usefulness.

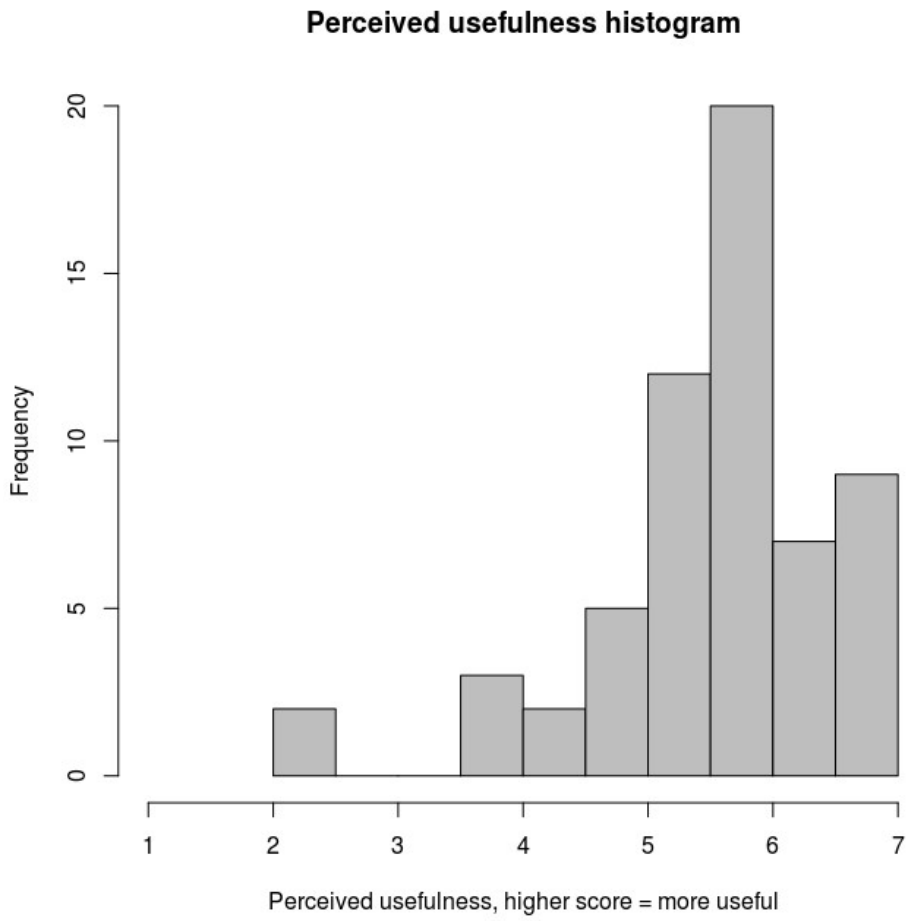


Figure 54: Perceived usefulness histogram

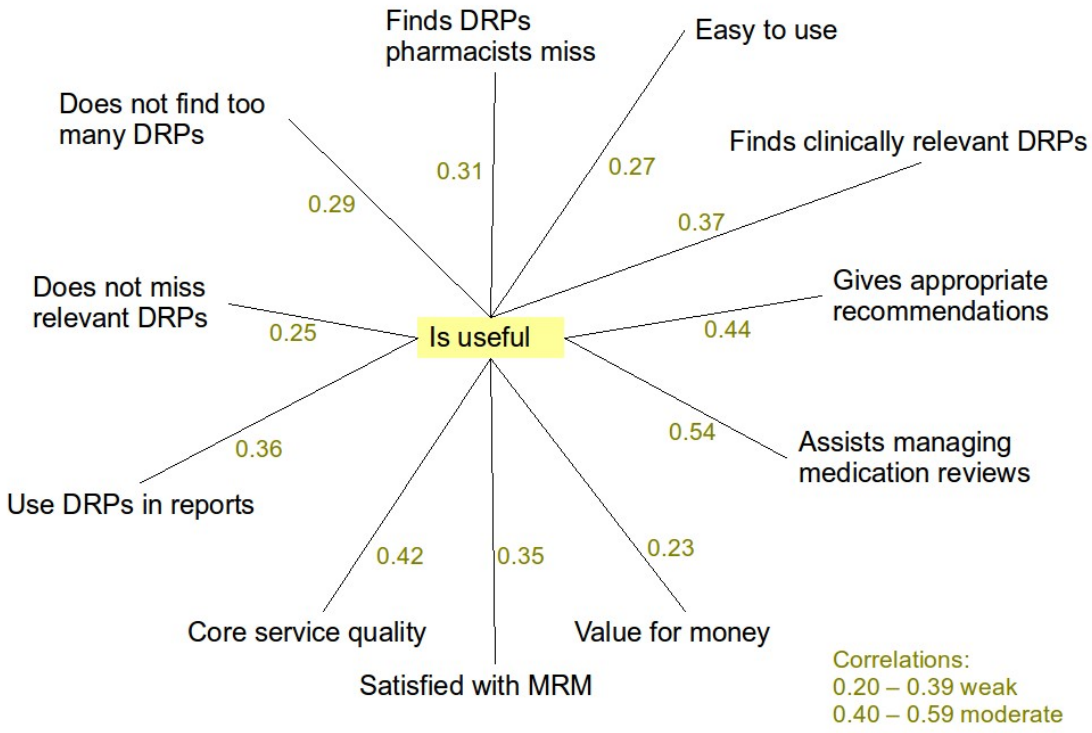


Figure 55: Factors associated with the perceived usefulness of MRM

9.3.5 Pharmacist opinion of decision support

Four statements in the user survey matched the statements presented to the expert panel to allow for comparison. The only difference was the pharmacists were presented with the full text *drug-related problem*, whereas the expert panel statements used the acronym DRP, which had been defined elsewhere on the expert panel website. A range of correlation tests were performed.

Clinical relevance of DRPs

Pharmacist responses to the statement "Overall, this source identified clinically relevant drug-related problems" are shown in Table 43. The majority of pharmacists, N = 44, indicated MRM identified clinically relevant DRPs.

There was a weak negative correlation between MRM identifying clinically relevant DRPs and perceived usefulness, Kendall's tau-b = -0.37, $p < 0.001$, with greater agreement MRM identified clinically relevant DRPs associated with greater perceived usefulness. The direction was negative because *Strongly agree* was assigned the value 1 and *Strongly disagree* was assigned the value 5. This finding was supported by a moderate positive correlation between MRM identifying clinically relevant DRPs and including MRM DRPs in medication review reports, Kendall's tau-b = 0.46, $p < 0.001$.

There was a weak positive correlation between MRM identifying clinically relevant DRPs and using MRM DRPs to prepare for a patient interview, Kendall's tau-b = 0.22, $p = 0.042$. There was a weak negative correlation between MRM identifying clinically relevant DRPs and the SUS, Kendall's tau-b = -0.39, $p <0.001$. The direction was negative because *Strongly agree* was assigned the value 1 and *Strongly disagree* was assigned the value 5. Correlations were also found with core service quality, value for money, appropriate recommendations and missed DRPs (see sections 9.3.5 and 9.3.6). Factors that correlated with finding clinical relevance are shown in Figure 56.

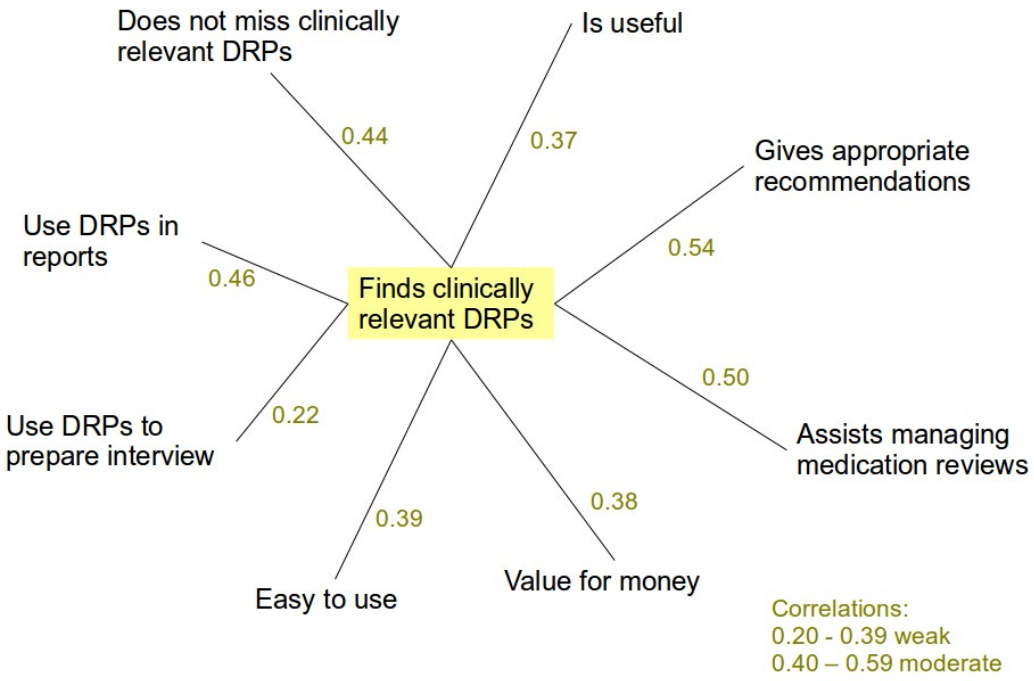


Figure 56: Factors associated with MRM identifying clinically relevant DRPs

Pharmacist responses were compared with responses obtained from the expert panel, see Table 43. Fisher's Exact Test showed no difference between the opinions of the expert panel and the opinions of the pharmacists, p = 0.267.

Table 43: MRM pharmacist opinion of MRM clinical relevance

Likert response	MRM pharmacists count (percent of total)	Expert panel count (percent of total)
Strongly agree	6 (10%)	17 (7%)
Agree	38 (63%)	176 (73%)
Neutral	9 (15%)	34 (14%)
Disagree	7 (11%)	12 (5%)
Strongly disagree	0 (0%)	1 (0%)

MRM missed DRPs

Pharmacist responses to the statement "Clinically relevant drug-related problems were not identified" are shown in Table 45. Almost half of pharmacists, N = 25, indicated MRM did not miss clinically relevant DRPs although an additional third, N = 20, were unsure.

Correlation tests between core service quality of the decision support and various factors were performed. Interestingly, many factors correlated with core service quality, shown in Table 44.

Table 44: Factors correlating with MRM missed DRPs

Factor	Test results	Correlation strength	Summary
MRM finding clinically relevant DRPs	Kendall's tau-b = -0.44, p < 0.001	moderate	There was greater agreement MRM did not miss clinically relevant DRPs associated with MRM finding clinically relevant DRPs
MRM identified DRPs pharmacists overlooked	Kendall's tau-b = -0.35, p = 0.002	weak	MRM identifying pharmacist overlooked DRPs associated with MRM not missing clinically relevant DRPs
MRM identified excessive number of DRPs	Kendall's tau-b = 0.26, p = 0.022	weak	MRM not missing clinically relevant DRPs associated with MRM not finding excessive DRPs
Perceived usefulness	Kendall's tau-b = 0.25, p = 0.015	weak	Greater agreement MRM did not miss clinically relevant DRPs associated with greater perceived usefulness
including MRM DRPs in medication review reports	Kendall's tau-b = -0.23, p = 0.047	weak	Pharmacists including MRM DRPs in reports associated with MRM not missing the identification of DRPs
Core service quality	Kendall's tau-b = 0.37, p < 0.001	weak	Increased disagreement of MRM missing clinically relevant DRPs associated with greater core service quality
Value for money	Kendall's tau-b = -0.22, p = 0.047	weak	Increased agreement with value for money was associated with MRM not missing DRPs

MRM pharmacist responses were compared with responses obtained from the expert panel, see Table 45. Fisher's Exact Test showed a significant difference between the opinions of the expert panel and the opinions of the pharmacists, p = 0.010. A greater proportion of the expert panel were of the opinion MRM missed clinically relevant DRPs whereas pharmacist opinions were fairly evenly divided.

Table 45: MRM pharmacist opinion of MRM missing the identification of clinically relevant DRPs

Likert response	MRM Pharmacists count (percent of total)	Expert panel count (percent of total)
Strongly agree	1 (2)	8 (3)
Agree	14 (23)	108 (45)
Neutral	20 (33)	54 (23)
Disagree	23 (38)	68 (28)
Strongly disagree	2 (3)	2 (1)

MRM excessive DRPs

Pharmacist responses to the statement "The number of drug-related problems identified was excessive" are shown in Table 46. The majority of responses, N = 31, disagreed MRM identified an excessive quantity of DRPs.

There was a weak positive correlation between MRM identifying excessive DRPs and perceived usefulness, Kendall's tau-b = 0.29, p = 0.005, with greater agreement MRM did not identify excessive DRPs associated with greater perceived usefulness. There was a weak positive correlation between MRM missed clinically relevant DRPs and MRM finding excessive DRPs, Kendall's tau-b = 0.26, p = 0.022, with MRM not missing clinically relevant DRPs associated with MRM not finding excessive DRPs.

Pharmacist responses were compared with responses obtained from the expert panel, see Table 46. Fisher's Exact Test showed a difference between the opinions of the expert panel and the opinions of the pharmacists, $p < 0.001$. A much greater proportion of pharmacists had a neutral opinion of MRM displaying excessive numbers of DRPs compared to the expert panel. A larger proportion of the expert panel were of the opinion MRM did not display excessive numbers of DRPs.

Table 46: MRM pharmacist opinion of MRM identified excessive DRPs, total (percent)

Likert response	MRM Pharmacists	Expert panel
Strongly agree	1 (2)	8 (3)
Agree	5 (8)	39 (16)
Neutral	23 (38)	38 (16)
Disagree	24 (40)	141 (59)
Strongly disagree	7 (12)	14 (6)

MRM recommendations

Pharmacist responses to the statement "Overall, this source offered appropriate recommendations" are shown in Table 47. The majority of pharmacists, N = 37, agreed MRM provided appropriate recommendations.

There was a moderate negative correlation between MRM providing appropriate recommendations and perceived usefulness, Kendall's tau-b = -0.44, $p < 0.001$, with greater agreement MRM provided appropriate recommendations associated with greater perceived usefulness. There was a moderate positive correlation between MRM providing appropriate recommendations and MRM identifying clinically relevant DRPs, Kendall's tau-b = 0.54, $p < 0.001$, with identifying clinically relevant DRPs associated with appropriate recommendations.

There was a weak negative correlation between MRM providing appropriate recommendations and the SUS score, Kendall's tau-b = -0.23, $p = 0.026$, with better usability associated with more agreement of MRM providing appropriate recommendations. The directions were negative because *Strongly agree* was assigned the value 1 and *Strongly disagree* was assigned the value 5. There was a weak positive correlation between MRM providing appropriate recommendations and including MRM DRPs in medication review reports, Kendall's tau-b = 0.35, $p = 0.002$, with greater agreement MRM provided appropriate recommendations associated with greater inclusion of MRM DRPs in medication review reports. Correlations were also found with core service quality and value for money (see section 9.3.6).

Pharmacist responses were compared with responses obtained from the expert panel, see Table 47. Fisher's Exact Test showed no difference between the opinions of the expert panel and the opinions of the pharmacists, p = 0.117.

Table 47: MRM pharmacist opinion of MRM provided appropriate recommendations, total (percent)

Likert response	MRM Pharmacists	Expert panel
Strongly agree	4 (7)	16 (7)
Agree	33 (55)	165 (69)
Neutral	16 (27)	48 (20)
Disagree	6 (10)	10 (4)
Strongly disagree	1 (2)	1 (0)

MRM identified DRPs pharmacists overlooked

Pharmacist responses to the statement "MRM identifies clinically relevant drug-related problems which you may have overlooked" are shown in Table 48. The majority of pharmacists, N = 44, indicated MRM did identify clinically relevant DRPs that they may have overlooked.

There was a weak negative correlation between MRM identifying DRPs overlooked by pharmacists and perceived usefulness, Kendall's tau-b = -0.31, p = 0.003, with greater agreement that MRM identified DRPs that pharmacists overlooked associated with greater perceived usefulness.

There was a weak positive correlation between MRM identifying DRPs overlooked by pharmacists and the inclusion of MRM DRPs in medication review reports, Kendall's tau-b = 0.24, p = 0.041, with greater agreement MRM identified DRPs that pharmacists overlooked with greater inclusion of MRM DRPs in medication review reports.

Table 48: MRM pharmacist opinion of MRM identified DRPs overlooked by pharmacists, total (percent)

Likert response	MRM Pharmacists
Strongly agree	8 (13)
Agree	36 (60)
Neutral	9 (15)
Disagree	7 (12)
Strongly disagree	0 (0)

9.3.6 Service and value for money

Service and value for money may likely have an impact on the use of software products. Likewise the usefulness and ease of use may affect the pharmacist software users perception of value for money.

Core service quality

Responses to the question "How would you rate the assistance MRM software provides for managing your medication reviews" were to be entered on a scale of 0 to 100. This question encompasses the core service quality of the MRM product. One response of 110 exceeded the maximum allowable score of 100 and was set to 100. Most pharmacists were of the opinion the core service quality of the Medscope company was good scoring 70 or more, mean 79 ± 14. A histogram of results shown in Figure 57.

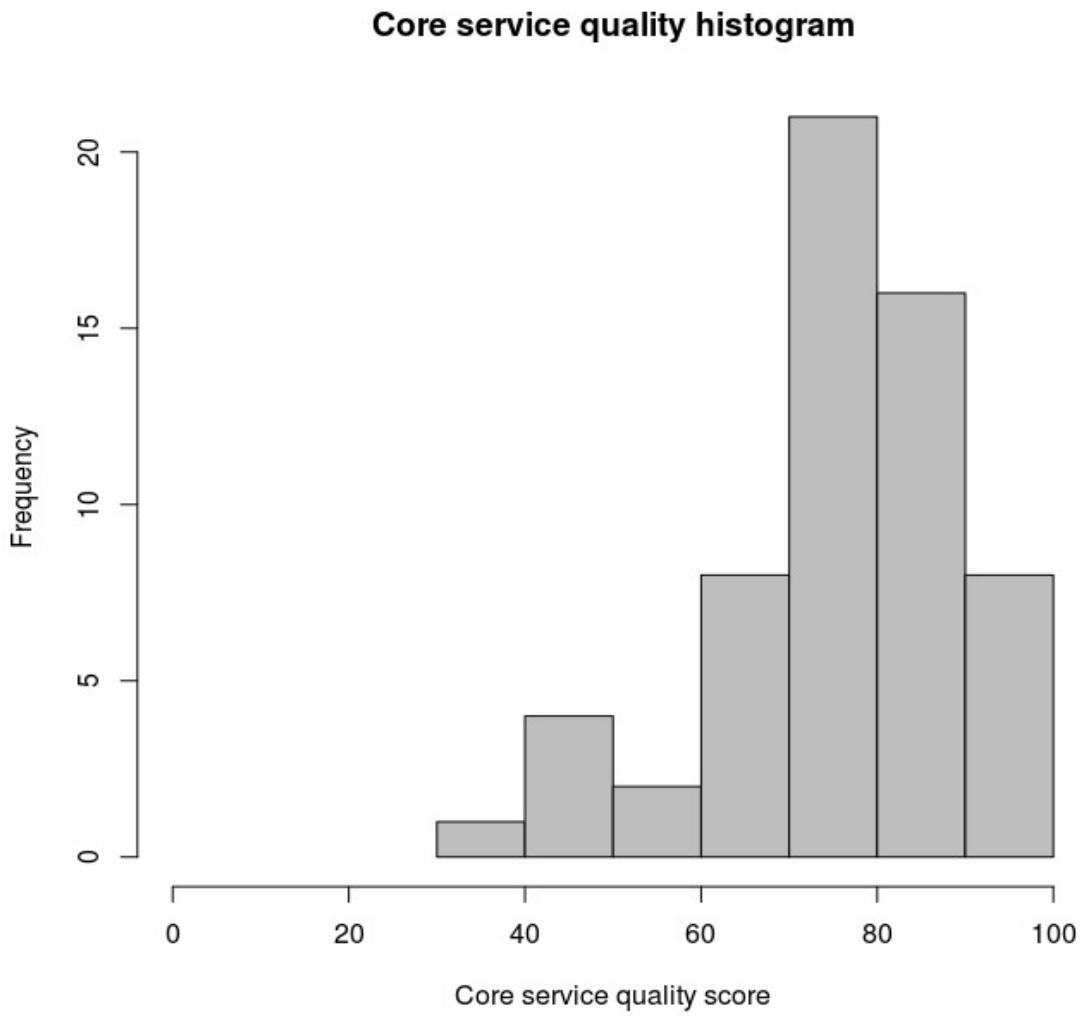


Figure 57: Medscope core service quality histogram

A Shapiro-Wilk test showed core service quality scores were not normally distributed, W = 0.9271, p = 0.002. Correlation tests between core service quality of the decision support and various factors were performed. Interestingly, many factors correlated with core service quality, shown in Table 49.

Table 49: Factors correlating with core service quality

Factor	Test results	Correlation strength	Summary
Perceived usefulness	Spearman's rho = 0.54, p < 0.001	moderate	Higher perceived usefulness associated with greater core service quality.
SUS	Spearman's rho = 0.45, p <	moderate	Higher SUS scores associated with greater

Factor	Test results	Correlation strength	Summary
	0.001		core service quality
MRM identified clinically relevant DRPs	Kendall's tau-b = -0.50, p < 0.001	moderate	More agreement of MRM's capacity to identify clinically relevant DRPs associated with greater core service quality
MRM missed clinically relevant DRPs	Kendall's tau-b = 0.37, p < 0.001	weak	More disagreement of MRM missing clinically relevant DRPs associated with greater core service quality
MRM provided appropriate recommendations	Kendall's tau-b = -0.40, p < 0.001	moderate	More agreement of MRM providing appropriate recommendations associated with greater core service quality
Included MRM DRPs in medication review reports	Kendall's tau-b = -0.29, p = 0.006	weak	Increased inclusion of MRM DRPs into reports associated with greater core service quality
Used MRM DRPs to prepare patient interviews	Kendall's tau-b = -0.27, p = 0.008	weak	Increased use of MRM DRPs to prepare for patient interviews associated with greater core service quality
Value for money	Kendall's tau-b = -0.40, p < 0.001	moderate	Increased agreement with value for money was associated with greater core service quality
Satisfaction	Kendall's tau-b = -0.53, p < 0.001	moderate	Greater satisfaction associated with greater core service quality.

The factors that correlated with core service quality are illustrated in Figure 58.

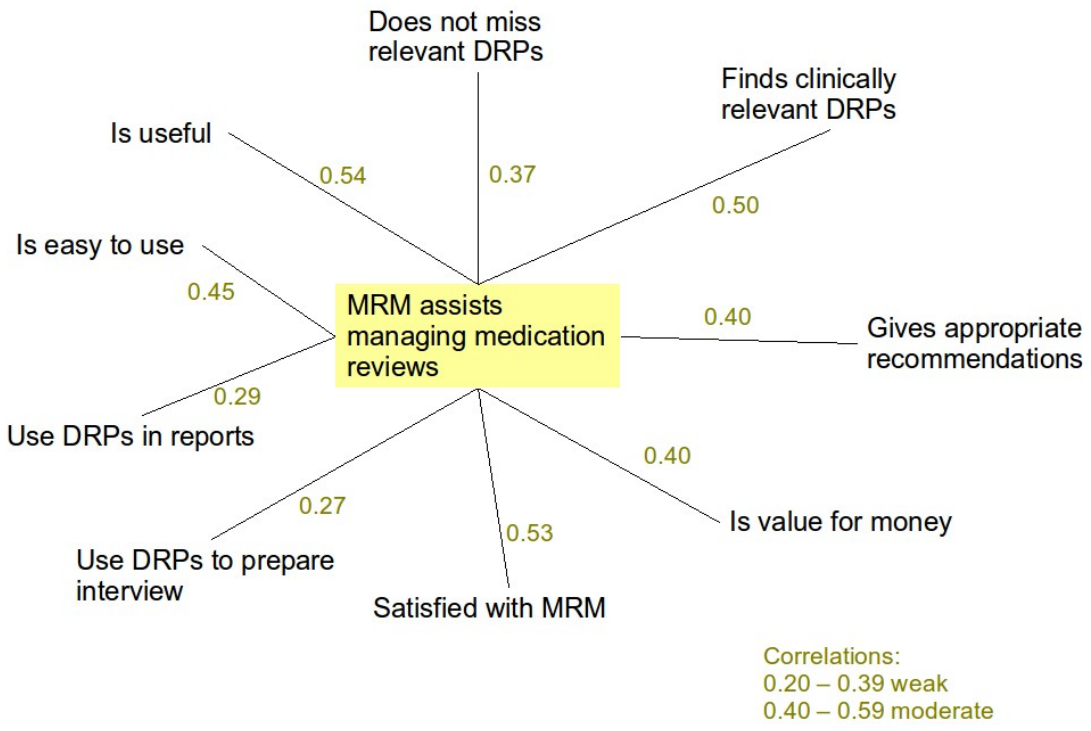


Figure 58: Factors associated with core service quality - managing medication reviews

Value for money

Responses to the statement "Overall MRM offers good value for money" are shown in Table 50. The majority of pharmacists agreed that the MRM software offered good value for money.

Table 50: Responses to MRM offers good value for money

Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
8	30	14	6	2

Correlation tests between value for money and various factors were performed. Interestingly, many factors correlated with value for money, shown in Table 51.

Table 51: Factors correlating with value for money

Factor	Test results	Correlation strength	Summary
Core service quality	Kendall's tau-b = -0.40, p < 0.001	moderate	Increased agreement with value for money was associated with greater core service quality
SUS	Kendall's tau-b = -0.30, p = 0.003	weak	Increased agreement with value for money associated with greater SUS score
Perceived usefulness	Kendall's tau-b = -0.23, p = 0.022	weak	Increased agreement with value for money associated with greater perceived usefulness
MRM identified clinically relevant DRPs	Kendall's tau-b = 0.38, p < 0.001	weak	Increased agreement with value for money associated with greater agreement that MRM identified clinically relevant DRPs
Providing appropriate recommendations	Kendall's tau-b = 0.41, p < 0.001	moderate	Increased agreement with value for money associated with greater agreement that MRM provided appropriate recommendations
MRM missed clinically relevant DRPs	Kendall's tau-b = -0.22, p = 0.047	weak	Increased agreement with value for money was associated with MRM not missing DRPs

Satisfaction with MRM

Responses to the statement "MRM meets my expectations" are shown in Table 52. The majority of pharmacists agreed that the MRM software met their expectations.

Table 52: Responses to MRM meets my expectations

Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
8	37	8	5	1

There was a moderate positive correlation between satisfaction and value for money, Kendall's tau-b = 0.53, $p < 0.001$, with increased satisfaction associated with greater value for money.

There was a moderate negative correlation between satisfaction and core service quality, Kendall's tau-b = -0.53, $p < 0.001$, with increased satisfaction associated with greater core service quality.

There was a moderate negative correlation between satisfaction and SUS scores, Kendall's tau-b = -0.44, $p < 0.001$, with increased satisfaction associated with greater SUS scores.

There was a weak negative correlation between satisfaction and perceived usefulness scores, Kendall's tau-b = -0.35, $p < 0.001$, with increased satisfaction associated with greater perceived usefulness scores.

9.3.7 Qualitative analysis of pharmacists who used MRM

Twenty-seven pharmacists provided additional comments via a free text field. Codes were assigned to the text and grouped by category where possible. Codes, code frequencies and categories are tabled in Appendix 21.

Satisfaction with Medscope and MRM

There were disparate views on whether pharmacists were satisfied with MRM although a greater number of coded comments indicated satisfaction rather than dissatisfaction. Eight comments displayed satisfaction with MRM, another 5 stated MRM represented good value for money and 4 stated that MRM saved time. Four comments indicated good customer service.

> "Because I don't do a lot of HMRs I find MRM helps me focus on pertinent points to include in my report to GP. It also gives me a consistent, easy to read format as a template and then gives me the option to reword, change and add to if I need." Pharmacist id 16

> "It has provided a big increase in efficiency" Pharmacist id 47

> "Using MRM and the HMR Alert software is the only reason I pursued setting up a business specialising in Home Medicine Reviews. Without it I would not have gone out on my own and would have continued to just do a few reviews each year." Pharmacist id 20

> "I like using the software as it is a safety net for me to make sure I haven't missed anything crucial" Pharmacist id 72

Pharmacists were sometimes dissatisfied with the DRPs that were identified by MRM, discussed later. Other problems were grouped under the category *product needs polish*. One pharmacist mentioned occasional bugs on saving information, another mentioned drug products were out-dated and new products were not added. Also, the video tutorial was also outdated. Several comments stated that using MRM was time consuming, tying in with the data entry aspect.

> "Data entry became far too time consuming" Pharmacist id 8

Several comments stated that layout, presentation, punctuation and spelling were not professional.

> "The layout and presentation of the final MRM product together with spelling mistakes and punctuation are far from professional. A proof reader should have been given the job to rectify all these oversights that should have been done in the first instance. I strongly believe these aspects should be part and parcel and a basic expectation of a professionally prepared (credible) document." Pharmacist id 9

DRPs could be better

Several problems with identified DRPs were stated: DRPs were contradictory, DRPs were not current practice, DRPs or recommendations were irrelevant, DRPs were duplicated, and data was incorrectly analysed.

> "All confidence in the program is lost when it fails to recognise that a pathology test has been entered and it then suggests in its recommendations that this pathology test be undertaken, saying that this area has not been investigated." Pharmacist id 63

> "Occasionally it gives the same recommendation with slightly different wording for the same patient" Pharmacist id 35

> "I find that the issues present often contradict themselves. Eg. Patient is on an NSAID prophylactic PPI therapy required, next issue: patient has been on a PPI long term consider ceasing" Pharmacist id 52

Confirmation of the validity of MRM-identified DRPs was requested through provision of references.

> "I would like to see reasons and references for recommendations." Pharmacist id 38

Time and efficiency

There were divided opinions concerning use of time, with five comments stating MRM was time consuming and four comments stating MRM saved time.

> "data entry became far too time consuming" Pharmacist id 8

> "The book keeping, reports and claiming are an awesome help to streamlining the process and allowing me to efficiently use my time" Pharmacist id 14

One pharmacist had a bet each way:

> "I am unable to simply download the report & send to the Dr - I usually need to 'polish' & personalise quite a lot which is time consuming. Having said that, it certainly saves time & eliminates a lot of double entry." Pharmacist id 5

One pharmacist stated MRM was slower to user than a competitor product:

> "frequently slower to work with than Mediflags" Pharmacist id 7

Additional functionality

Pharmacists expressed the need for additional features. Several pharmacists wanted the software to be able to store their own comments to apply to particular DRPs.

> "I would like to be able to save my own comments, etc into my system to save copy and pasting." Pharmacist id 10

Other functionality requests were: the ability to directly download patient information from GP surgeries, ordering the medication list by medical condition, a report section for RMMR staff, add in standard drug interaction capability, electronic form to fill in during an interview.

9.4 Discussion

Most pharmacists who used MRM were experienced with medication reviews and many years pharmacy experience. Most pharmacists performed HMRs whereas only half of respondents performed RMMRs. The majority of pharmacists used a range of published prescribing guidelines to assist with the identification of DRPs and to make recommendations. However, the Beers, STOPP/START and PIEA prescribing criteria intended for use in older people and recommended by the Pharmaceutical Society of Australia were only rarely used by pharmacists.[25] The rare use of these materials may be because these materials are not actively promoted to pharmacists, and pharmacists have to actively search for them through bibliographic databases such as PubMed. Materials such as the Therapeutic Guidelines and NPS guidelines are actively and directly promoted to pharmacists in Australia.

The amount of patient information manually entered by the pharmacist was anticipated to affect the software's findings and consequently pharmacist opinion of the software's findings. For many pharmacists data entry was a major bugbear, with pharmacists finding the process cumbersome and time consuming.

> "It's slow and boring! And information that is given back is only as good as the data entered in the first place!" Pharmacist id 15

According to the TAM, pharmacist attitude towards and actual use of MRM are dependent on the perceived usefulness and ease of use of the software.[195] Software must be relatively easy to use if people are likely to make use of it. Technology usability is one core constituent of the Technology Acceptance Model (TAM) – a model based on the theory of reasoned action to explain actual acceptance and use of technology, see section 3.6. The perceived ease of use of technology has been defined as "the degree to which a person believes that using a particular system would be free of effort"[195] Both ease of use and usability scored highly, suggesting that pharmacists were accepting, or willing to use, the software.

> "All over I have found the MRM program very useful" Pharmacist id 19

Most pharmacists perceived MRM's clinical decision support to be useful. Many of the central medication review decision processes such as identifying clinically relevant DRPs and providing appropriate recommendations were associated with the usefulness of the decision support shown in Figure 55. Perhaps in part due to the usefulness of MRM, pharmacists were satisfied with the software as they thought MRM helped manage their medication reviews and provided value for money. The use of the software"s findings for patient interview preparations and for GP reports strongly indicate pharmacists found MRM's decision support to be useful in their medication review work.

Pharmacists generally thought MRM did identify clinically relevant DRPs and did provide appropriate recommendations to resolve DRPs. These opinions were supported by the opinions of the expert panel, with no statistically significant differences. Pharmacist opinion was less strong on whether MRM missed the identification of DRPs, with nearly half of pharmacists indicating DRPs were not missed and another third unsure. The majority of pharmacists thought MRM did not identify too many DRPs which may be due to suitable patient context through the use of AI. A range of factors were associated with the identification of clinically relevant DRPs, shown in Figure 56.

Pharmacist opinions showed that the pharmacists did not absolutely rely on the decision support and that MRM did not always produce good results. However, the rule base for this software can continually evolve through the addition of new rules and refinement of existing rules. Feedback from the pharmacists who are using the software to those who implement and refine rules in Medscope company is an important pathway for improvement. The company in turn need to verify rule additions and refinement are valid and to respond promptly to user feedback to enhance MRM's usefulness from the user perspective. The use of clinical guidelines, such as the Therapeutic Guidelines,[303] by many pharmacists confirms pharmacists do not rely on MRM alone.

> “I find that you can't rely on it entirely” Pharmacist id 72

> “I don't use the decision support very much as I find that many of the recommendations aren't clinically relevant” Pharmacist id 36

> "On some occasions I have found PPI use is stated no indication for use, because no GORD but does not identify that long-term prednisolone is used for RA etc." Pharmacist id 28

MRM's core service quality, the provision of assistance to pharmacists for the management of medication reviews, was mostly very positive. Core service quality was also associated with identification of clinically relevant DRPs and provision of appropriate recommendations. Core service quality was associated with many factors, shown in Figure 58, which unsurprisingly included perceived usefulness and system usability. Additionally, most pharmacists thought MRM met their expectations and was value for money and these factors were not unexpectedly associated with core service quality. Although value for money did appear to depend on the frequency and type of reviews performed.

> "It is not cost effective if I only average 12 hmmrs [*sic*] per year" Pharmacist id 29

> "Needs to be cheaper so I can use for RMMRs" Pharmacist id 48

A compelling argument for the use of MRM comes from the opinions of the majority of pharmacists that MRM identified clinically relevant DRPs that were missed by the pharmacists themselves.

> "I like using the software as it is a safety net for me to make sure I haven't missed anything crucial" Pharmacist id 72

Earlier examinations of expert systems have found thoroughness in the identification of DRPs.[167,178,239] Thoroughness and consistency of findings were benefits suggested by Bindoff *et al*. through work on prototype software which formed the basis of MRM.[178] Previous work, see Chapter 7, showed that pharmacists and MRM generally find different problems in different patients. The use of MRM to supplement the work of the pharmacist is expected to add this consistency and thoroughness to the pharmacists medication review reports as indicated by the pharmacists who use the software. This finding was hypothetically proposed by Bindoff *et al.* and appears to be justified.[167,178]

10 Discussion

10.1 Background

Medication reviews are conducted for the benefit of patients who may be at risk of medication misadventure. The process begins with the identification of a suitable patient, patient interview, preparation of a report of findings and recommendations for the patient's GP. The GP and patient discuss a medication management plan culminating ideally in improved patient health and quality use of medicines.[25] Pharmacist expertise of medication knowledge is applied to identify clinically relevant DRPs and provide recommendations for their resolution. A survey of accredited pharmacists found that assessment of the clinical appropriateness of medication therapy was considered the most important duty in performing HMRs.[273]

Identification of clinically relevant DRPs requires proficient knowledge of medications, common health conditions and evidence-based guidelines. Observational results and laboratory test results add to the conglomeration of patient medical information. Other factors such as health literacy, poverty, compliance, and physical limitations increase the complexity of determining suitably relevant DRPs and recommendations to resolve those DRPs.

Commercial decision support tools have been developed to aid pharmacists with the identification of DRPs. Two commercially-available software applications (MRM abd MRX), as well as well known sets of prescribing criteria, were assessed for their capacity to identify DRPs. Through the early phase of this investigation, neither of the commercial products had published assessments of their capacity to identify clinically relevant DRPs.

During this investigation one article was published regarding MRX applied to community-based elderly.[220] The authors concluded MRX "... was successful at identifying those [patients] with a high risk of drug-related geriatric syndromes." although the justification for this conclusion was not entirely clear. The impression was that the software identified broad classes of potential drug-related problems whether such problems existed or not. When compared, within the article, to an assessment by a geriatric-specialised pharmacist MRX appeared to overestimate the incidence of these syndromes. However, MRX identification of anticholinergics was in line with PIMs identified by the pharmacist.

These applications were not assessed for their ability to collect or organise patient data, although this was a central function of both products. These applications were assessed specifically on their decision support capabilities. Both companies – Medscope™ and Monitor-Rx stated claims purporting the benefit their decision support provided, but these claims cannot be truly justified without scientific assessment.

The Monitor-Rx website stated:

> "... clinical tool that assists in identifying, resolving and preventing medication-related problems ... identifies medications that may cause, aggravate, or contribute to common geriatric problems... "[260]

The Medscope™ Medication Review Mentor website stated:

> "... takes into account the patient's entire profile and identifies the issues that matter ... Missing medications are identified "[307]

To be effective as decision support, both applications must justify their stated claims and they must be practically useful to the end user – the pharmacist conducting the medication review. This practical usefulness is defined as software validation and has been clearly expressed in a 2002 FDA report *General principles of software validation*:

> "confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled."[308]

Validation of MRM and MRX was based on the output resultant from the input of patient information from the VALMER HMR data. Both MRM and MRX applications were black boxes, defined in the Oxford English dictionary as:

> "**2.** A device which performs intricate functions but whose internal mechanism may not readily be inspected or understood; (hence) any component of a system specified only in terms of the relationship between inputs and outputs."[309]

The decision support tools were black boxes, however it was known each differed in the scope of information utilised for the determination of actual or potential DRPs. MRX

produced results based solely on the presence of selected medications used in chronic medical conditions. MRM produced results based on a wide range of data including patient medications, strength, directions, daily dose, diagnoses, observations and laboratory test results. The difference in the breadth of information analysed is likely to be one of the primary drivers between the markedly different results reported in this document.

10.1.1 Evaluation with DOCUMENT classification

Using the DOCUMENT classification system, pharmacists not unexpectedly, found the widest range of DRPs covering all of the eight DOCUMENT categories. MRM similarly identified a wide range of DRPs, six of eight categories, but nothing in the *compliance* or *not-classifiable* categories.

In contrast with MRM, MRX exclusively identified medications for chronic conditions in the elderly that required *monitoring*. In other words, a screening tool, producing a check-list of potential problems which may be caused by medications. Potential problems were described in detail as well as descriptions of their signs and symptoms. No contextualisation or incorporation of drug dosages of these monitoring problems was performed by the software. The findings of the automated prescribing criteria were also examined. Unlike pharmacists, MRM, or MRX, each set of prescribing criteria identified fewer instances of DRPs and the main classification of DRPs identified were associated with the *drug selection* category.

On application of the DOCUMENT classification system, the assessment of MRM and MRX showed strong differentiation: the seemingly excessive number of DRPs identified by MRX and MRX's narrow scope of DRP types contrasted with MRM. MRM seemed excessive in the number of DRPs identified compared with pharmacists but not when compared with MRX. MRM also showed the ability to identify a range of problem types. The information obtained using DOCUMENT classification is of interest however there were two drawbacks: the types of DRP identified were classified in a general manner without any detail of drug class or any associated disease, and there was no information relating to the clinical relevance of identified DRPs.

10.1.2 Descriptive classifications

The assessment using DOCUMENT classifications offered a broad overview of the frequency and type of DRPs identified by the software. This method of assessment was extended through the development of descriptive classifications - detailed classifications which captured the central issue of each DRP and, through comparison with sets of prescribing criteria, some measure of clinical relevance.

Looking at the cohort of 570 patients, there were nearly seventy different types of descriptive classifications where MRM and pharmacists found the same problem in one or more of the same patients. The most commonly occurring example was *osteoporosis (or risk) may require calcium and or vitamin D*. This particular issue was identified by both MRM and by pharmacists in the same patients on nearly fifty occasions. However, this same problem was identified in an additional nearly ninety patients by MRM. Pharmacists also identified nearly another seventy patients which who were had this under-treatment problem. This situation repeated itself throughout the majority of the descriptive classifications where there was overlap of findings between pharmacists and MRM.

This situation did not occur across all classifications. For nine classifications MRM identified every instance where the pharmacist found a problem, and MRM found more, for example: *calcium channel blocker and reflux*. MRM also identified the majority of issues found by pharmacists in other areas such as: *hyperlipidaemia undertreated*. Conversely, pharmacists identified every instance where MRM found the problem *vitamin no indication*.

On looking at the varying levels of overlap, two questions arose: Why did MRM find problems that pharmacists did not? And why did pharmacists find problems that MRM did not?

10.1.3 Why did pharmacists find problems and MRM did not?

The classifications *vitamin no indication* provided a strong clue as to the reason pharmacists found issues where MRM did not. Herbal medications and various multivitamin preparations were not listed in MRM and so were not able to be assessed. This line of reasoning may explain why pharmacists could find problems that MRM could not – namely that pharmacists had information that was not available to MRM. That is, they had a greater range of

accessible data. There are two likely explanations behind this – information was available to the pharmacists but not recorded for entry into MRM, and the knowledge domain model used by MRM may not have been adequately designed to capture and utilise some of this expert knowledge. The higher proportion of DOCUMENT toxicity findings also suggests pharmacists had additional information, likely gleaned from the patient interviews. Another possible explanation may be that pharmacists identified irrelevant or incorrect problems. Research conducted on community pharmacists in Ireland discovered those pharmacists lacked knowledge of EBM,[310] however Australian studies have shown pharmacists do follow evidence-based guidelines.[42,311] However, results from the expert panel assessment indicated that both MRM and pharmacists identified clinically relevant problems for the most part.

10.1.4 Why did MRM find problems that pharmacists did not?

Realising pharmacists had a greater range of available data makes this question particularly pertinent – several suggestions are postulated. Overall, MRM did identify many more problems than pharmacists, even when excluding MRM's duplicate DRPs.

The first possibility is , again that MRM identified issues which were irrelevant or incorrect. There has been much discussion and research surrounding the issue of alert fatigue and accuracy (see section 3.6) impacting on relevance. For many of the various themes MRM identified more instances of problems than pharmacists. This may indicate lack of relevance which may have been the case involving calcium channel blockers. Calcium channel blockers may aggravate reflux disease, as was consistently identified by MRM, yet this issue was identified on only one occasion by a pharmacist, suggesting MRM was either thorough, or was over-exaggerating a minor issue. However, the lack of relevance theory was not supported by the expert panel, nor was it supported by the majority of surveyed pharmacists who used MRM. Although some comments from pharmacists who used MRM did indicate that lack of relevance was, at least sometimes, a concern. The smaller quantity of pharmacist DRPs may indicate that pharmacists prioritised problems of greater importance and did not report on lesser problems. A survey of pharmacists who provided the data for this investigation found that pharmacists did prioritise their findings.[273]

The second possibility is that MRM may be more consistent at identifying DRPs, perhaps through not prioritising DRPs. Consistency was a finding from three expert system studies including two precursor systems to MRM.[167,178,239] Certainly, consistency was clearly shown for several classifications: *dextropropoxyphene prescribed, quinine prescribed*. These medications no longer have a place in current practice, with the exception of quinine treatment for chloroquine resistant strains of *Plasmodium falciparum* malaria.[312] Unlike MRM, why did pharmacists not identify these problem medications in more patients? Quinine was extremely commonly prescribed for nocturnal cramp and the risk of quinine-induced thrombocytopenia has been known for many years.[312,313] Dextropropoxyphene products were initially removed from the register of therapeutic goods in Australia in 2012.[314,315] However, recent appeals have allowed dextropropoxyphene products to continue to be marketed in Australia albeit with increased prescribing restrictions.[316,317]

The likelihood of greater consistency in the identification of DRPs by MRM is an important point. The combination of MRM's ability to find, with machine regularity, a wide range of potential problems in medication review patients is likely to make this software a useful tool to complement the pharmacist's assessments. The only proviso in this discussion so far is the possibility that MRM has identified issues which were irrelevant or plain wrong.

10.1.5 Why did MRX find problems that pharmacists did not?

Similar to MRM, MRX also highlighted many potential DRPs which pharmacists did not. The same suggestions are postulated as for MRM – that is, MRX's findings may be irrelevant or incorrect and/or MRX may be more consistent at identifying DRPs. However, the nature of DRP detection was very different with MRX. The DOCUMENT classifications of DRPs showed that MRX identified both a much greater volume of DRPs than MRM, or any other method of DRP detection, yet a much narrower scope of problem types.

When looking at descriptive classifications, MRX identified only four classifications which overlapped with pharmacists findings. This is in stark contrast to the many classifications that overlapped between MRM and pharmacists. This again emphasises the narrow scope of issues that could be identified by MRX (see Appendix 19). One of those issues, *falls*

risk/history and sedatives/ antihypertensives/ other, was associated with every single one of the 100 patients entered into MRX (see Figure 35).

The second difference was where MRX overlapped with pharmacists. In this rare circumstance, MRX *always* found every instance of the pharmacist identified problems. This indicates MRX was very sensitive in finding problems within its scope of knowledge, that is, purely the presence of a medication of interest. This leads to the two possibilities, was MRX simply extremely consistent and clinically relevant in the rare overlapping circumstances, or was MRX simply excessively sensitive and clinically irrelevant?

10.2 Resolving the issue of relevance

Both MRM and MRX found descriptive classifications which overlapped with pharmacist findings and they both found more of the same kinds of problems in additional patients where the pharmacist did not identify that problem. Also both software sources did find issues which pharmacists did not find, or prioritise, at all such as for MRM: *aspirin or thiazide contraindicated in gout, NSAID without acid suppressant, opioid sedation;* and examples for MRX: *medication monitoring for cognitive or communication problems, medication monitoring for nutritional status* and *medication monitoring for urinary incontinence*. The issue of software identifying more problems than pharmacists needed to be investigated with consideration of clinical relevance. It would be reasonable to expect pharmacists prioritised their DRP findings and chose not to include minor problems. This expectation was confirmed through a survey of accredited medicines review pharmacists conducted by Dr Andrew Stafford.[273] However, if the software was finding more clinically relevant problems than pharmacists, then such software may be considered to be a beneficial tool to assist pharmacists conducting HMRs. Conversely, if the software was finding a lot of irrelevant problems then the decision support functionality is likely to frustrate the user, and result in alert fatigue.

10.2.1 Original pharmacist findings as a measure of clinical relevance

The original pharmacists findings may be the best measure of clinical relevance as these pharmacists were likely to have the best knowledge of the clinical situation of each patient through the additional information obtained from patient interviews. Secondly, they were

likely to have prioritised the most important DRPs in their GP reports. MRM identified more of the same descriptive classifications in the same patients as those identified by pharmacists than did MRX. In contrast MRX identified very few of the same descriptive classifications in the same patients as did pharmacists. This comparison clearly suggests that MRM had greater clinical relevance than MRX, at least in the view of the reviewing pharmacist.

10.2.2 Prescribing criteria as a measure of clinical relevance

The findings of MRM, MRX and pharmacists were compared with the explicit criteria from the Beers03, Beers12, PIEA and STOPP/START prescribing criteria. The assumption was that such criteria were clinically relevant, being mostly based on expert consensus and developed mainly in agreement with supporting evidence.

MRX was found to have more in common with both sets of Beers criteria than pharmacists, but less in common with STOPP/START or PIEA than pharmacists, see Tables 25 and 36. Such a finding is expected as MRX was designed in part around the Beers03 criteria and HEDIS 2006 criteria.[38,318,319] One of the main themes identified by MRX was *anticholinergic use not elsewhere specified*, anticholinergic medications feature prominently within these criteria.[38,320]

MRM was found to have more in common with all four criteria than pharmacists, yet was less aligned with either of the Beers criteria than MRX. This finding reinforces the wider scope of problems that were able to be identified by MRM, illustrated in Figure 23.

Comparisons with prescribing criteria showed mixed results. Certainly alignment with Beers criteria may be a positive finding. However, it should be noted that the Beers03 criteria has come under some criticism as several listed medications were either rarely prescribed or had insufficient evidence to be included in the criteria.[63,103,117] As is shown in Figure 25, other criteria identified a wider scope of issues including problems relating to undertreatment. Do these associations with differing prescribing criteria truly reflect MRM and MRX's ability to detect clinically relevant DRPs? Perhaps. An assessment of clinical relevance based on comparison with prescribing criteria was somewhat limited as it was dependent on which prescribing criteria were preferred. An investigation into a preferred prescribing criteria was subsequently performed.

Several studies have given greater preference to STOPP/START over the Beers03 criteria.[45,103,118] The findings from STOPP/START were also assessed by the expert panel and the panel found the STOPP/START findings, although fewer in number than other sources, were clinically relevant. The STOPP/START criteria were more in alignment with pharmacists findings by both frequency and scope of problems identified, than either the Beers12 or the PIEA criteria. The findings discussed in this paragraph suggest the STOPP/START criteria have the most suitable clinical relevance of those investigated.

Considering STOPP/START as the best prescribing criteria for the measure of clinical relevance, MRX sat at the bottom, pharmacists came a strong second and MRM was marked as the most relevant. Still do these rankings truly reflect MRM and MRX's ability to detect clinically relevant DRPs? The two main limitations are that STOPP/START cannot address DRPs outside of it's scope and that DRPs within scope are not sufficiently tailored for individual patient context. Other approaches were attempted to help answer the clinical relevance conundrum.

10.2.3 Expert and user opinion as a measure of clinical relevance

Expert opinion indicated that pharmacists, MRM and the STOPP/START criteria could all identify clinically relevant DRPs in the sample of cases examined. It is worth noting that MRM identified more DRPs than pharmacists yet was still considered just as relevant. The opposite view was held of MRX. These opinions add clarity to the lack of overlap in the descriptive classifications analysis between pharmacists and MRX.

The question of why MRX found problems that pharmacists did not can now be answered. The issues identified by MRX lacked clinical relevance. In addition, experts thought that MRX identified an excessive quantity of DRPs. Despite these findings MRX had much in common with the Beers criteria and several expert panel assessors thought MRX may be useful as a screening tool to assist in targeting interview questions.

Why did MRM find problems and pharmacists did not? Part of the reason is the additional 10% of repetitious findings, but even after excluding repetitious DRP findings MRM did identify a greater volume of DRPs. Experts generally did not think MRM identified an excessive number of DRPs (see Figure 43). Additionally, experts and the pharmacists who

used MRM mostly thought MRM was clinically relevant. The mechanical consistency of MRM when detecting a wide scope of relevant DRPs appeared to be the primary reason why more DRPs were identified. Despite finding a greater frequency of DRPs than pharmacists, MRM was still thought by experts to sometimes miss the detection of clinically relevant DRPs, but less so than the original pharmacists. The survey of pharmacists who used MRM showed that MRM identified clinically relevant DRPs that the pharmacists themselves had missed. This was a distinct advantage of the software as a decision support tool and a good reason why MRM was finding more DRPs. Earlier work by Bindoff *et al*. on prototype systems upon which MRM's decision support capabilities were based, showed that experts did routinely miss DRPs that were identified by the software.[167,178] This situation occurred despite the fact that the experts knew of the specific problems, as was evidenced by their identification of such problems in earlier and later cases.[178] MRM's recommendations to resolve DRPs were also considered to be appropriate, by both the expert panel and by pharmacists who use MRM, likely adding to the impression of clinical relevance.

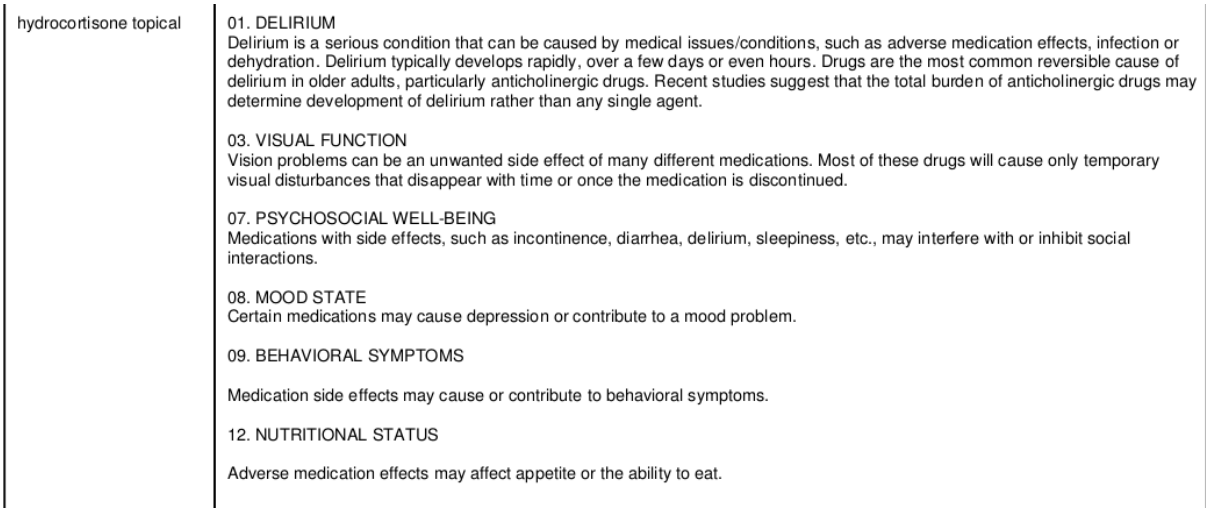
10.3 Summary of clinical relevance

When trying to determine how clinically relevant a particular DRP is in a particular patient, it was difficult to get a definitive answer. MRX found many DRPs and these were mostly irrelevant DRPs. MRX identified few types of descriptive classifications with few in common with pharmacists.

However, MRM found many more DRPs when compared to pharmacists, yet was considered by both the expert panel members and by pharmacists who used the product to find clinically relevant DRPs and surprisingly to find a not excessive number of DRPs. The wide variety of descriptive classifications identifiable by MRM including some overlap with pharmacists findings for many different classification types and in many patients adds to the opinion of relevance.

The implementation of software like MRX which assesses minimal information, presence of a medication, is not recommended when attempting to deliver quality decision support services. Many expert panel assessors were exasperated examining the MRX tool, which appeared to replicate the alert fatigue problems discussed under section 3.6.1. Additionally,

some DRPs were presented which appeared to have so little clinical relevance as to be almost laughable, an example of potential problems from a patient using topical hydrocortisone cream is shown in Figure 59.



hydrocortisone topical	01. DELIRIUM Delirium is a serious condition that can be caused by medical issues/conditions, such as adverse medication effects, infection or dehydration. Delirium typically develops rapidly, over a few days or even hours. Drugs are the most common reversible cause of delirium in older adults, particularly anticholinergic drugs. Recent studies suggest that the total burden of anticholinergic drugs may determine development of delirium rather than any single agent. 03. VISUAL FUNCTION Vision problems can be an unwanted side effect of many different medications. Most of these drugs will cause only temporary visual disturbances that disappear with time or once the medication is discontinued. 07. PSYCHOSOCIAL WELL-BEING Medications with side effects, such as incontinence, diarrhea, delirium, sleepiness, etc., may interfere with or inhibit social interactions. 08. MOOD STATE Certain medications may cause depression or contribute to a mood problem. 09. BEHAVIORAL SYMPTOMS Medication side effects may cause or contribute to behavioral symptoms. 12. NUTRITIONAL STATUS Adverse medication effects may affect appetite or the ability to eat.

Figure 59: Excerpt from MRX Med-Problem Report

MRM on the other hand, was able to incorporate a wide range of patient data available in the VALMER records and assess this data using an advanced AI-based approach. This capability gave MRM the ability to identify a reasonable quantity and reasonable scope of clinically relevant DRPs. While the scope of DRPs was less than that of pharmacists it was still sufficiently broad so as to cover 100 different descriptive classifications of which 90 were classifications also found by pharmacists. Another advantage of the AI approach used for MRM, was the functionality that enables an expert in the medication review domain, an accredited pharmacist, to readily add rules and refine existing rules stored in the knowledge base. Through the implementation of MCRDR, incremental improvements in the precision of rules in context of the uniquely varied patient situations developed more precise assessments of problems encountered. Direct improvements to the knowledge base also allows for change which is a constant in the medical field, as the development of new treatment options and methods need to be included into such software on an ongoing basis in order to maintain clinical relevance.

One salient point was that MRM identified many more DRPs than pharmacists, however, the majority of those DRPs were considered to be clinically relevant. Essentially MRM was

identifying DRPs that were missed by pharmacists. This is an important feature and has been mentioned in association with other AI software.[167,178,239] This was clearly stated by one pharmacist who used MRM:

> "I like using the software as it is a safety net for me to make sure I haven't missed anything crucial" Pharmacist id 72

The majority of pharmacists who used MRM were of the opinion that MRM identified clinically relevant DRPs that they had overlooked and unsurprisingly this was associated with pharmacists opinions that MRM was useful. Not only did MRM identify clinically relevant DRPs and find DRPs pharmacists missed, but MRM was considered, by both the expert panel assessors and by pharmacists who use MRM, to provide appropriate recommendations to resolve the identified DRPs.

Having established MRM, unlike MRX, is a clinically relevant tool is not the end of the evaluation. There are several further considerations still to be made; particularly, is the CDSS used appropriately by pharmacists?

10.3.1 Use of MRM by pharmacists

The majority of pharmacists who used MRM thought MRM identified clinically relevant DRPs, in fact there was no statistical difference in the range of opinions when compared to the expert panel. Similar to the expert panel, the pharmacists generally thought MRM's recommendations to resolve DRPs were appropriate, likely adding to the impression of clinical relevance.

However, it may not matter how clinically relevant the CDSS is, if the CDSS is not used appropriately. No comments made by pharmacists suggested they solely relied on the CDSS and no comments stated that the CDSS was completely ignored. MRM's decision support was received with healthy scepticism:

> "I find that you can't rely on it entirely, and I often add extra points that are more relevant to that particular report" Pharmacist id 72

MRM was found to identify clinically relevant DRPs and provide appropriate recommendations within its scope of knowledge. Pharmacists who used MRM found MRM

helped them manage medication reviews. Management of patient details and organising reports and interviews involves software functionality other than clinical decision support, however, many clinical decision support factors were associated with the management of medication reviews assisted by MRM. Many factors were associated with the ability to manage medication reviews, including factors which appear separate from decision support functionality. Decision support factors included identification of clinically relevant DRPs, providing appropriate recommendations, not missing relevant DRPs, using MRM DRPs in medication review reports and using MRM DRPs to prepare for patient interviews. Not surprisingly many pharmacists found MRM to be useful and were satisfied with the software. The MRM product was certainly not without problems, with repetitive identification of the same DRPs in the same patients accounting for 10% if its output, some identification of irrelevant DRPs and some lack of finesse of spelling and punctuation in DRP wording. Yet the overall opinions of clinical relevance, usefulness and satisfaction with the product were good.

10.4 CDSS Technology

Information technology is an integral component of current work practice. This has been spurred in part by increased electronic data storage and interoperability through the development of the personally controlled EHR and Australian data standards promoted by NEHTA.[321] Electronic data storage and data standards provide the substrate for proactive CDSS implementations. That is software that actively alerts, reminds or otherwise assists as a decision aid.

The technology underpinning MRM was MCRDR. This AI approach allows the software to incrementally learn how the expert applies their knowledge, while they routinely use the system. This approach allows the expert to gradually build up and refine the knowledge base, utilising all the factors of the patient case as inputs. This means that the rules are not simplistic, they may combine many variables. They are also not static, they can be incrementally improved or adjusted as new evidence or expert knowledge comes to light, without requiring any intervention from a software developer or knowledge engineer.

MRX implemented simplistic rules focusing only on the presence or absence of medications of interest. This simplicity resulted in generic and repetitive advice provided by the software. There was no patient contextualisation, not even by drug dosage nor any drug-interaction checking. It was summed up by an expert panel assessor:

> "This source has little patient relevance and is more of a generic list of ADEs which offers no clinical decision support." general practitioner, id 23

The MCRDR approach appeared to be successfully implemented in the medication review domain, although through discussions with Medscope and analysis of the user feedback it was clear that there was still room for improvement in the way it has been implemented. For instance, MRM is known to not correctly model combination therapeutic products. Additionally, it is thought to have only partially implemented the validation stage of MCRDR, which may result in slower than expected rule refinement processes, requiring more refinements to achieve equivalent accuracy. In spite of these minor shortcomings in the MRM implementation, this AI technology has shown remarkably good performance, and is considered likely to be able to offer similarly good results if it were included in other related medical domains, such as community and hospital pharmacy and general and specialist practice. This approach may be expected to reduce the alert fatigue that has previously been observed, and increase the likelihood of consistent and relevant decision-making. There were a range of pharmacist identified DRPs that were out of scope of MRM, such as compliance-related DRPs. Future implementations of the MCRDR technology might integrate a greater range of patient variables to enable a wider scope of DRP detection.

10.5 Automated prescribing criteria

Automated prescribing criteria were used as a measure of clinical relevance, yet they were also CDSS. In complexity they sit between the complex MCRDR approach of MRM and the simple presence of a drug approach used by MRX.

Sufficient information was obtained for many HMR patients to allow detailed application of the four sets of prescribing criteria. Whilst only explicit criteria were able to be automated, this encompassed the majority of criteria from each of the four sets of prescribing criteria. The main limitation with the implementation of explicit criteria was lack of information,

specifically lack of information regarding the purpose for which certain medications were prescribed or for the duration of use of certain medications.

This research has shown the various prescribing criteria have a limited scope for detection of DRPs, concentrating on problems concerning drug selection, overdosage and under-treatment (see Figure 25). The STOPP/START criteria were favourably assessed by the expert panel, with the STOPP/START DRPs generally considered to be clinically relevant although the actual number of problems found was low compared with MRM, MRX and the original pharmacists' findings. This reflects the limited set of criteria present in such a guideline. Not only were the STOPP/START criteria considered relevant by expert panel assessors but the comparison with Beers12 and PIEA also suggested STOPP/START were the preferred option. As Levy *et al.*[103] suggested:

> "No one set of criteria may ever be commonly applicable across the globe, although STOPP/START criteria appear to be the most universal and may have an advantage over others."

10.6 Future research

The simplistic one factor rules used by MRX should not be utilised in future research as the results of this thesis have shown this approach produces an excess of irrelevant findings.

The AI approach used by MRM was successful in supplementing clinically relevant DRPs to the DRPs identified by pharmacists, so enhancing the consistency and thoroughness of the pharmacists reports. However, several implementation problems were identified which may be improved in future designs:

- There were a number of instances where MRM identified and presented the same findings twice. This situation may have been improved through improved software construction.
- The treatment context of the patient needed to be considered, particularly ongoing therapy versus end-of-life therapy. If an additional variable was present to determine if the patient was nearing end of life then many DRPs associated with under-treatment for chronic medical conditions may have been avoided.

- The ATC coding used to classify medications limited analysis when combination medications were assessed by MRM, e.g. paracetamol codeine combination products. The Australian Medicines Terminology available through NEHTA provide the capacity to identify individual components within a combination medication product.[321]
- A history of unsuccessful past treatments may have allowed the software to refine the DRPs that were displayed, so avoiding presenting DRPs findings which lacked applicability due to previous treatment failure.
- Incorporating the history of medications dispensed to the patient may identify both adherence and non-adherence to treatment for routinely used chronic medications. However, it is acknowledged that access to this information may be difficult to obtain, as patients may frequent multiple pharmacies and such pharmacies nay be reluctant to divulge this information.
- Incorporating treatment costs, both cost to patient and cost to the public health systems may allow the software to make recommendations that may reduce costs to either the patient or the public health system or both. Costs to patients are a factor implicated in therapy adherence.[71]

Future versions of this software should aim to include some or all of these recommendations for improvement to further refine the software's ability to identify various types of DRP and enhance their clinical relevance. Future implementations may be able to incorporate a wealth of data present within EHRs. The advantage of this source of data would be to reduce the time taken to manually enter data and also to reduce the opportunity for data transposition errors.

This thesis examined a real-world implementation of AI approach that was specifically designed to assist pharmacists with medication reviews. This AI approach may be able to utilise similar, if not identical data, in other contexts. Examples include incorporating such software within general practice surgeries, hospital pharmacy, hospital prescriber order entry systems and community pharmacy.

Evaluation of future software that utilise the MCRDR approach may draw from both this thesis and from previous research conducted by Dr Ivan Bindoff. Bindoff *et al.* compared DRPs identified by an pharmacist expert against those identified by software as the expert was entering rules into the software through a case-by-case to develop the knowledge-base. This approach could determine the frequency DRPs missed by the expert and the frequency of incorrect DRPs identified by the software. However, this evaluation was comparable to an *in vitro* study without real-world involvement. This thesis added real-world evaluation methodologies including the comparative assessment of DRPs identified by pharmacists in the real-world against DRPs identified by the software. The application of descriptive classifications provided the opportunity to identify the amount of DRP overlap that occurred between pharmacists and software. The second useful evaluation method was the employment of an expert panel to independently judge the quality of DRPs identified by pharmacists and by software. The final approach was to obtain information from the pharmacists who used the software in their day-to-day work, to get their hands-on opinions of the software. The combination of these methodologies is anticipated to be beneficial in future analyses of this technology.

10.7 Limitations

This research evaluated the capacity of two commercial CDSS designed to assist pharmacists performing medication reviews. The core features of assessment were the identification of clinically relevant problems and provision of appropriate recommendations. Interpretation of the results must include consideration of the limitations of this evaluation.

10.7.1 Data entry errors

A large amount of data had to be entered for assessment by MRM and a lesser amount of data had to be entered for assessment by MRX. Checks of 20% of cases entered into each product were performed to confirm data was entered correctly. Errors were identified and corrected in these cases. Subsequent errors were identified and corrected when they became known. It is possible that additional data entry errors were present in the data and not corrected. However, based on the results of the validation check, errors are likely to be present in less than 1% of cases, making this a relatively minor limitation.

10.7.2 Descriptive classifications

The development of the descriptive classifications was an iterative process based initially on common DRP concepts found within prescribing criteria and both expanded and refined to include all DRPs identified by all sources. The initial 'final' set of classifications was validated by a second pharmacist and supervisor, Gregory Peterson. This resulted in several minor adjustments. It is considered that the validation process may have provided reliability to the final set of classifications. However, alternative approaches may have resulted in a different set of classifications, which in turn may have lead to differing results.

The second limitation was the mapping of DRPs to classifications. This mapping was undertaken solely by the author, Colin Curtain. The mapping process was not validated by a second person. This lack of confirmation of the mapping process may have affected the results obtained from examining the descriptive classifications, although this process was in most cases considered to be fairly straightforward, so the effect of this should not be great.

10.7.3 DOCUMENT classifications

DOCUMENT classifications were assigned to DRPs by the author, Colin Curtain. Assignment of DOCUMENT classifications to DRPs were guided by the notes and examples provided in the *Standard and guidelines for pharmacists performing clinical interventions*.[278] The assignment process was not undertaken by a second person to confirm the accuracy of the assignment process, so it is possible that some errors of classification occurred. However, the standards are quite easy to apply, and the author is very experienced with the DOCUMENT classification system, so errors are considered unlikely to be common.

10.7.4 Prescribing criteria

Prescribing criteria from Beers03, Beers12, PIEA and STOPP/START were implemented electronically. Several assumptions were made in the application of these criteria, possibly limiting their effectiveness or accuracy when identifying specific DRPs. The main limitations were not knowing the prescribed purpose of medications, not knowing the duration of use of medications and not having sufficient information recorded to accurately implement criteria or even to implement criteria at all. Additionally, a number of patients did not have any information recorded for diagnoses, laboratory tests or observational measurements.

Therefore, for a small number of criteria, the number of patients identified as having DRPs using the automated database query method may be understated.

10.7.5 Expert panel DRP errors

One set of six DRPs associated with MRX were to be included in the expert panel assessment but were missed. One STOPP DRP was included which on revision of the STOPP SQL queries should have been excluded. However, these errors were very minor, and unrelated to the major conclusions of this study, so are considered unlikely to have any significant effect on the results.

11 Conclusion

The systematic literature review uncovered a variety of CDSS which had the capability to align with the medicines review process to aid health professional activities. The use of knowledge based software which incorporates many patient variables did lead to improved expert practitioner performance[167,178,232,246] and prototype systems of this nature also reported improved consistency for the detection of DRPs.[167,178,239] However, many studies of knowledge based software were prototypes and low uptake and acceptance of CDSS was identified in many of the studies that evaluated real world implementations.[235,246–250] From this review it became apparent that one of the key drivers for poor acceptance and uptake was software presenting an excessive number of alerts that were too often irrelevant, and failed to consider enough of the patient context. The ramifications of this are serious, since there is no value in identifying a problem if it is then ignored.

The implementation of overly simple CDSS rules, such as the mere presence of a medication as was used by MRX, was insufficient to provide good decision support. The problem with such simple rules was the excessive abundance of a narrow range of generally clinically irrelevant DRPs. No contextual recommendations were possible, due to the simplicity of the rules. The excessive abundance of mostly irrelevant DRPs is considered likely to have severely hampered any potential benefit from the decision support provided by MRX, and this view was reinforced by the comments of the expert reviewers. Additionally, many clinically relevant DRPs including drug-drug or drug-disease interactions were not able to be identified by MRX. At best, MRX could be used as a tool to pre-screen patients who may require the need for medication review services as a result of a higher burden of sedative or anticholinergic medications, or perhaps as a tool to prepare lines of questioning prior to a medication review interview.

Automated versions of the prescribing criteria STOPP/START, PIEA, and Beers proved to be a slightly better tool for identifying DRPs. These tools took into account a broader spectrum of information about the patient's condition (typically diagnoses), allowing them to identify more targeted and relevant problems. The patient data present in the VALMER dataset was sufficient to be able to implement and evaluate most of these rules. Of the four sets of prescribing criteria evaluated, the STOPP/START criteria were found to be the most

representative of the original pharmacists findings in terms of both scope and the frequency with which problems fell into certain categories. Incorporation of the STOPP/START criteria to medical and pharmacy software may be readily achievable and may be able to provide basic, but clinically relevant decision support. Definitely more than simple solutions such as MRX, but not as broad, contextualised or detailed as more advanced systems such as MRM.

The most noteworthy result of this thesis was the good performance of MRM. The relatively detailed and well-formed underlying patient record, combined with the AI technology used by MRM, allowed for extensive contextualisation of findings, resulting in a wide variety of clinically relevant DRPs. The associated recommendations were also appropriately contextualised, and were considered by both the pharmacist users of the software, as well as the expert panel, to be of high quality and value. The identification of DRPs incorporating patient context is vital, as this appears to be the key to maximising clinical relevance and minimising irrelevant findings. The opinions from the expert panel strongly supported the clinical relevance of these contextualised DRPs, rating them as highly as those identified by the original pharmacist reviewers, despite the fact that MRM identified substantially more DRPs than the pharmacists. These opinions were further supported by the pharmacist subscribers of MRM, who generally indicated a high regard for the findings and recommendations made by MRM and they were satisfied with the product. They found the CDSS to be useful, and importantly, quite capable of identifying clinically relevant DRPs that they might otherwise have overlooked themselves.

The overlap of the same DRPs found in the same patients by both pharmacists and MRM was low. However, both MRM and pharmacists identified differing although clinically relevant DRPs in both the same and different patients. This finding highlights the advantage of using this software to complement the pharmacists findings. The software supplements pharmacists findings with clinically relevant DRPs so that pharmacists have a wider range of DRPs to present in their medication review reports. The additional software-found DRPs promote the consistency and thoroughness of the pharmacists work. The prepared wording in MRM for DRP resolutions presented more suitable wording than the pharmacists own wording.

However, MRM was not without problems. The first and most evident problem was the presentation of essentially duplicated DRPs, which made up ten percent of the DRP volume.

The second problem was the presentation of DRPs based on one rule that did not appear to be clinically relevant. MRM found over one hundred instances of calcium channel blockers associated with reflux, however, this problem was identified only once by a pharmacist. However, this problem is considered to be relatively minor, since the rule can easily be refined until it no longer appears erroneously. This is a strength of the MCRDR approach that underpins the CDSS within MRM, where rules can easily and naturally be continually refined and improved upon while the system is in routine use, without the need for intervention by a software developer or knowledge engineer.[167]

In light of the performance of MRM seen in this research, it is reasonable to expect that future CDSS applications using the MCRDR approach could provide significant benefits over the much simpler technologies that are typically utilised, with very limited success, worldwide. These benefits include the identification of clinically relevant problems both more frequently, and more consistently, yet with very few clinically irrelevant problems identified. Furthermore, this consistently high performance level leads to better uptake and acceptance rates by users, ensuring that the problems are not only identified, but are actually acted upon when appropriate to do so. Such CDSS implementations might be successfully incorporated into a wide variety of healthcare settings, such as hospital, general and specialist practice, and community pharmacy. Given the results of this thesis, that the technology now exists, and that quality patient EHR data is gradually becoming more available, it seems that the time has come for this technology to be applied more widely.

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Appendix 1 Prescribing criteria and automation

Table 53: Beers03 prescribing criteria

Criterion	Implemented	DOCUMENT	Description	Descriptive classification ID
Beers table 1: PIMs independent of diagnoses or conditions				
1	Y	D6	(dextro)propoxyphene and combination products	118
2	Y	D6	Muscle relaxants and antispasmodics, oxybutinin	11,
3	Y	D6	Amitriptyline	11
4	Y	D6	Doxepin	11
5	Y	O1	Lorazepam >3mg oxazepam >60mg alprazolam >2mg temazepam >15mg triazolam >0.25mg	12
6	Y	D6	Long acting benzodiazepines	12
7	Y	D6	Disopyramide	118
8	Y	O1	Digoxin > 0.125mg/day	1
9	N		Dipyridamole, short-acting	
10	Y	D6	Methyldopa	100
11	N		Chlorpropamide	
12	Y	D6	Gastrointestinal antispasmodics	11
13	Y	D6	Anticholinergics and antihistamines	11
14	Y	O1	Ferrous sulphate > 325mg/day	91
15	Y	D6	Pethidine (meperidine)	118
16	Y	D6	Ticlopidine	118
17	Y	D6	Ketorolac	19
18	Y	D6	Amphetamines and anorexic agents	118
19	Y	D6	Long term use of full-dosage non-COX selective NSAIDS – piroxicam 20mg, naproxen 1000mg	19
20	Y	D6	Daily fluoxetine	114
21	Y	D6	Long term stimulant laxatives	55
22	Y	D6	Amiodarone	113
23	Y	D6	Nitrofurantoin	63
24	Y	D6	Thioridazine	118
25	Y	D6	Short-acting nifedipine	118
26	Y	D6	Clonidine	100
27	Y	D6	Mineral oil	56
28	Y	D6	Cimetidine	118
29	Y	D6	Estrogens only (oral)	105
49	Y	D6	Indomethacin	19
50	Y	D6	Diphenhydramine	11
51	Y	D6	Ergot mesyloids	118
52	Y	D6	Orphenadrine	118
53	Y	D6	Methyltestosterone	118
54	Y	D6	Amphetamines excluding methylphenidate and anorexics	118
55	Y	D6	Ethacrynic acid	118
	N		Pentazocine	
	N		Trimethobenzamide	
	N		Flurazepam	
	N		Doxazosin	
	N		Meprobamate	
	N		Reserpine	
	N		Methyltestosterone	
	N		Mesoridazine	

Criterion	Implemented	DOCUMENT	Description	Descriptive classification ID
	N		Desiccate thyroid	
	N		Guanethidine	
	N		Guanadrel	
	N		Cyclandelate	
	N		Isoxsurpine	
Beers table 2: PIMs considering diagnoses or conditions				
30	Y	D6	Heart failure and disopyramide or high sodium drugs	36, 118
31	Y	D6	Hypertension and pseudoephedrine or amphetamines	104
32	Y	D6	Gastric or duodenal ulcers and NSAIDs or higher dose aspirin	19
33	Y	D6	Seizures or epilepsy and clozapine or thioridazine	15
34	Y	D6	Blood clotting disorders or receiving anticoagulant therapy and aspirin, NSAIDs, dipyridamole, ticlopidine or clopidogrel	10, 19
35	Y	D6	Bladder outflow obstruction and anticholinergics, antihistamines, oxybutinin, TCAs	11
36	Y	D6	Stress incontinence and alpha-blockers, anticholinergics, TCAs, long-acting benzodiazepines	11,
37	Y	D6	Arrhythmias and TCAs	11
38	Y	D6	Insomnia and theophylline, methylphenidate, mono-amine oxidase inhibitors or amphetamine	104
39	Y	D6	Parkinson disease and metoclopramide, conventional antipsychotics or tacrine	14
40	Y	D6	Cognitive impairment and barbiturates, anticholinergics, antispasmodics, CNS stimulants	42
41	Y	D6	Depression and long-term benzodiazepines or methyldopa	104
42	Y	D6	Anorexia and malnutrition and amphetamine, methylphenidate or fluoxetine	104
43	Y	D6	Syncope or falls and benzodiazepines, TCAs,	25
44	Y	D6	Syndrome of inappropriate antidiuretic hormone secretion/hyponatraemia and SSRIs	104
45	Y	D6	Seizure disorder and bupropion	15
46	Y	D6	Obesity and olanzapine	104
47	Y	D6	COPD and long-acting benzodiazepines, beta-blockers	2
48	Y	D6	Chronic constipation and calcium channel blockers, anticholinergics, TCAs	17, 62

68 Beers03 criteria, 53 implemented, 15 not implemented. The criterion number matches the order of implementation, not the order of appearance in the Beers03 criteria.

Table 54: STOPP prescribing criteria

Criterion	Implemented	DOCUMENT	Description	Descriptive classification ID
A1	Y	O1	Digoxin at a long-term dose > 125 µg/day with impaired renal function	1
A2	Y	D7	Loop diuretic for dependent ankle edema only	69
A3	Y	D6	Loop diuretic as first-line monotherapy for hypertension	82
A4	Y	D6	Thiazide diuretic with a history of gout	97
A5	Y	D6	Non-cardioselective beta-blocker with Chronic Obstructive Pulmonary Disease	2
A6	Y	D2	β-blocker in combination with verapamil	86

Criterion	Implemented	DOCUMENT	Description	Descriptive classification ID
A7	Y	D6	Use of diltiazem or verapamil with NYHA class III or IV heart failure	3
A8	Y	D6	Calcium channel blockers with chronic constipation	62
A9	Y	D2	Use of aspirin and warfarin in combination without histamine H_2-receptor antagonist or proton pump inhibitor	150
A10	Y	D7	Dipyridamole as monotherapy for cardiovascular secondary prevention	118
A11	Y	D6	Aspirin with a past history of peptic ulcer disease without histamine H_2-receptor antagonist or proton pump inhibitor	10
A12	Y	O1	Aspirin at a dose > 150mg/day	8
A13	Y	D7	Aspirin with no history of coronary, cerebral or peripheral vascular symptoms or occlusive event	9
A14	N		Aspirin to treat dizziness not clearly attributable to cerebrovascular disease	
A15	N		Warfarin for first uncomplicated deep venous thrombosis for longer than 6 months duration	
A16	N		Warfarin for first uncomplicated pulmonary embolus for longer than 12 months duration	
A17	Y	D6	Aspirin, clopidogrel, dipyridamole or warfarin with concurrent bleeding disorder	10
B1	Y	D6	TCAs with dementia	42
B2	Y	D6	TCAs with glaucoma	11
B3	Y	D6	TCAs with cardiac conductive abnormalities	11
B4	Y	D6	TCAs with constipation	17
B5	Y	D2	TCAs with an opiate or calcium channel blocker	17
B6	Y	D6	TCAs with prostatism or prior history of urinary retention	11
B7	Y	D7	Long-term, long-acting benzodiazepines	12
B8	N		Long-term neuroleptics as long-term hypnotics	
B9	Y	D6	Long-term neuroleptics in those with parkinsonism	14
B10	Y	D6	Phenothiazines in patients with epilepsy	15
B11	Y	D2	Anticholinergics to treat extrapyramidal side effects of neuroleptic medications	11
B12	Y	D6	Selective serotonin re-uptake inhibitors with a history of clinically significant hyponatremia	104
B13	Y	D7	Prolong use of first-generation antihistamines	42
C1	N		Diphenoxylate, loperamide or codeine phosphate for treatment of diarrhoea of unknown cause	
C2	Y	D6	Diphernoxylate, loperamide or codeine phosphate for treatment of severe infective gastroenteritis	104
C3	Y	D6	Prochlorperazine or metoclopramide with parkinsonism	14
C4	Y	O1	PPI for peptic ulcer disease at full therapeutic dosage for > 8 weeks	7
C5	Y	D6	Anticholinergic anstispasmodic drugs with chronic constipation	17
D1	Y	D7	Theophylline as monotherapy for COPD	118
D2	Y	D5	Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-to-severe COPD	126
D3	Y	D6	Nebulized ipratropium with glaucoma	11
E1	Y	D6	NSAID with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent histamine H2-receptor antagonist or PPI or misoprostol	19
E2	Y	D6	NSAID with moderate-to-severe hypertension	19
E3	Y	D6	NSAID with heart failure	19
E4	Y	D0	Long-tern use of NSAID for symptom relief of mild osteoarthritis	19
E5	Y	D2	Warfarin and NSAID together	4

Criterion	Implemented	DOCUMENT	Description	Descriptive classification ID
E6	Y	D6	NDAIS with chronic renal failure	20
E7	Y	D6	Long-term corticosteroids as monotherapy for rheumatoid arthritis or osteoarthritis	127
E8	Y	D6	Long-term NSAID for colchicine for chronic treatment of gout where there is no contradiction to allopurinol	19
F1	Y	D6	Bladder antimuscarinic drugs with dementia	42
F2	Y	D6	Antimuscarinic drugs with chronic glaucoma	11
F3	Y	D6	Antimuscarinic drugs with chronic constipation	17
F4	Y	D6	Antimuscarinic drugs with chronic prostatism	11
F5	Y	D6	α-blockers with frequent incontinence	82
F6	N		α-blockers with long-term urinary catheter in situ	
G1	Y	D6	Glibenclamide or chlorpropamide with type 2 diabetes mellitus	24
G2	N		β-blockers in those with diabetes mellitus and frequent hypoglycemic episodes	
G3	Y	D6	Estrogens with a history of breast cancer or venous thromboembolism	105
G4	Y	U1	Estrogens without progestogen in patients with intact uterus	105
H1	Y	D6	Benzodiazepines and fallers	25
H2	Y	D6	Neuroleptic drugs and fallers	25
H3	Y	D6	First-generation antihistamines and fallers	25
H4	Y	D6	Vasodilator drugs with persistent postural hypotension	25
H5	Y	D6	Long-term opiates in those with recurrent falls	25
I1	N		Use of long-term powerful opiates as first-line therapy for mild-to-moderate pain	
I2	Y	U3	Regular opiates for more than 2weeks in those with chronic constipation without concurrent use of laxatives	26
I3	Y	D6	Long-term opiates in those with dementia unless indicated for palliative care or management of moderate/severe chronic pain syndrome	104
J	Y	D1	Any duplicate drug class prescription	49

65 STOPP criteria, 57 implemented, 8 not implemented

Table 55: START prescribing criteria

Criterion	Implemented	DOCUMENT	Description	Descriptive classification ID
A1	Y	U2	Warfarin in the presence of chronic atrial fibrillation	27
A2	Y	U2	Aspirin in the presence of chronic atrial fibrillation, where warfarin is contraindicated, but not aspirin	27
A3	Y	U2	Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm	28
A4	Y	U2	Antihypertensive therapy where systolic blood pressure consistently > 160mmHg	52
A5	Y	U2	Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, where the patient's functional status remains independent for activities of daily living and life expectancy is greater than 5 years	29
A6	Y	U2	ACEI with chronic heart failure	30
A7	Y	U2	ACEI following acute myocardial infarction	125

Criterion	Implemented	DOCUMENT	Description	Descriptive classification ID
A8	Y	U2	β-blocker with chronic stable angina	31
B1	Y	U2	Regular inhaled β_2-agonist or anticholinergic agent for mild-to-moderate asthma or COPD	
B2	N		Regular inhaled corticosteroid for moderate/severe asthma or COPD, where predicted $FEV_1 < 50\%$	
B3	N		Home continuous oxygen with documented chronic type 1 or type 2 respiratory failure	
C1	N		L-DOPA in idiopathic Parkinson's disease with definite functional impairment and resultant disability	
C2	Y	U2	Antidepressant drug in the presence of moderate/severe depressive symptoms lasting at least three months	121
D1	N		PPI with severe gastroesophageal acid reflux disease or peptic stricture requiring dilation	
D2	Y	U2	Fibre supplement for chronic, symptomatic diverticular disease with constipation	62
E1	N		Disease-modifying antirheumatic drug with active moderate/severe rheumatoid disease lasting > 12 weeks	
E2	Y	U2	Bisphosphonates in patients taking maintenance corticosteroid therapy	67
E3	Y	U2	Calcium and vitamin D supplement in patients with known osteoporosis	33
F1	Y	U2	Metformin with type 2 diabetes ± metabolic syndrome	58
F2	Y	U2	ACEI or ARB in diabetes with nephropathy	34
F3	Y	U2	Antiplatelet therapy in diabetes mellitus with coexisting major cardiovascular risk factors	28
F4	Y	U2	Statin therapy in diabetes mellitus of coexisting major cardiovascular risk factors present	29

22 START criteria, 17 implemented, 5 not implemented

Table 56: PIEA prescribing criteria

Criterion	Implemented	DOCUMENT	Description	Descriptive classification ID
1	Y	U1	Patient taking an antihypertensive is NOT at their target blood pressure	52
2	Y	U1	Patient at high risk of cardiovascular event is NOT taking an HMG-CoA reductase inhibitor	29
3	Y	U1	Patient with IHD or history of MI is NOT taking a beta-blocker	31
4	Y	U1	Patient with IHD or a history of MI is NOT taking an antiplatelet agent unless taking an oral anticoagulant	28
5	Y	U1	Patient with heart failure is NOT taking a beta-blocker	31
6	Y	U1	Patient with heart failure is NOT taking an ACEI or ARB	30
7	Y	D6	Patient with heart failure IS taking medications that may exacerbate heart failure	3, 19, 36, 104
8	Y	D6	Patient with heart failure or hypertension IS taking high sodium-containing medications	36
9	Y	U1	Patient with AF is NOT taking an oral anticoagulant	27
10	Y	O0	Patient with AF taking an anticoagulant DOES NOT have an INR between 2 and 3	70
11	Y	U1	Patient with a history of non-haemorrhagic stroke or TIA is NOT taking	28

Criterion	Implemented	DOCUMENT	Description	Descriptive classification ID
			an antiplatelet agent unless taking an anticoagulant	
12	Y	O1	Patient with risk factors for myopathy IS taking >= 40mg/day simvastatin or atorvastatin	64
13	Y	D6	Patient with cardiovascular disease IS taking an NSAID	19
14	N		Patient with cardiovascular, respiratory disease or diabetes mellitus who smokes has NOT been offered smoking cessation	
15	Y	U1	Patient with type 2 diabetes and hypertension and albuminuria is NOT taking an ACE inhibitor or ARB	34
16	Y	U1	Patient with diabetes at high risk of cardiovascular event is NOT taking an antiplatelet agent unless taking an anticoagulant	28
17	Y	D6	Patient with diabetes IS taking a medication that may increase or decrease blood glucose concentrations	44
18	Y	M1	Patient with diabetes has NOT had an HBA1c measurement within the previous 6 months	137
19	Y	O1	Patient taking metformin for diabetes has NOT had the dose adjusted for creatinine clearance	71
20	Y	D6	Patient taking metformin for diabetes IS concurrently taking glibenclamide	24
21	N		Patient with OA pain interfering with daily activities has NOT been trialled on paracetamol 2-4g daily	
22	N		Patient taking analgesics DOES have pain that interferes with daily activities	
23	Y	U2	Patient taking an opioid is NOT taking prophylactic treatment for constipation	26
24	Y	D6	Patient with risk factors for impaired renal function IS taking an NSAID	20
25	Y	D2	Patient IS concurrently taking an ACEI or ARB, diuretic and NSAID (excluding low-dose aspirin)	21
26	Y	D6	Patient with sleep disturbance or anxiety HAS been taking benzodiazepines for >4 weeks	12
27	Y	D6	Patient with depression IS taking anticholingeric-type antidepressants	11
28	Y	D6	Patient with a history of falls IS taking psychotropic medications	25
29	Y	D2	Patient taking an SSRI IS concurrently taking medications known to increase the risk of gastrointestinal bleeding	4
30	Y	D2	Patient taking an SSRI IS concurrently taking other medications that may contribute to serotonin syndrome	66
31	Y	D6	Patient with dementia IS receiving anticholinergic medication	42
32	Y	D2	Patient IS taking more than one medication with anticholinergic activity	11
33	Y	D2	Patient taking a PPI IS taking a medication that may cause dyspepsia	101
34	Y	D6	Patient with COPD IS taking benzodiazepines	37
35	Y	U1	Patient with asthma using an inhaled LABA is NOT also using an inhaled corticosteroid	32
36	N		Patient using salbutamol or terbutaline inhaler more than three times a week for reversible airways disease has NOT been prescribed an inhaled corticosteroid	
37	Y	D6	Patient with asthma IS taking a medication that may worsen asthma	2
38	Y	U1	Female patient with recurrent UTI has NOT been prescribed intravaginal oestrogen	82
39	Y	D6	Patient with a creatinine clearance <60ml/min IS receiving nitrofurantoin for UTI	63
40	Y	D6	Patient with a creatinine clearance <50ml/min IS receiving methenamine for UTI prophylaxis	95
41	N		Patient with an URTI IS receiving antibacterials	

Criterion	Implemented	DOCUMENT	Description	Descriptive classification ID
42	N		Patient with osteoporosis who is not receiving at least 600IU vitamin D daily from diet is NOT receiving supplementation with vitamin D	
43	N		Patient with osteoporosis who is not receiving at least 1200mg calcium daily from diet is NOT receiving calcium supplementation	
44	Y	U2	Patient with osteoporosis is NOT receiving anti-osteoporotic medication	67
45	N		Patient using topical corticosteroids DOES have itch or discomfort that interferes with daily activities	
46	N		Patient has NOT received influenza and pneumococcal vaccination	
47	N		Patient HAS significant medication interactions	
48	N		Patient HAS HAD significant change in medications in the previous 90 days	

48 PIEA criteria, 37 implemented, 11 not implemented

Table 57: Beers12 prescribing criteria

Criterion	Implemented	DOCUMENT	Description	Descriptive classification ID
Beers table 2: PIMs				
1	Y	D6	First generation antihistamines	11
2	Y	D6	Antiparkinson agents	11
3	Y	D6	Antispasmodics	11
4	N		Dipyridamole, short-acting	
5	Y	D6	Ticlopidine	118
6	Y	D6	Nitrofurantoin	63
7	Y	D6	Alpha blockers	118
8	Y	D6	Alpha blockers central	100
9	Y	D6	Antiarrhythmic drugs	113
10	Y	D6	Disopyramide	118
11	Y	D6	Dronedarone	118
12	Y	O1	Digoxin > 0.125mg/d	1
13	Y	D6	Nifedipine, immediate release	118
14	Y	O1	Spironolactone > 25mg/d	91
15	Y	D6	Tertiary TCAs	11
16	Y	D6	Antipsychotics	104
17	Y	D6	Thioridazine	104
18	Y	D6	Barbituates	12
19	Y	D6	Benzodiazepines	12
20	Y	D6	Chloral hydrate	12
21	Y	D6	Meprobamate	12
22	Y	D6	Nonbenzodiazepine hypnotics	12
23	Y	D6	Ergot mesyloids	118
24	Y	D6	Androgens	118
25	N		Dessicated thyroid	
26	Y	D6	Estrogens with or without progestins	105
27	Y	D6	Growth hormone	118
28	Y	D6	Insulin, sliding scale	118
29	Y	D6	Megestrol	118

Criterion	Implemented	DOCUMENT	Description	Descriptive classification ID
30	Y	D6	Sulphonylureas, long duration	24
31	Y	D6	Metoclopramide	14
32	Y	D6	Mineral oil, oral	56
33	N		Trimethobenzamide	
34	Y	D6	Pethidine (meperidine)	118
35	Y	D6	Non-COX-selective NSAIDS, oral	19
36	Y	D6	Indomethacin, Ketorolac	19
37	N		Pentazocine	
38	Y	D6	Skeletal muscle relaxants	25, 42
Beers table 3: PIMs considering drug-disease or drug-syndrome interactions				
1 (39)	Y	D6	Heart failure	19, 60, 149, 3
2 (40)	Y	D6	Syncope	25
3 (41)	Y	D6	Chronic seizures or epilepsy	15
4 (42)	Y	D6	Delirium	42, 25
5 (43)	Y	D6	Dementia and cognitive impairment	42,104
6 (44)	Y	D6	History of falls or fractures	25
7 (45)	Y	D6	Insomnia	118
8 (46)	Y	D6	Parkinson's disease	14
9 (47)	Y	D6	Chronic constipation	17,62
10 (48)	Y	D6	History of gastric or duodenal ulcers	19
11 (49)	Y	D6	Chronic kidney disease Stages	20,
12 (50)	Y	D6	Urinary incontinence (all types) in women	104
13 (51)	Y	D6	Lower urinary tract symptoms, benign prostatic hyperplasia	104
14 (52)	Y	D6	Stress or mixed incontinence	104

52 Beers12 criteria, 48 implemented, 4 not implemented. The criterion number matches the order as listed in Beers12 Table 2 *2012 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults* and following on in Table 3 *2012 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults Due to Drug-Disease or Drug-Syndrome Interactions That May Exacerbate the Disease or Syndrome*.

Each criterion in these sets of prescribing criteria can be matched using the descriptive classification ID to the to the descriptive classifications listed in tables in Appendix 9.

Appendix 2 Changes from Beers03 to Beers12

Table based on Marcum and Hanlon's article on the new Beers criteria.[322]

Inappropriate medications in Beers03 excluded from Beers12

Amphetamines and anorexic agents
Chloral hydrate
Fluoxetine
Ethacrynic acid
Cimetidine
Long-term use of stimulant laxatives (except in the presence of opioid use)
Ferrous sulfate > 325 mg/d
Propoxyphene and combination products

Inappropriate medications new additions to Beers12

Anticholinergics to treat extrapyramidal side effects of neuroleptic medications
Antipsychotics (for behavioral problems of dementia)
Nonbenzodiazepine ("Z") hypnotics
Aspirin for primary prevention (to be used with caution in adults ≥80 years old for primary prevention of cardiac events
Spironolactone > 25 mg/day
Glibenclamide
Growth hormone
Megesterol
Sliding scale insulin
Metoclopramide

Medication - disease interactions in Beers03 excluded from Beers12

CNS stimulants (e.g., dextroamphetamine, methylphenidate, methamphetamine, pemolin) and anorexia or malnutrition
Tricyclic antidepressants and cardiac conduction abnormalities
propranolol and COPD
barbiturates, CNS stimulants and dementia or cognitive impairment
long-term benzodiazepines, methyldopa, reserpine, guanethidine and depression
disopyramide, high-sodium content drugs and systolic heart failure
amphetamines, diet pills, NSAIDs, phenylpropanolamine, pseudoephedrine and hypertension
mono-amine-oxidase inhibitors, oral decongestants and insomnia
olanzapine and obesity
tacrine and parkinsons disease
long-acting benzodiazepines and stress incontinence

Medication - disease interactions new additions to Beers12

Antipsychotics and chronic constipation
Bladder antimuscarinic drugs (e.g., oxybutynin) and chronic constipation
NSAIDS, Triamterene and chronic kidney disease
Anticholinergics, Benzodiazepines, Chlorpromazine, Corticosteroids, H 2 -receptor antagonists, Meperidine, Sedative hypnotics, Thioridazine, Tricyclic antidepressants and delirium
antipsychotics, benzodiazepines, H 2 -receptor antagonists, tricyclic antidepressants, zolpidem and dementia or cognitive impairment
thiazolidinediones and hear failure
estrogen with history of breast cancer or venous thromboembolism
anticonvulsants, antipsychotics, SSRIs, nonbenzodiazepine hypnotics and history of falls or fractures
promethazine and parkinson's disease

maprotiline, tramadol and seizures
acetylcholinesterase inhibitors, alpha-blockers, chlorpromazine, olanzapine, thioridazine and syncope
estrogen and urinary incontinence in women

Appendix 3 MedOptz replaces Monitor-Rx

From: Colin Curtain
Sent: Tuesday, 22 January 2013 8:59 AM
To: Douglas Allen
Cc: g.peterson@utas.edu.au; Ivan Bindoff (ibindoff@utas.edu.au); Juanita Westbury
Subject: Feedback regards Monitor-Rx

Dear Doug,

I was provided access to Monitor-Rx on a trial basis during 2011.
As discussed in an email, Oct 5 2011, my intention was to investigate, as a component of a PhD, the potential of Monitor-Rx to support consultant pharmacists in producing consistent quality reports for physicians. My intention was to compare software conclusions against conclusions produced by consultant pharmacists. I note an article in The Consultant Pharmacist, volume 27 no 2, by Lukazewski et al, compared findings of pharmacists with findings of Monitor-Rx.
I entered the details of 108 patients into Monitor-Rx for assessment and I decided at the time the findings obtained from the software were sufficient for my needs. I believe Monitor-Rx is useful for screening patients for medication-related geriatric syndromes.
You did ask for feedback for my use of the product, to which I provided some feedback at the time, October 31st 2011. I have since looked at the Monitor-Rx responses in greater depth and thought you may be interested:
I employed a panel of 12 experts in pharmacology to assess potential drug-related problems (DRPs) found in 20 patients. DRPs were identified, among others, by consultant pharmacists (73 potential DRPs) and by geriatric syndrome using Monitor-Rx (259 potential DRPs).
I presented a statement for each DRP, the findings are shown:
"The DRP is clinically relevant in this case, i.e. if unresolved the DRP would have resulted in a suboptimal outcome (e.g. under treatment, patient harm)"

Likert response	Consultant pharmacists	Monitor-Rx
Strongly agree	13%	1%
Agree	60%	19%
Neutral	18%	15%
Disagree	8%	36%
Strongly disagree	0%	29%

Several tables of expert panel results presented here

It seems that Monitor-Rx does not incorporate factors such as patient diagnoses and symptoms or pathology or observational results to produce a contextualised assessment for individual patients. This leads to the results shown above. My intention would be to publish articles which include these results in health-related or information technology-related journals. Such articles will likely compare the advantages and limitations of decision support applications which can assist medication therapy assessment.
Monitor-Rx certainly has a place as a screening tool, definitely suited to preparing consultant pharmacists for patient assessment by directing questions around any potential geriatric syndromes which might arise from medication use. From my findings, the main types of problems identified surrounded prescribed anticholinergics and sedatives leading to geriatric syndromes, and risk of falls with prescribed medications. Understandably, Monitor-Rx is probably less suited to the Australian context of community-based medications reviews.
Monitor-Rx certainly has a beneficial role in aged care facilities to prioritize patient assessments. Monitor-Rx also has potential to incorporate diagnoses in combination with medication therapy to improve patient context.

I hope this feedback is some use. If you have any comments please get in touch with me,

Figure 60: An email providing feedback of expert panel responses was sent to Douglas Allen on 22nd January 2013

Introducing MedOptz

David Dring <dave@dring.org>

You forwarded this message on 1/02/2013 8:24 AM.

Important

Sent: Thu 31/01/2013 7:36 PM

To:

Hello Friends -

Thank you for your past interest in and support of Monitor-Rx. Today marks an important step in the journey of creating a tool that will help professionals practice medication therapy management. Today, we've softly launched MedOptz, the next version of an online service to help consultant pharmacists and others provide effective and efficient MTM services. This is a long journey and we have a lot of work to do, but as of today Monitor-Rx is now replaced by MedOptz.

If you are still a subscriber, your Monitor-Rx credential will let you log into MedOptz.com and your data from Monitor-Rx was transferred to MedOptz. in fact, you'll probably notice that there are a lot of similarities between two services. We are in the development of many new features that will be released in the near future and we're planning a more formal launch in the next couple of months.

If you're no longer a subscriber but would be interested in a trial account, let me know and I'll get one set-up for you.

Best wishes!
-david

Figure 61: Email from MedOptz co-founder David Dring sent on 31 January 2013

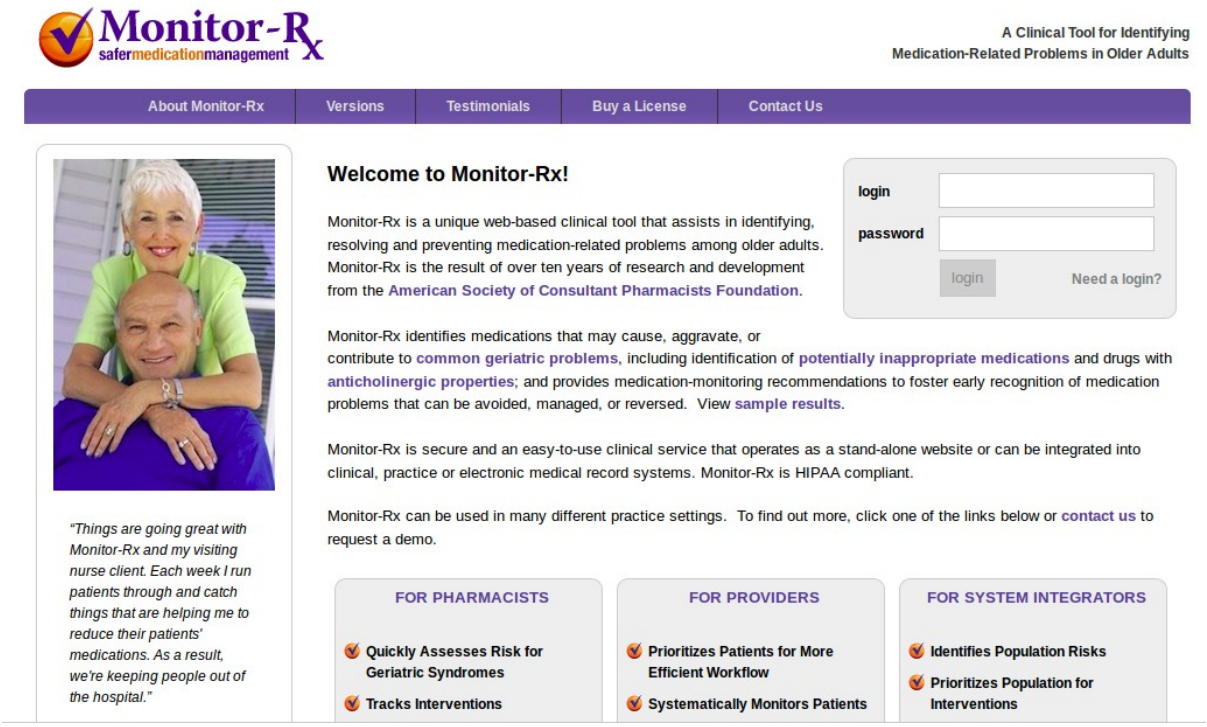

Figure 62: Monitor-Rx home page screenshot taken 8th May 2012 (www.monitor-rx.com)

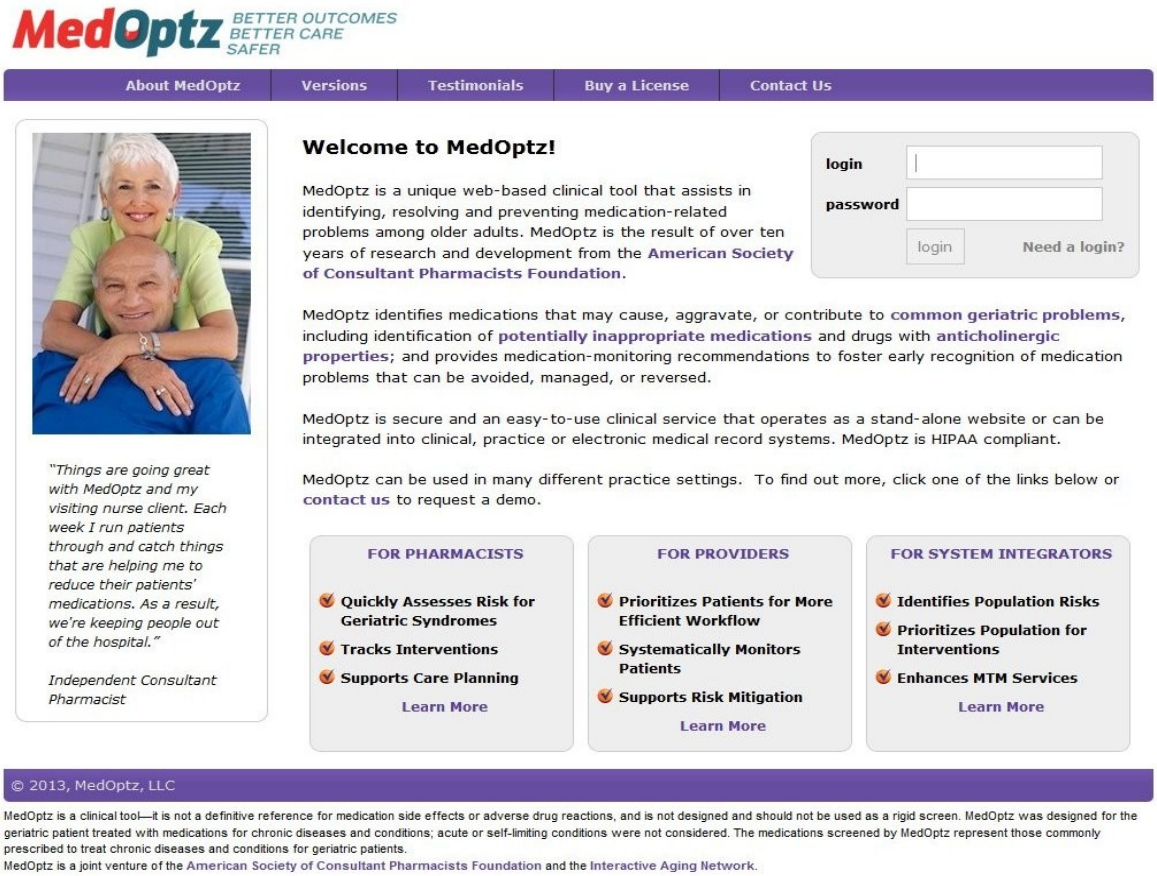

Figure 63: MedOptz home page screenshot taken 21st Feb 2013 (www.medoptz.com)

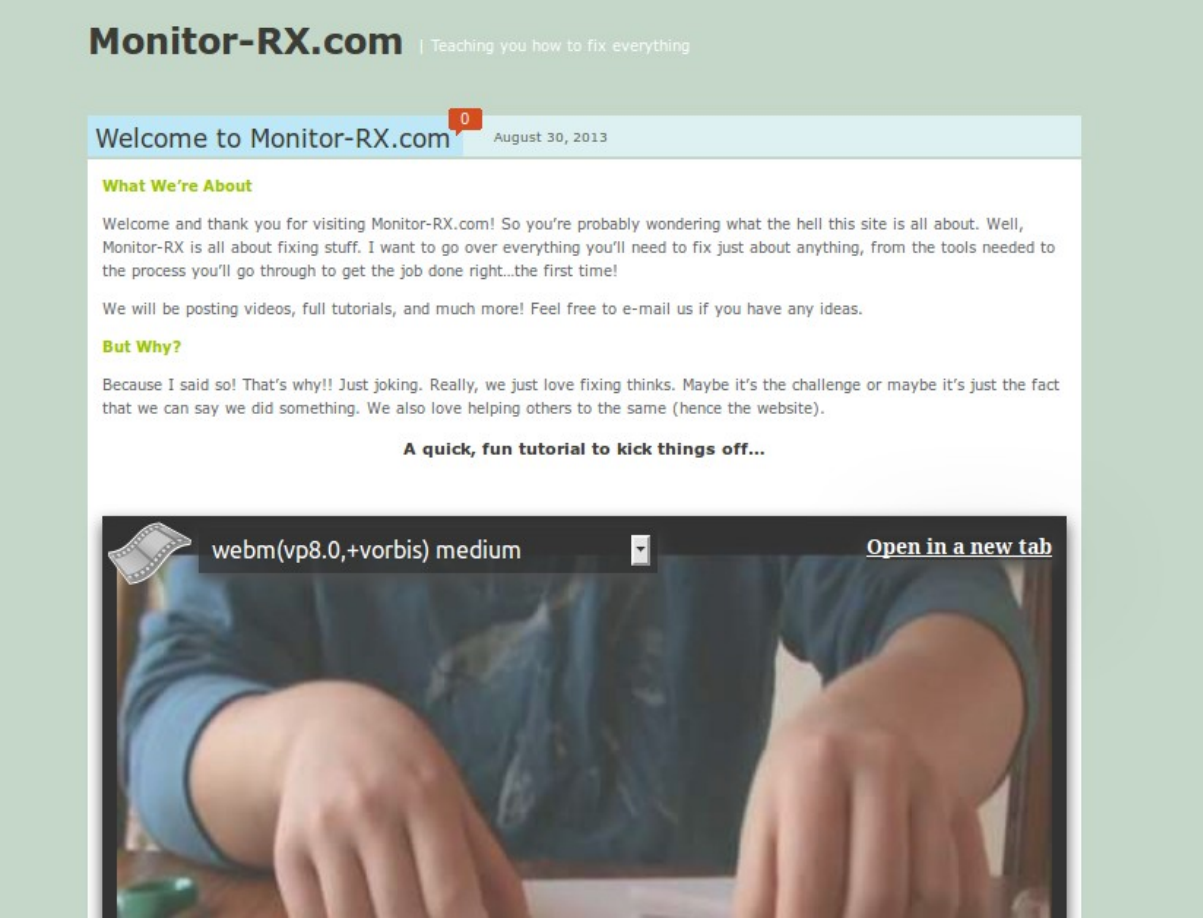

Figure 64: Monitor-RX home page screenshot taken 27 March 2014 (www.monitor-rx.com)

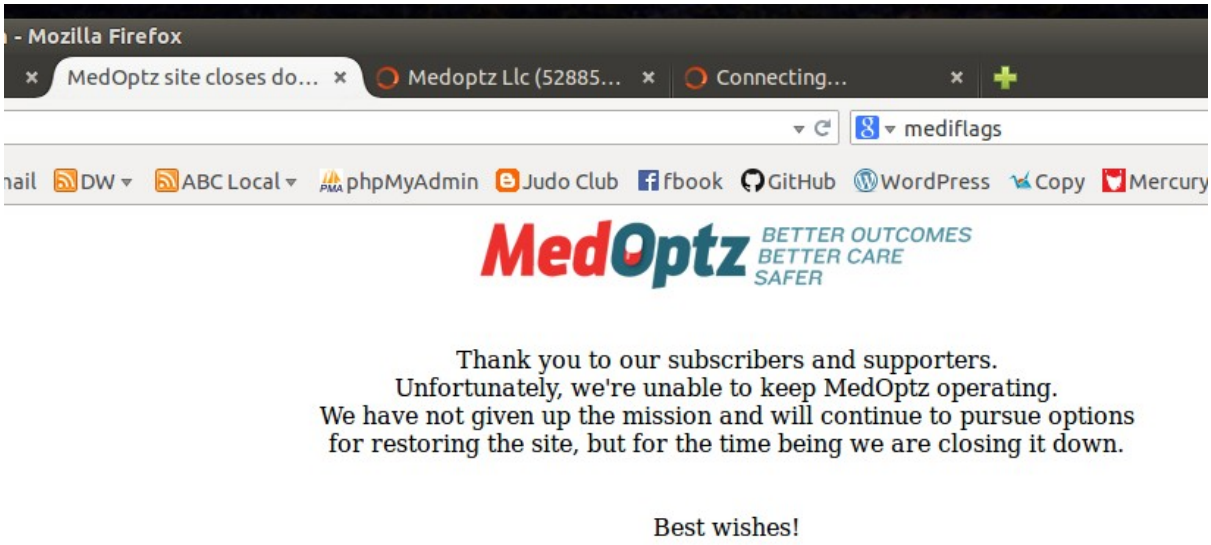

Figure 65: Medoptz website screenshot taken 14th July 2014 (www.medoptz.com)

Appendix 4 Prescribing criteria automation limitations

Beers03 limitations

Interpretation of criteria

Accurate information regarding several patient conditions was not available so umbrella grouping terms were used.

- Criterion 19 – "Long-term use of full-dosage, longer half-life, non-COX selective NSAIDs … naproxen … piroxicam ..." Full daily dosage was obtained from eMIMs[281] as being 20mg for piroxicam and 1000mg for naproxen.
- Criterion 35 – Bladder outflow obstruction was grouped under *U08 Urinary Retention.* All cases assigned *U08* were identified.
- Criterion 36 – Stress incontinence was grouped under *U04 incontinence urine*). All cases assigned *U04* were identified.
- Criterion 44 – Syndrome of inappropriate antidiuretic hormone did not have a specific category in the ICPC-2 plus classifications so the hyponatraemia term (TermID 6087) was used.

Assumption of long term medication use

No information was available to determine whether patients were using certain medications over the long term. The assumption was made that patients were using medications long term.

- Criterion 19 – The use of non-COX selective NSAIDs over a long term.
- Criterion 21 – The use of stimulant laxatives over a long term except when using opiates.

Medications not available in Australia

Several medications were not incorporated into automated queries as they were not available in Australia: pentazocine, trimethobenzamide, methocarbamol, carisoprodol, chlorzoxazone,

metaxalone, cyclobenzaprine, flurazepam, chlordiazepoxide-amitriptyline, perphenazine-amitriptyline, meprobamate, chlordiazepoxide, clidinium-chlordiazepoxide, quazepam, halazepam, clorazepate, methyldopa-hydrochlorothiazide, reserpine, chlorpropamide, dicyclomine, hydroxyzine, tripelennamine, hydergine, cyclandelate, barbiturates (excluding phenobarbitone), oxaprozin, guanethidine, guanadrel, isoxsuprine, doxazosin, mesoridazine, desiccated thyroid, phenylpropanolamine, thiothixene, flavoxate, tacrine, pemolin.

Beers12 limitations

Interpretation of criteria

The following criteria were triggered by the presence of the medication and/or disease state but may be erroneous because insufficient information was available to accurately match the requirements of the criteria.

- Criterion 7 – Insufficient information available to determine if alpha-blockers were primarily prescribed as antihypertensives.
- Criterion 8 – Insufficient information available to determine if clonidine was used as a first-line antihypertensive.
- Criterion 9 – Insufficient information available to determine if antiarrhythmic drugs were prescribed as first line treatment for atrial fibrillation.
- Criterion 16 – This criterion was triggered if the patient had a diagnosis of dementia and had been prescribed an antipsychotic. Insufficient information was available to determine the success or failure of non-pharmacological options.
- Criterion 49 – Any diagnosis of chronic kidney disease was used to trigger this criterion.

Assumptions of long term medication use

No information was available to determine whether patients were using certain medications over the long term. The assumption was made that patients were using medications long term for the following criteria:

- Criterion 6 – Insufficient information was available to determine long term use of nitrofurantoin.
- Criterion 22 – Insufficient information was available to determine long term use of non-benzodiazepine hypnotics.

Medications not available in Australia

Several medications were not incorporated into automated queries as they were not available in Australia: carbinoxamine, clemastine, dexbrompheniramine, hydroxyzine, dofetilide, ibutilide, propafenone, dronedarone, guanabenz, guanfacine, pentazocine, trimethobenzamide, methocarbamol, carisoprodol, chlorzoxazone, metaxalone, cyclobenzaprine, flurazepam, estazolam, chlorazepate, chlordiazepoxide-amitriptyline, perphenazine-amitriptyline, meprobamate, chlordiazepoxide, quazepam, clidinium-chlordiazepoxide, reserpine, eszopiclone, zaleplon, etodolac, fenprofen, meclofanamate, nambumetone, tolmetin, carisoprodol, chlorzoxazone, cyclobenzprine, metaxalone, chlorpropamide, maprotiline, dicyclomine, hydroxyzine, barbiturates (excluding phenobarbitone), oxaprozin, isoxsurpine, doxazosin, darifenacin, fesoterodine, trospium, dessicated thyroid, thiothixene(tiotixine), flavoxate.

PIEA limitations

Interpretation of criteria

Several rules required knowledge of laboratory test results or observational results, such as blood pressure measurements. Whilst results were available for some cases, other cases had no laboratory test results or observational data at all.

- Indicator 1 – The most recent blood pressure reading was used. The rule was not implemented for patients with proteinurea > 1g per day as this information was not available.
- Indicator 10 – The query found patients with AF and warfarin and showed all patients who had an INR outside the reference range of 2.0 to 3.0. Some patients had multiple INRs and this query did not limit results to the most recent and most relevant INR.

- Indicator 11 – The query found patients who had a history of transient cerebral ischaemia and attempted to find patients with a history of non-haemorrhagic stroke. Insufficient information was available to clearly determine whether strokes were haemorrhagic or not, so a range of ICPC-2 terms were used that may have included a diagnosis of haemorrhagic stroke. The diagnosis terms used for this query were: cerebral artery thrombosis, cerebral embolism, cerebral occlusion, cerebrovascular accident, cerebral infarction, carotid disease, stroke, precerebral occlusion, cerebral ischaemia, precerebral embolism.

- Indicator 12 – No provision was made to investigate medication directions in sufficient detail to identify and exclude patients taking *half* of a 40mg atorvastatin or simvastatin tablet each day.

- Indicator 18 – This query did not identify diabetic patients who had *no* HbA1c measurement recorded. It only identified those patients where the most recent recorded HbA1c was over 6 months old.

- Indicator 31 and 32 – Inhaled ipratriopium was not listed in the AMH anticholinergics table[323], however, all instances of inhaled ipratropium were included in the query results.

Assumptions of long term medication use

No information was available to determine whether patients were using certain medications over the long term. The assumption was made that patients were using the medications long term if the medication was listed.

- Indicator 26 – "Patient with sleep disturbance or anxiety has *not* been taking benzodiazepines for >4 weeks". The assumption was made the patient had been using the medication for 4 weeks or more.

Criteria which were not implemented

- Indicator 14 – Insufficient information available to determine whether patients who smoked had been (or had not been) offered smoking cessation therapy.

- Indicator 21 – Insufficient information to determine if the patient has been trialled with paracetamol, and also insufficient information concerning the impact of osteoarthritis on daily activities.
- Indicator 22 – An implicit criterion where insufficient information was available to determine whether patient pain is interfering with daily activities.
- Indicator 36 – Insufficient information was available to be certain of the actual weekly use of salbutamol or terbutaline inhalers.
- Indicator 41 – There was insufficient information to determine whether an antibiotic was prescribed specifically for URTI or for another purpose.
- Indicator 42 – Insufficient information available to determine patient's daily intake of vitamin D.
- Indicator 43 – Insufficient information available to determine patient's daily calcium intake.
- Indicator 45 – An implicit criterion where insufficient information was available to determine whether patient itch or discomfort was interfering with daily activities.
- Indicator 46 – In the majority of cases vaccination data was not collected.
- Indicator 47 – Patient has no significant medication interactions (agreement between two medication interaction databases). Too difficult to implement this implicit criterion.
- Indicator 48 – Patient has had no significant change in medications in the previous 90 days. An implicit criterion, too difficult to implement this criterion.

STOPP limitations

Long term medication usage assumptions

No information was available to determine whether patients were using certain medications over the long term. The assumption was made that patients were using the medications long term if the medication was listed.

- A1 – "Digoxin at long term dose > 125mcg/day"
- B7 – "Long-term (i.e. > 1 month), long-acting benzodiazepines…"
- B9 – "Long-term neuroleptics (>1 month) in those with parkinsonism"
- C4 – "PPI for peptic ulcer disease at full therapeutic dosage for > 8 weeks"
- E4 – "Long term use of NSAID (> 3 months)…"
- E7 – "Long-term corticosteroids (> 3 months)…"
- E8 – "Long-term NSAID or colchicine for chronic treatment of gout…"
- I2 – "Regular opiate for more than 2 weeks..."
- I3 – "Long-term opiates in those with dementia…"

Interpretation of criteria

Some interpretation of the STOPP criteria was required to match as closely as possible the data available in the patient cases. In some cases insufficient information was available.

- A2 – "Loop diuretic for ankle oedema only, i.e. no clinical signs of heart failure", was triggered by a diagnosis of foot or ankle oedema and no diagnosis of heart failure.
- A3 – "Loop diuretic as first-line monotherapy for hypertension". There was insufficient information to confirm this was first-line monotherapy so the rule was triggered by existence of a loop diuretic and hypertension and no other antihypertensives.
- A7 – "Use of diltiazem or verapamil in NYHA class III or IV heart failure". There was insufficient information to determine the state of heart failure, so any recorded diagnosis of heart failure was used for this rule.

- B12 – Any diagnosis of hyponatremia was used to assist triggering this rule.
- C4 – Full therapeutic daily dosage of PPIs for peptic ulcer disease were based on the British National Formulary, No.62 (September 2011) - esomeprazole 20mg, lansoprazole 30mg, omeprazole 20mg, pantoprazole 80mg, rabeprazole 20mg.
- D2 – It was assumed oral corticosteroids were prescribed for COPD if the patient had COPD listed as a diagnosis.
- E2 – No code was available to indicate the severity of hypertension. This rule was triggered by the existence of an NSAID, a diagnosis of hypertension and either an average systolic blood pressure over 159 mmHg or an average diastolic blood pressure over 99 mmHg.
- E4 – This query selected all patients who were prescribed NSAIDs whether or not other analgesics were prescribed.
- E8 – An assumption was made an NSAID was prescribed for gout
- F5 – Presence of a diagnosis of urinary incontinence was used for this query. Insufficient information was available to determine "frequent incontinence".
- H4 – Patients with a diagnosis of hypotension triggered this rule.
- I3 – The presence of a diagnosis of dementia and opiates were used for this query. Insufficient information was available to exclude patients who were being treated for palliative care or moderate/severe chronic pain.
- J – Duplicate drug classes, this query detected all duplicate instances of the ATC fourth level chemical subgroup, whilst excluding all duplicate instances of ATC fifth level medications, an example would be to trigger where a patient was taking pravastatin and simvastatin, but not two different strengths of pravastatin. Glyceryltrinitrate (GTN) was excluded from triggering this rule as a combination of quick acting GTN with oral or transdermal nitrate is considered standard therapy. Based on this implementation several duplications would be overlooked. An example:

Fentanyl transdermal and morphine are ATC level 3 matching (N02A opioids), and were not matching at ATC level 4 (**N02A**A morphine, **N02A**B fentanyl). Substantial work would have been required to implement a database query with this degree of accuracy and was not undertaken. Likewise, a query based on detecting all duplicate instances of ATC level 3 medications was not implemented, as too many false positives would have occurred. An example: a patient who used allopurinol (ATC: **M04A**A01) as preventative therapy for gout and also had prescribed colchicine (ATC: **M04A**C01) for flare-ups of gout.

Criteria which were not implemented

It was impossible to develop rules to match some STOPP criteria. These rules required knowledge of the specific intention for the prescribing of a medication which was not captured in the dataset.

- A14 – "Aspirin to treat dizziness" – insufficient information available.
- A15 – "Warfarin for first, uncomplicated deep venous thrombosis for longer than six months duration" – insufficient information available.
- A16 – "Warfarin for first uncomplicated pulmonary embolus for longer than 12 months duration" – insufficient information available.
- B8 – "Long-term … neuroleptics as long-term hypnotics" – insufficient information available to determine the purpose of treatment.
- C1 – "…treatment of diarrhoea of unknown cause" – Insufficient information was available to determine if the cause of diarrhoea was known or unknown so this criterion was not implemented.
- F06 – "α-blockers with long-term urinary catheter…" – Patients were living at home and no patients were known to be catheterised so this criterion was not utilised.
- G2 – "β-blockers in those with diabetes mellitus and frequent hypoglycaemic episodes" – Insufficient information was available to identify patients with frequent hypoglycaemic episodes.

- I1 – "Use of long-term opiates…as first-line therapy…" – There was insufficient information available to determine if opiates were used as first-line therapy.

START limitations

Interpretation of criteria

- A2 – This rule was triggered in patients who did not have a diagnosis of heart failure and did have a loop diuretic and swollen ankles. The assumption made was the diuretic was being used to treat the patient's swollen ankles, although it may have been prescribed for another purpose.
- A3 - "Aspirin or clopidogrel with a documented history of atherosclerotic, coronary, cerebral or peripheral vascular disease in patients with sinus rhythm" Triggered if patient did not have aspirin, clopidogrel or warfarin in medication list, and no diagnosis of atrial fibrillation or arrhythmia, yet did have a diagnosis of atherosclerosis or peripheral vascular disease.
- A4 – This rule was triggered if patients were treated with antihypertensives and all recorded systolic blood pressure readings were over 160mmHg.
- B1 – It was assumed the patient had mild to moderate asthma or COPD.

Criteria which were not implemented

- B2 – "Regular inhaled corticosteroid for moderate/severe asthma or COPD, where predicted FEV1 < 50%" – Insufficient information was available to implement this criterion.
- B3 – "Home continuous oxygen…" – Either no patients used home continuous oxygen or no information was supplied which indicated its use.
- C1 – "L-DOPA in idiopathic Parkinson's disease with definite functional impairment and resultant disability" – Insufficient information was available to determine the patient's functional impairment and resultant disability.

- D1 – "Proton pump inhibitor with severe gastroesophageal acid reflux disease or peptic stricture requiring dilation" – Insufficient information was available to determine severity of reflex or if patient with peptic stricture required dilation.
- E1 – "Disease-modifying antirheumatic drug (DMARD) (with active moderate/severe rheumatoid disease lasting > 12 weeks" – Insufficient information was available to determine severity or length of the disease, or even if it was active or in remission.

Appendix 5 Ethics approvals

Social Science Ethics Officer
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Marilyn.pugsley@utas.edu.au

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

30 May 2011

Professor Gregory Peterson
Pharmacy
Private Bag 26
Hobart Tasmania

Dear Professor Peterson

Re: MINIMAL RISK ETHICS APPLICATION APPROVAL
Ethics Ref: H0011845 - Patient medication reviews and computerised decision support software.

We are pleased to advise that acting on a mandate from the Tasmania Social Sciences HREC, the Chair of the committee considered and approved the above project on 30 May 2011.

Please note that this approval is for four years and is conditional upon receipt of an annual Progress Report. Ethics approval for this project will lapse if a Progress Report is not submitted.

The following conditions apply to this approval. Failure to abide by these conditions may result in suspension or discontinuation of approval.

1. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval, to ensure the project is conducted as approved by the Ethics Committee, and to notify the Committee if any investigators are added to, or cease involvement with, the project.

2. Complaints: If any complaints are received or ethical issues arise during the course of the project, investigators should advise the Executive Officer of the Ethics Committee on 03 6226 7479 or human.ethics@utas.edu.au.

3. Incidents or adverse effects: Investigators should notify the Ethics Committee immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.

A PARTNERSHIP PROGRAM IN CONJUNCTION WITH THE DEPARTMENT OF HEALTH AND HUMAN SERVICES

4. Amendments to Project: Modifications to the project must not proceed until approval is obtained from the Ethics Committee. Please submit an Amendment Form (available on our website) to notify the Ethics Committee of the proposed modifications.

5. Annual Report: Continued approval for this project is dependent on the submission of a Progress Report by the anniversary date of your approval. You will be sent a courtesy reminder closer to this date. **Failure to submit a Progress Report will mean that ethics approval for this project will lapse.**

6. Final Report: A Final Report and a copy of any published material arising from the project, either in full or abstract, must be provided at the end of the project.

Yours sincerely

Katherine Shaw
Acting Executive Officer

Social Science Ethics Officer
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Tasmania 7001 Australia
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Katherine.Shaw@utas.edu.au

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

17 January 2012

Professor Gregory Peterson
School of Pharmacy
Private Bag 26
Hobart Tasmania

Student Researcher: Colin Curtain

Dear Professor Peterson

Re: MINIMAL RISK ETHICS APPLICATION APPROVAL
Ethics Ref: **H0012269 - Patient Medication Reviews and Computerised Decision Support - Assessment by an Expert Panel**

We are pleased to advise that acting on a mandate from the Tasmania Social Sciences HREC, the Chair of the committee considered and approved the above project on 16 January 2012.

Please note that this approval is for four years and is conditional upon receipt of an annual Progress Report. Ethics approval for this project will lapse if a Progress Report is not submitted.

The following conditions apply to this approval. Failure to abide by these conditions may result in suspension or discontinuation of approval.

1. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval, to ensure the project is conducted as approved by the Ethics Committee, and to notify the Committee if any investigators are added to, or cease involvement with, the project.

2. Complaints: If any complaints are received or ethical issues arise during the course of the project, investigators should advise the Executive Officer of the Ethics Committee on 03 6226 7479 or human.ethics@utas.edu.au.

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5. Annual Report: Continued approval for this project is dependent on the submission of a Progress Report by the anniversary date of your approval. You will be sent a courtesy reminder closer to this date. **Failure to submit a Progress Report will mean that ethics approval for this project will lapse.**

6. Final Report: A Final Report and a copy of any published material arising from the project, either in full or in abstract, must be provided at the end of the project.

Yours sincerely

Ethics Officer

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Katherine.Shaw@utas.edu.au

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

06 May 2013

Professor Gregory Peterson
Faculty of Health Science
Private Bag 26

Dear Professor Peterson

Re: MINIMAL RISK ETHICS APPLICATION APPROVAL
Ethics Ref: H0013161 - Usability assessment of an artificial intelligence medication review product

We are pleased to advise that acting on a mandate from the Tasmania Social Sciences HREC, the Chair of the committee considered and approved the above project on 07 April 2013.

This approval constitutes ethical clearance by the Tasmania Social Sciences Human Research Ethics Committee. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approval of other bodies or authorities is required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

Please note that this approval is for four years and is conditional upon receipt of an annual Progress Report. Ethics approval for this project will lapse if a Progress Report is not submitted.

The following conditions apply to this approval. Failure to abide by these conditions may result in suspension or discontinuation of approval.

1. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval, to ensure the project is conducted as approved by the Ethics Committee, and to notify the Committee if any investigators are added to, or cease involvement with, the project.

2. Complaints: If any complaints are received or ethical issues arise during the course of the project, investigators should advise the Executive Officer of the Ethics Committee on 03 6226 7479 or human.ethics@utas.edu.au.

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4. Amendments to Project: Modifications to the project must not proceed until approval is obtained from the Ethics Committee. Please submit an Amendment Form (available on our website) to notify the Ethics Committee of the proposed modifications.

5. Annual Report: Continued approval for this project is dependent on the submission of a Progress Report by the anniversary date of your approval. You will be sent a courtesy reminder closer to this date. **Failure to submit a Progress Report will mean that ethics approval for this project will lapse.**

6. Final Report: A Final Report and a copy of any published material arising from the project, either in full or abstract, must be provided at the end of the project.

Yours sincerely

Lauren Black
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Office of Research Services
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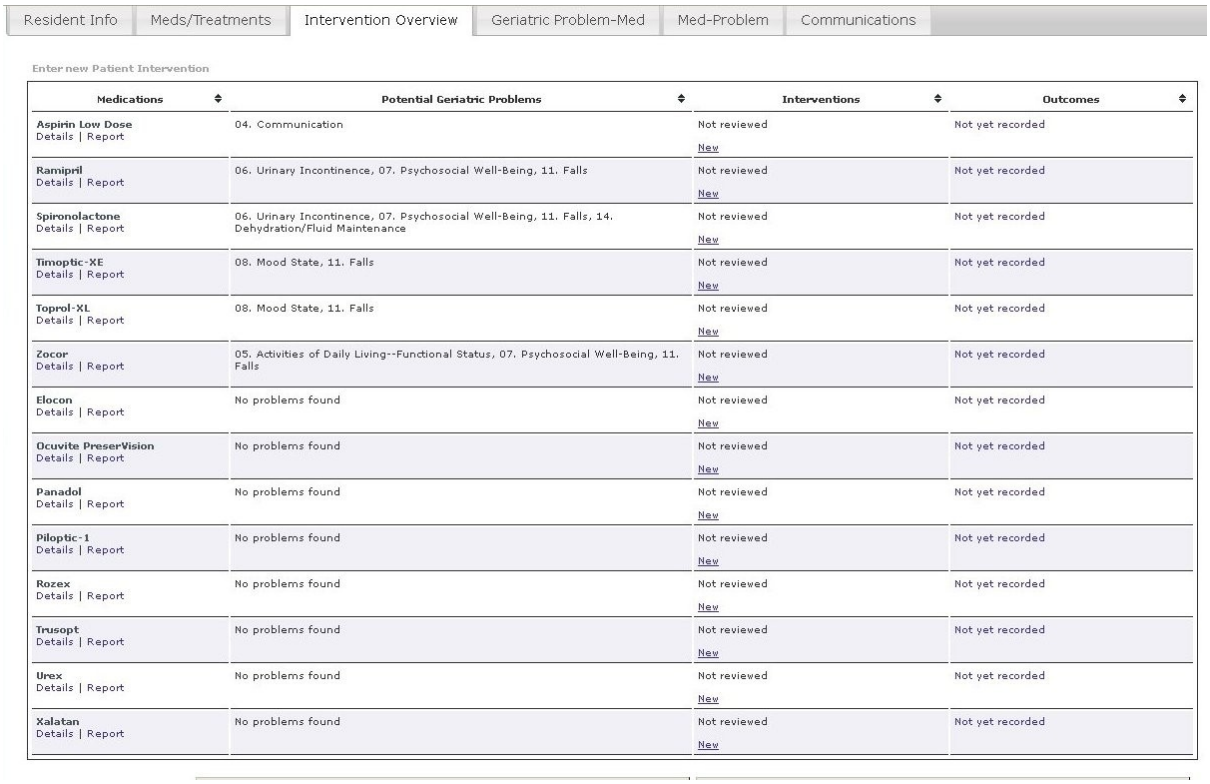
Private Bag 01 Hobart Tas 7001

Appendix 6 Monitor-Rx reports



Medications	Potential Geriatric Problems	Interventions	Outcomes
Aspirin Low Dose Details | Report	04. Communication	Not reviewed New	Not yet recorded
Ramipril Details | Report	06. Urinary Incontinence, 07. Psychosocial Well-Being, 11. Falls	Not reviewed New	Not yet recorded
Spironolactone Details | Report	06. Urinary Incontinence, 07. Psychosocial Well-Being, 11. Falls, 14. Dehydration/Fluid Maintenance	Not reviewed New	Not yet recorded
Timoptic-XE Details | Report	08. Mood State, 11. Falls	Not reviewed New	Not yet recorded
Toprol-XL Details | Report	08. Mood State, 11. Falls	Not reviewed New	Not yet recorded
Zocor Details | Report	05. Activities of Daily Living--Functional Status, 07. Psychosocial Well-Being, 11. Falls	Not reviewed New	Not yet recorded
Elocon Details | Report	No problems found	Not reviewed New	Not yet recorded
Ocuvite PreserVision Details | Report	No problems found	Not reviewed New	Not yet recorded
Panadol Details | Report	No problems found	Not reviewed New	Not yet recorded
Piloptic-1 Details | Report	No problems found	Not reviewed New	Not yet recorded
Rozex Details | Report	No problems found	Not reviewed New	Not yet recorded
Trusopt Details | Report	No problems found	Not reviewed New	Not yet recorded
Urex Details | Report	No problems found	Not reviewed New	Not yet recorded
Xalatan Details | Report	No problems found	Not reviewed New	Not yet recorded

Figure 66: Overview report showing a summary of potential problem medications and notes relating to interventions and outcomes

UMORE, School of Pharmacy, University of

Phone: 03 6226 1096 | Fax: 03 6226 7627

Geriatric Problem-Med Report

11/02/2011 at 1:13 AM

ID: 28, male, 08/04/1932

Medications Screened
Aspirin Low Dose, Ramipril, Spironolactone, Timoptic-XE, Toprol-XL, Zocor

Medications not screened (may also contribute to the risk for a geriatric problem, but for various reasons, e.g., newly marketed or not for chronic use in geriatric patients, were not evaluated)
Elocon, Ocuvite PreserVision, Panadol, Piloptic-1, Rozex, Trusopt, Urex, Xalatan

Problem	Problem Description	Medication	Monitoring Indicators
04. Communication	Some medications may cause or contribute to communication deficits. Ototoxicity (ear damage) can occur during aminoglycoside antibiotic therapy, which can be manifest as high-frequency hearing loss, tinnitus (ringing in the ears), vertigo, dizziness, or nausea. Hearing loss may occur in patients receiving high-dose and/or long-term aspirin therapy; these effects are early manifestations of salicylate toxicity. Psychoactive medications and some Parkinson's medications may cause expressive communication problems, such as changes/difficulties in speech and voice production, finding appropriate words, transmitting coherent statements, describing objects and events.	Aspirin Low Dose (Ototoxicity)	Signs/symptoms of ototoxicity: • New onset hearing problem (B0200) • High-frequency hearing loss • Tinnitus (ringing in the ears) • Vertigo • Dizziness • Nausea Indicators of expressive communication problem: • Problem with voice production, low volume (B0600) • Unclear speech - slurred or mumbled words (B0600-1) • Impaired ability to make self understood (B0700) • Difficulty putting sentence together (C1300B)
05. Activities of Daily Living--Functional Status	Adverse medication effects, such as confusion, muscle weakness (asthenia) and inability to coordinate voluntary muscle movements or unsteady gait (ataxia), may interfere with ADL performance and contribute to functional decline.	Zocor (Asthenia, muscular weakness)	Medication effects that may affect function: • Asthenia (muscle weakness) • Ataxia • Unsteady gait • Confusion
06. Urinary Incontinence	Many medications can affect the bladder and urethra and result in urinary incontinence (UI). For example, diuretics (N0400G) can cause urge incontinence, anticholinergics can lead to overflow incontinence, sedative/hypnotics (N0400B, N0400D) may cause confusion and alter the ability to recognize the urge to void and lead to UI.	Ramipril (Urinary incontinence) Spironolactone (Diuresis, Polyuria; Urinary incontinence)	Symptoms of urinary incontinence: • Loss of urine when coughing, sneezing, laughing, exercising or lifting something heavy (stress incontinence). • Sudden, intense urge to urinate, followed by an involuntary loss of urine (urge incontinence). • Frequently or constantly dribble urine, feeling that bladder never completely empty, weak stream of urine (overflow incontinence).
07. Psychosocial Well-Being	Medications with side effects, such as incontinence, diarrhea, delirium, sleepiness, etc., may interfere with or inhibit social interactions.	Ramipril (Urinary incontinence) Spironolactone (Urinary incontinence) Zocor (Drowsiness,	Assess for medication effects that interfere with social interactions.

Figure 67: Problem-Med report extract showing the first page of the report

UMORE, School of Pharmacy, University of

Phone: 03 6226 1096 | Fax: 03 6226 7627

Med-Problem Report

11/02/2011 at 1:13 AM

ID: 28, male, 08/04/1932

Medications Screened
Aspirin Low Dose, Ramipril, Spironolactone, Timoptic-XE, Toprol-XL, Zocor

Medications not screened (may also contribute to the risk for a geriatric problem, but for various reasons, \ne.g., newly marketed or not for chronic use in geriatric patients, were not evaluated)
Elocon, Ocuvite PreserVision, Panadol, Piloptic-1, Rozex, Trusopt, Urex, Xalatan

Medication	Problem Description
Aspirin Low Dose	04. COMMUNICATION Some medications may cause or contribute to communication deficits. Ototoxicity (ear damage) can occur during aminoglycoside antibiotic therapy, which can be manifest as high-frequency hearing loss, tinnitus (ringing in the ears), vertigo, dizziness, or nausea. Hearing loss may occur in patients receiving high-dose and/or long-term aspirin therapy; these effects are early manifestations of salicylate toxicity. Psychoactive medications and some Parkinson's medications may cause expressive communication problems, such as changes/difficulties in speech and voice production, finding appropriate words, transmitting coherent statements, describing objects and events.
Ramipril	06. URINARY INCONTINENCE Many medications can affect the bladder and urethra and result in urinary incontinence (UI). For example, diuretics (N0400G) can cause urge incontinence, anticholinergics can lead to overflow incontinence, sedative/hypnotics (N0400B, N0400D) may cause confusion and alter the ability to recognize the urge to void and lead to UI. 07. PSYCHOSOCIAL WELL-BEING Medications with side effects, such as incontinence, diarrhea, delirium, sleepiness, etc., may interfere with or inhibit social interactions. 11. FALLS Certain medications can contribute to the risk for falls by causing problems such as dizziness, drowsiness, low blood pressure, muscle rigidity, impaired balance, tremors, and decreased alertness.
Spironolactone	06. URINARY INCONTINENCE Many medications can affect the bladder and urethra and result in urinary incontinence (UI). For example, diuretics (N0400G) can cause urge incontinence, anticholinergics can lead to overflow incontinence, sedative/hypnotics (N0400B, N0400D) may cause confusion and alter the ability to recognize the urge to void and lead to UI. 07. PSYCHOSOCIAL WELL-BEING Medications with side effects, such as incontinence, diarrhea, delirium, sleepiness, etc., may interfere with or inhibit social interactions. 11. FALLS Certain medications can contribute to the risk for falls by causing problems such as dizziness, drowsiness, low blood pressure, muscle rigidity, impaired balance, tremors, and decreased alertness. 14. DEHYDRATION/FLUID MAINTENANCE

Figure 68: Med-problem report extract showing the first page of the report

Appendix 7 DOCUMENT classifications

Code	Description	Code	Description
D	Drug selection	D1	Duplication
		D2	Drug interaction
		D3	Wrong drug
		D4	Incorrect strength
		D5	Inappropriate dosage form
		D6	Contraindications apparent
		D7	No indication apparent
		D0	Other drug selection problems
O	Over or underdose	O1	Prescribed dose too high
		O2	Prescribed dose too low
		O3	Incorrect or unclear dosing instructions
		O0	Other dose problems
C	Compliance	C1	Taking too little
		C2	Taking too much
		C3	Erratic use of medication
		C4	Intentional drug misuse
		C5	Difficulty using dosage form
		C0	Other compliance problem
U	Undertreated	U1	Condition undertreated
		U2	Condition untreated
		U3	Preventative therapy required
		U0	Other untreated indication problem
M	Monitoring	M1	Laboratory monitoring
		M2	Non-laboratory monitoring
		M0	Other monitoring problem
E	Education or information	E1	Patient requests drug information
		E2	Patient requests disease management advice
		E0	Other education or information problem
N	Not classifiable	N0	Problems that cannot be classified under another category
T	Toxicity or adverse reaction	T1	Toxicity, allergic reaction or adverse effect present

Appendix 8 Similarities between sets of prescribing criteria

These tables were initially based on an article by Chang and Chan.[104]

Table 58: Similarity between prescribing criteria – PIMs

Medication	Beers03	Beers12	STOPP	PIEA
Long-acting benzodiazepines	√	√	√	
Tricyclic antidepressants	√	√	√	√
First generation antihistamines	√	√	√	
Dipyridamole	√	√	√	
Digoxin	√	√	√	
Glibenclamide		√	√	√
Theophylline	√	√	√	
NSAIDs	√	√	√	√
Warfarin			√	√
Aspirin	√	√	√	√
Anticholinergics	√	√	√	√
Sedatives/hypnotics	√	√	√	√
Beta-blockers	√	√	√	√
Oestrogens	√	√	√	√
Proton pump inhibitors			√	√
SSRIs	√	√	√	√
Alpha-blockers	√	√	√	
Amiodarone	√	√		
Disopyramide	√	√		
Nifedipine non-SR	√	√		
Barbiturates	√	√		
Ergot mesylates	√	√		
Androgens	√	√		
Oral mineral oil	√	√		
Pethidine	√	√		

Table 59: Similarity between prescribing criteria – PIM and interaction with drug or diagnosis

Medication and diagnosis	Beers03	Beers12	STOPP	PIEA
Alpha–blockers and urinary incontinence	√	√	√	
Anticholinergic use not elsewhere specified	√	√	√	√
Anticholinergics and bladder outflow/urinary retention	√	√	√	
Anticholinergics and cognitive impairment/dementia	√	√	√	
Anticholinergics and constipation	√	√	√	
Bleeding disorder and antiplatelet or anticoagulant	√		√	
COPD and benzodiazepines	√			√
COPD and beta–blocker	√			√
Epilepsy and antipsychotics	√	√	√	
HF and high sodium content medications	√			√
HF and NSAIDs (non-steroidal antiinflammatory drugs)		√	√	√
HF and thiazolidinediones		√		√
HF and verapamil or diltiazem		√	√	√
NSAIDs and blood clotting disorders	√		√	
NSAIDs and renal failure, including triple whammy	√	√	√	√
NSAIDs SSRIs (selective serotonin re-uptake inhibitors) and/or anticoagulants and gastric bleeding risk or peptic ulcer disease	√	√(excl SSRIs)	√	√
Parkinson's and antipsychotics or metoclopramide	√	√	√	
Sedatives or antipsychotics and falls	√	√	√	√
Sedatives, long acting or for more than 4 weeks	√	√	√	√

Table 60: Similarity between prescribing criteria - treatment omission

Medication	STOPP	PIEA
AF requiring aspirin or warfarin	√	√
Asthma - moderate/severe requires inhaled corticosteroid	√	√
Cardiovascular disease requiring antiplatelet	√	√
Cardiovascular disease/risk requires statin	√	√
CHF requires ACEI or ARB	√	√
Diabetes and cardiovascular risk requires antiplatelet	√	√
Diabetes and renal disease requires ACEI or ARB	√	√
HF or angina requires beta-blocker	√	√
Opioid requiring preventative laxatives	√	√
Osteoporosis requires calcium and/or vitamin D supplementation	√	√

Appendix 9 Descriptive classifications

Table 61: Descriptive classifications

Category	Descriptive classification	Descriptive classification ID
Analgesia	Analgesia optimisation with regular paracetamol needed	39
Analgesia	Dextropropoxyphene prescribed	53
Analgesia	Opioid constipation may require laxative or increased lax therapy	26
Analgesia	Opioid sedation	144
Analgesia	Pain un(der)treated	127
Analgesia	Quinine prescribed	51
Anticholinergic	Anticholinergic use not elsewhere specified	11
Anticholinergic	Anticholinergics and cognitive impairment	42
Anticholinergic	Anticholinergics and constipation	17
Coagulation/platelet	AF requires aspirin or warfarin	27
Coagulation/platelet	Anticoagulant toxicity	146
Coagulation/platelet	Antiplatelet not indicated	9
Coagulation/platelet	Bleeding disorder and antiplatelet or anticoagulant	10
Coagulation/platelet	Bleeding risk interacting drugs	4
Coagulation/platelet	Cardiovascular disease/risk requires antiplatelet	28
Coagulation/platelet	Clopidogrel and aspirin interaction	151
Coagulation/platelet	INR outside therapeutic range	70
Coagulation/platelet	PPI and clopidogrel interaction	153
Coagulation/platelet	Warfarin and aspirin interaction	150
Compliance	Can reduce daily drug frequency	99
Compliance	Compliance - Confusion about therapy	84
Compliance	Compliance - using too little medication	75
Compliance	Compliance - using too much medication	103
Compliance	Difficulty using dosage form	74
Compliance	Medication regimen complicated	94
Compliance	Timing of dose inappropriate	115
Constipation	Calcium channel blocker and constipation	62
Constipation	Constipation un(der)treated	122
Constipation	Iron and constipation	61
Constipation	Mineral oil laxative prescribed	56
Constipation	Stimulant laxative long term use	55
Cost	Cost of therapy concern	102
Cost	Eligible for DVA funded DAA	73
Diabetes	Antidiabetic drug no indication	134
Diabetes	Diabetes and taking medication that affects glucose levels	44
Diabetes	Diabetes monitoring required	137
Diabetes	Diabetes undertreated (HBA1c or BSLs high)	58
Diabetes	Glibenclamide prescribed	24
Diabetes	Pioglitazone and HF	149
Diabetes	Rosiglitazone and (risk of) HF	60
Digoxin	Digoxin dose over 125mcg or considered too high	1
Digoxin	Digoxin monitoring required	138
Digoxin	Digoxin toxicity	145
Dose or duration of therapy	Duration of therapy may be excessive	89
Dose or duration of therapy	Nitrate free period required	98
Dose or duration of therapy	Therapeutic dose too high	91
Dose or duration of therapy	Therapeutic dose too low	90
Education	Patient disease management education provided/required	79
Education	Patient drug education provided/required	78

Category	Descriptive classification	Descriptive classification ID
Education	Smoking cessation education required/provided	80
GORD	Calcium channel blocker and reflux	96
GORD	Drug causing dyspepsia with PPI	101
GORD	GORD drug no indication	130
GORD	PPI high dose	7
Gout	Antigout medication (might) not be indicated	46
Gout	Aspirin or thiazide contraindicated in gout	97
Heart failure	Heart failure and concurrent verapamil or diltiazem	3
Heart failure	Heart failure or hypertension and using high sodium or salt retaining drugs	36
Heart failure	Heart failure or IHD requires beta-blocker	31
Heart failure	Heart failure requires ACEI or ARB	30
Interaction	Other drug interaction	86
Lipidaemia	Antilipidaemic drug no indication	135
Lipidaemia	Cardiovascular disease/risk requires statin	29
Lipidaemia	Hyperlipidaemia under/untreated	57
Lipidaemia	Lipid monitoring required	139
Lipidaemia	Statin myopathy risk	64
Lipidaemia	Statin toxicity	147
Mineral/vitamin supplementation	Iron no indication	131
Mineral/vitamin supplementation	Vitamin no indication	136
Mineral/vitamin supplementation	Vitamin B12 and or folate deficiency possible	47
Monitoring	Haematology monitoring required	141
Monitoring	Medication monitoring - cognitive	111
Monitoring	Medication monitoring - communication/social problems	107
Monitoring	Medication monitoring - dehydration	112
Monitoring	Medication monitoring - nutritional status or dental care	109
Monitoring	Medication monitoring - pressure ulcers	110
Monitoring	Medication monitoring - urinary incontinence	108
Monitoring	Medication monitoring - visual disturbance	106
Monitoring	Other monitoring (lab) required	81
Monitoring	Other monitoring (non-lab) required	93
Monitoring	Thyroid function monitoring required	140
Neurologic (Epilepsy/parkinsons/other)	Depression un(der)treated	121
Neurologic (Epilepsy/parkinsons/other)	Epilepsy and medication affecting seizure threshold	15
Neurologic (Epilepsy/parkinsons/other)	Fluoxetine prescribed	114
Neurologic (Epilepsy/parkinsons/other)	Lithium monitoring required	143
Neurologic (Epilepsy/parkinsons/other)	Parkinsonism and antipsychotics or metoclopramide	14
Neurologic (Epilepsy/parkinsons/other)	Serotonergic drugs interaction	66
No indication	Antibiotic no indication	129
No indication	Other drug no indication	69
NSAID	Aspirin high dose not indicated	8
NSAID	NSAID combined with ACEI or ARB, diuretic - triple whammy	21
NSAID	NSAID not recommended (CV/HF/bleed/other)	19

Category	Descriptive classification	Descriptive classification ID
NSAID	NSAID used with (risk of) renal failure	20
NSAID	NSAID without acid suppressant	5
Osteoporosis	Medication monitoring - calcium intake	116
Osteoporosis	Osteoporosis (or risk) may require calcium and or vitamin D	33
Osteoporosis	Osteoporosis (or risk) requires antiosteoporotic	67
Other	Combine medications into combination product	54
Other	Communication breakdown, documentation insufficient	83
Other	Falls risk/history and sedatives/antihypertensives/other	25
Other	Lifestyle issues - overweight	85
Other	Medication expired	72
Other	Medication monitoring - Potassium	77
Other	Oestrogens and thromboembolism or cancer risk	105
Other	Other DRP MRM	120
Other	Other DRP pharmacist	119
Other	Other drug disease contraindication	104
Other	Other PIM	118
Other	Therapy duplication	49
Other cardiovascular	Amiodarone or other antiarrythmic prescribed	113
Other cardiovascular	Beta-blocker for hypertension	117
Other cardiovascular	Calcium channel blocker and peripheral oedema	59
Other cardiovascular	Cardiovascular drug no indication	132
Other cardiovascular	Heart disease un(der)treated	125
Other cardiovascular	Hydralazine monitoring required	142
Other cardiovascular	Hyperkalaemia (or risk of) and medication	50
Other cardiovascular	Hypertension under/untreated	52
Other cardiovascular	Methyldopa or clonidine prescribed	100
Other cardiovascular	Other cardiovascular drug toxicity	148
Other cardiovascular	Short acting nitrate required	88
Renal impairment	Allopurinol and reduced renal function	154
Renal impairment	Diabetes and CV risks or renal disease requires ACEI or ARB or CCB	34
Renal impairment	Hexamine prescribed (poor renal clearance)	95
Renal impairment	Metformin dose high with renal impairment	71
Renal impairment	Nitrofurantoin prescribed	63
Renal impairment	Renal impairment and using or check for renally excreted drugs	45
Respiratory	Airway disease un(der)treated	126
Respiratory	Asthma moderate/severe requires inhaled corticosteroid	32
Respiratory	COPD and using benzodiazepines	37
Respiratory	COPD/Asthma and using a beta blocker	2
Sedative	Sedatives long-acting or long-term	12
Toxicity	ACEI cough	48
Toxicity	Hyponatremia drug toxicity	65
Toxicity	Other toxicity - drug suspected	92
Undertreatment	Current therapy insufficient	82
Undertreatment	Family history disease risk, preventative therapy indicated	87
Undertreatment	Glaucoma untreated	128
Undertreatment	Other disease/symptoms untreated	68
Undertreatment	Skin disease un(der)treated	123
Undertreatment	Vaccination required (influenza, pneumonia)	76
Undertreatment	Weight loss un(der)treated	124

Appendix 10 Expert panel information sheet

Private Bag 26,
Hobart, Tasmania 7001 Australia
Tel: 61 6226 2190 Fax: 61 6226 2870
www.utas.edu.au/umore

UMORE
UNIT FOR MEDICATION OUTCOMES RESEARCH AND EDUCATION
Innovative research. Inspired results.

Are you interested in assessing drug-related problems?

You are invited to participate in a research study to determine whether computer detection of drug-related problems (DRPs) could be a beneficial tool for identifying clinically relevant problems and provide recommendations for their resolution.

We would like you to be a part of our panel of experts to assess the clinical relevance of each DRP and recommendation for their resolution.

The details of home medication reviews undertaken in 2008 are being used for this assessment. The medication reviews were submitted by accredited pharmacists who identified potential problems and provided recommendations for their resolution. Each of these reviews has also been entered into three different computer analysis tools designed to detect DRPs; an Australian system, an American system and an automated version of published inappropriate prescribing guidelines.

Having expert input into assessing the DRPs identified by both pharmacists and computer tools will help researchers compare the benefits and flaws of each source of DRPs, and ideally, provide justification for or against the use of computer technology in this area.

You will be required to assess 20 patient cases, each with multiple DRPs. Each case is estimated to take up to half an hour to complete, overall 6 to 8 hours. Assessment requires determining if each DRP was relevant, on a 5 point scale; determining if any recommendation was appropriate on a 5 point scale and an option for comments. In addition the assessment would include an overall assessment of each source of identified DRPs for each patient case, with a 5 point scale of appropriateness, a 5 point scale of finding an excessive number of DRPs, a 5 point scale indicating missing DRPs and space for comments if you think that any important drug-related problems had been missed. Assessment of cases will be available through a website.

There are no foreseeable risks associated with your participation in this study. You are free to withdraw at any time and do not need to provide an explanation. Full reimbursement of $500 will be provided on completion of all 20 cases, and reduced proportionately with fewer cases completed. All information will be treated confidentially and stored securely on the University of Tasmania Health Science Server. Information will only be accessed by investigators and will be securely destroyed after five years. Study results may be published in a thesis and in scientific journals. You will not be personally identified in any publication.

The assessment will need to be completed by 30-April-2012.

This research project is being conducted as partial fulfilment of a PhD for Colin Curtain under the supervision of Professor Gregory Peterson and Dr Ivan Bindoff.

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If you are interested in participating in this project or have further questions please contact Colin Curtain at the School of Pharmacy, University of Tasmania on 03 6226 1096, or by email: colin.curtain@utas.edu.au. This information sheet is for you to keep. If you are able to participate, a consent form will be posted to you with a pre-paid return-addressed envelope.

Thank you,

Colin Curtain (PhD candidate)
Professor Gregory Peterson (supervisor)
Dr Ivan Bindoff (supervisor)
Unit for Medications Outcomes Research and Education
School of Pharmacy
University of Tasmania

This study has been approved by the Tasmania Social Sciences Human Research Ethics Committee. If you have any concerns or complaints about the conduct of this study, please contact the Executive Officer of the HREC (Tasmania) Network on (03) 6226 7479 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. Please quote ethics reference number H12269.

Appendix 11 Expert panel website

Example screen shots showing various aspects of the expert panel website.

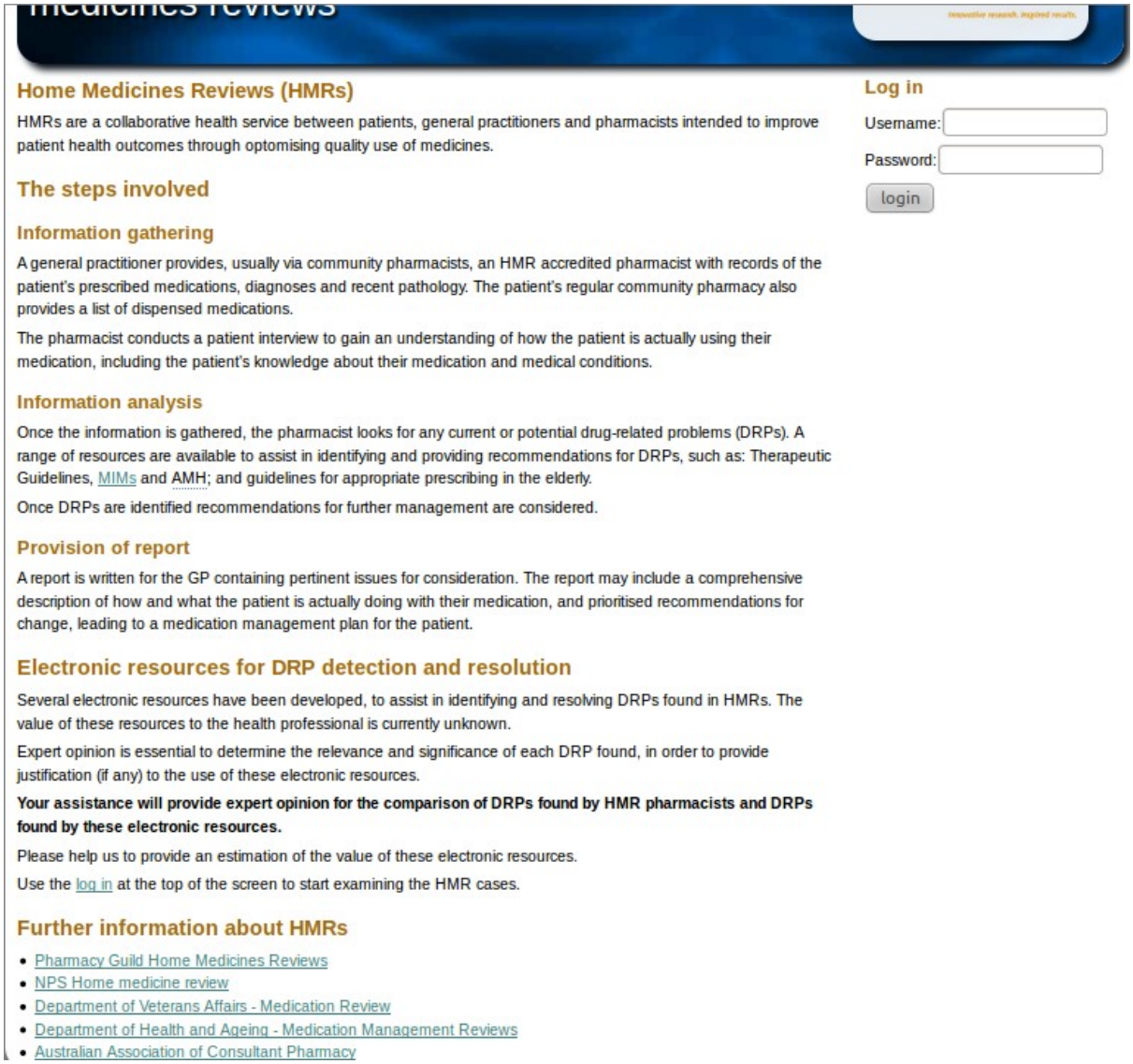
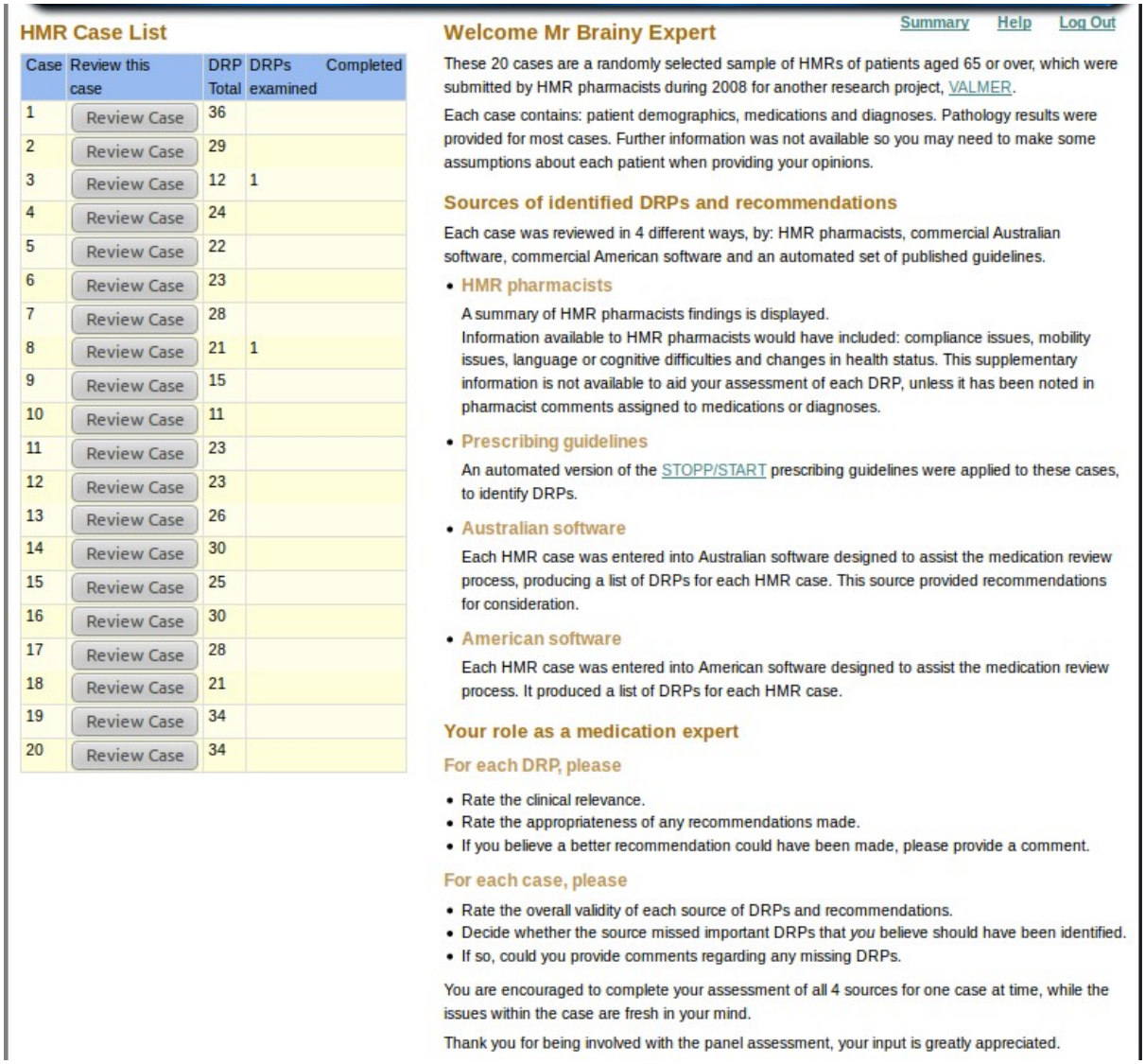


Figure 69: Home page and log in



HMR Case List

Case	Review this case	DRP Total	DRPs examined	Completed
1	Review Case	36		
2	Review Case	29		
3	Review Case	12	1	
4	Review Case	24		
5	Review Case	22		
6	Review Case	23		
7	Review Case	28		
8	Review Case	21	1	
9	Review Case	15		
10	Review Case	11		
11	Review Case	23		
12	Review Case	23		
13	Review Case	26		
14	Review Case	30		
15	Review Case	25		
16	Review Case	30		
17	Review Case	28		
18	Review Case	21		
19	Review Case	34		
20	Review Case	34		

Summary Help Log Out

Welcome Mr Brainy Expert

These 20 cases are a randomly selected sample of HMRs of patients aged 65 or over, which were submitted by HMR pharmacists during 2008 for another research project, VALMER.

Each case contains: patient demographics, medications and diagnoses. Pathology results were provided for most cases. Further information was not available so you may need to make some assumptions about each patient when providing your opinions.

Sources of identified DRPs and recommendations

Each case was reviewed in 4 different ways, by: HMR pharmacists, commercial Australian software, commercial American software and an automated set of published guidelines.

- **HMR pharmacists**

  A summary of HMR pharmacists findings is displayed.
  Information available to HMR pharmacists would have included: compliance issues, mobility issues, language or cognitive difficulties and changes in health status. This supplementary information is not available to aid your assessment of each DRP, unless it has been noted in pharmacist comments assigned to medications or diagnoses.

- **Prescribing guidelines**

  An automated version of the STOPP/START prescribing guidelines were applied to these cases, to identify DRPs.

- **Australian software**

  Each HMR case was entered into Australian software designed to assist the medication review process, producing a list of DRPs for each HMR case. This source provided recommendations for consideration.

- **American software**

  Each HMR case was entered into American software designed to assist the medication review process. It produced a list of DRPs for each HMR case.

Your role as a medication expert

For each DRP, please

- Rate the clinical relevance.
- Rate the appropriateness of any recommendations made.
- If you believe a better recommendation could have been made, please provide a comment.

For each case, please

- Rate the overall validity of each source of DRPs and recommendations.
- Decide whether the source missed important DRPs that *you* believe should have been identified.
- If so, could you provide comments regarding any missing DRPs.

You are encouraged to complete your assessment of all 4 sources for one case at time, while the issues within the case are fresh in your mind.

Thank you for being involved with the panel assessment, your input is greatly appreciated.

Figure 70: HMR cases for assessment

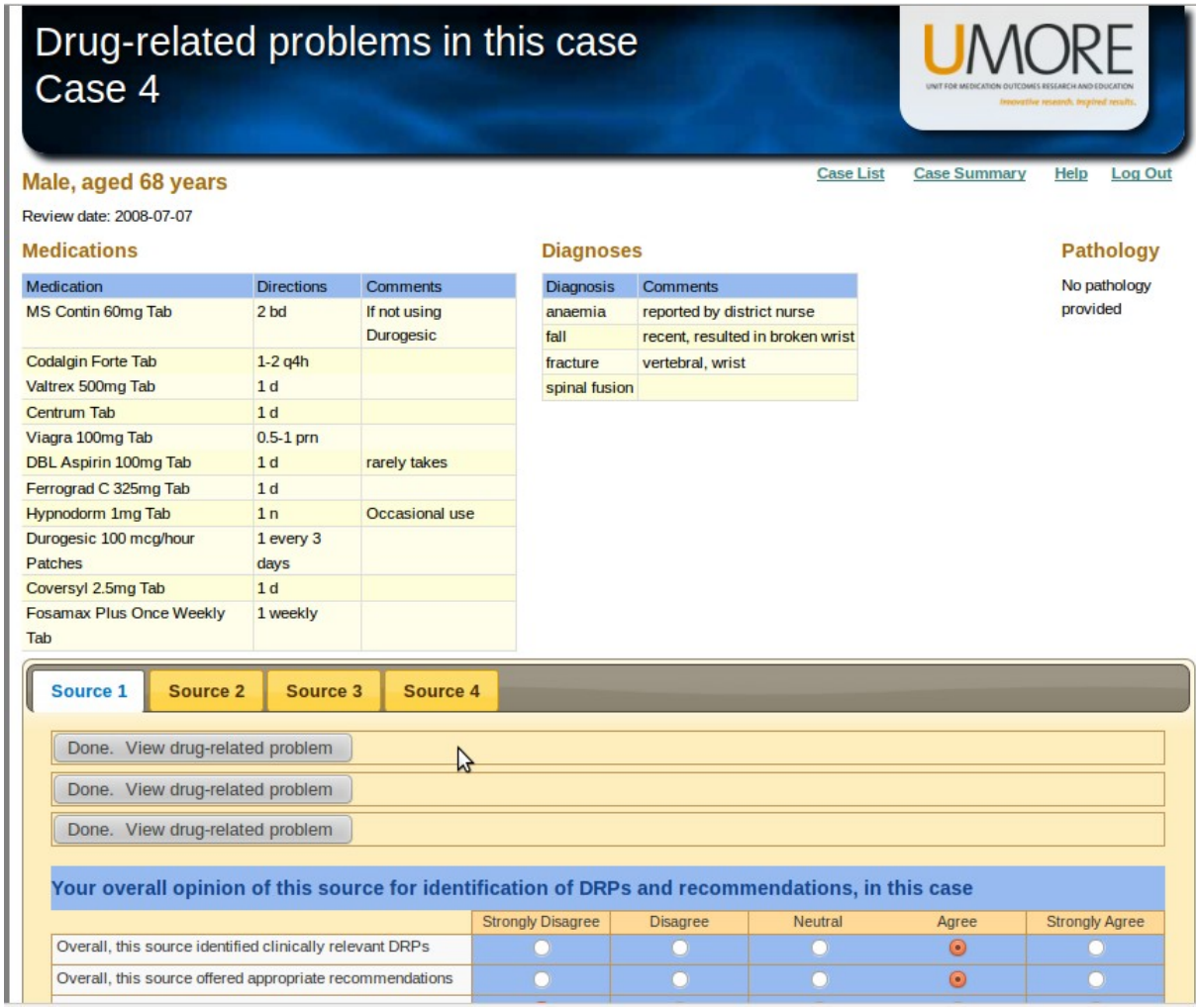


Figure 71: An HMR case showing patient demographics, medications, diagnoses. No pathology was available for this case

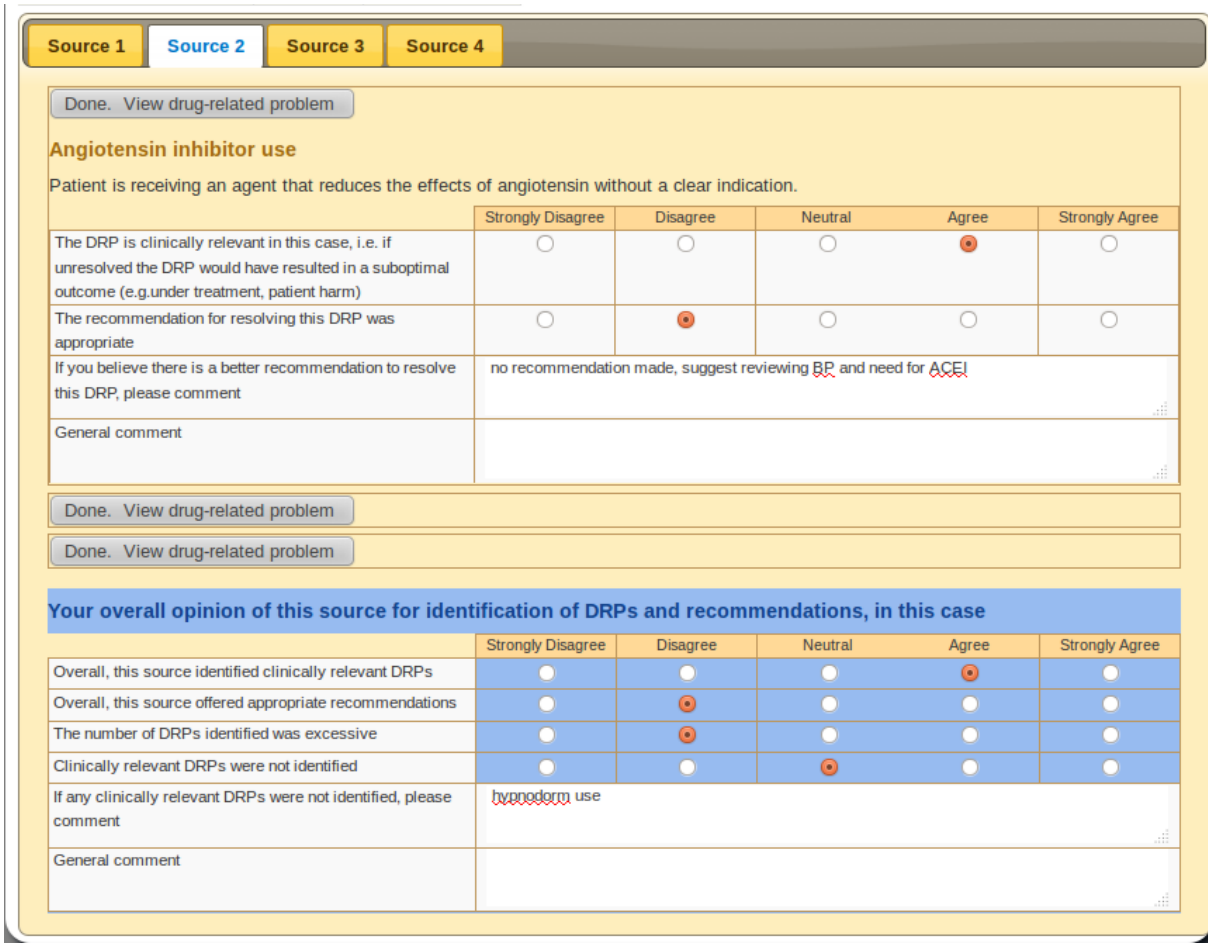
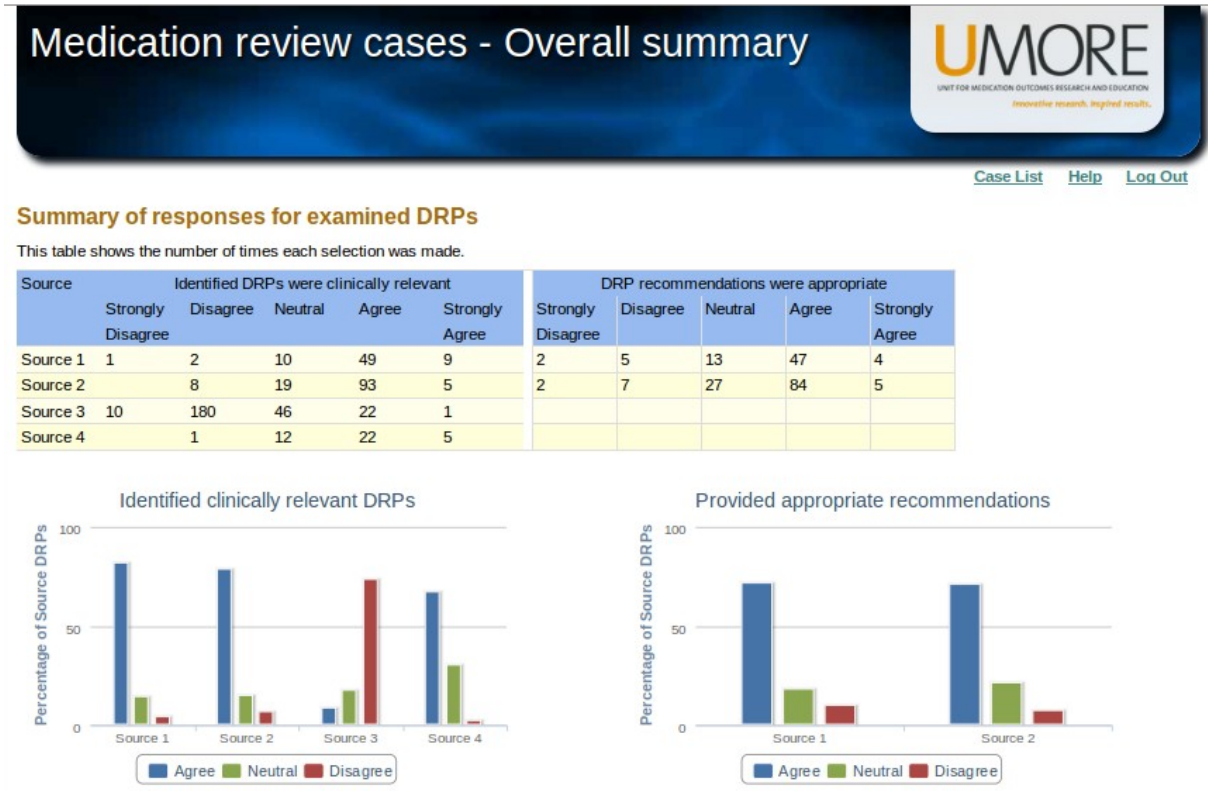
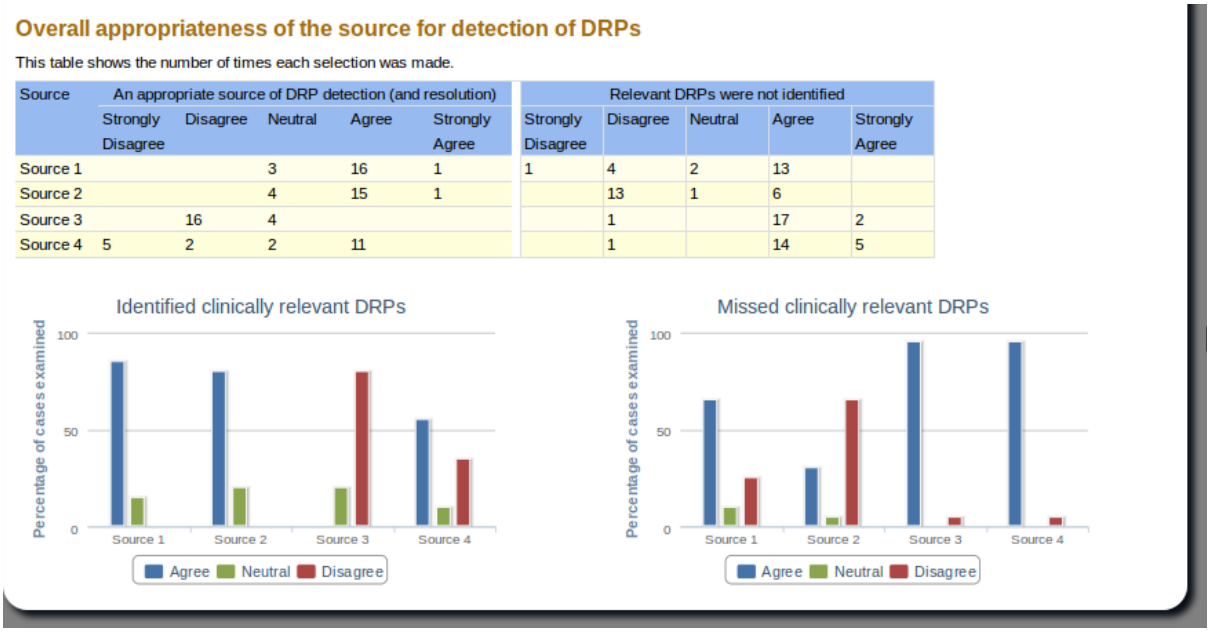


Figure 72: The DRPs from each source could be opened allowing expert assessment. The blue section provided for an overall assessment of the source in the specific case



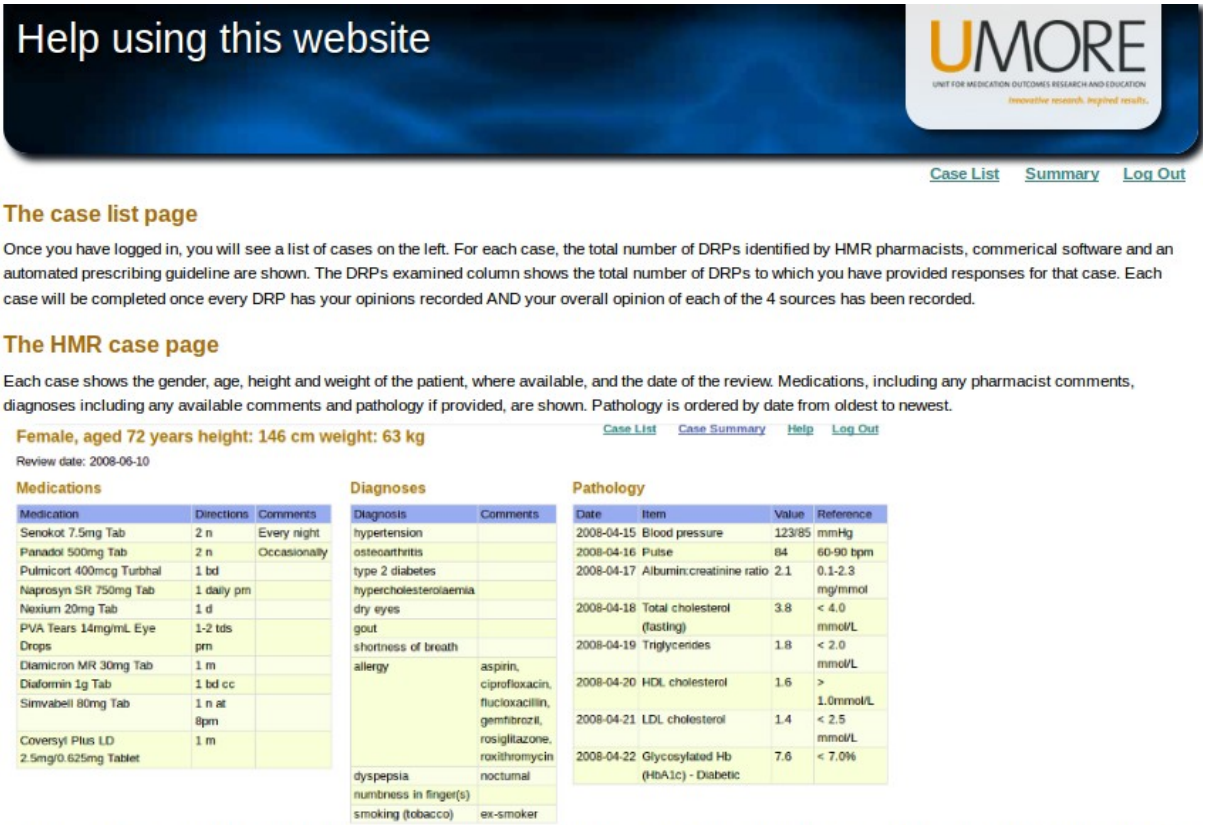
Source	Identified DRPs were clinically relevant					DRP recommendations were appropriate				
	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Source 1	1	2	10	49	9	2	5	13	47	4
Source 2		8	19	93	5	2	7	27	84	5
Source 3	10	180	46	22	1					
Source 4		1	12	22	5					

Figure 73: Summary of an expert's responses of assessment of each individual DRP



Source	An appropriate source of DRP detection (and resolution)					Relevant DRPs were not identified				
	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
Source 1			3	16	1	1	4	2	13	
Source 2			4	15	1		13	1	6	
Source 3		16	4				1		17	2
Source 4	5	2	2	11			1		14	5

Figure 74: Summary of an expert's responses to overall opinion of each source



Help using this website

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Case List Summary Log Out

The case list page

Once you have logged in, you will see a list of cases on the left. For each case, the total number of DRPs identified by HMR pharmacists, commerical software and an automated prescribing guideline are shown. The DRPs examined column shows the total number of DRPs to which you have provided responses for that case. Each case will be completed once every DRP has your opinions recorded AND your overall opinion of each of the 4 sources has been recorded.

The HMR case page

Each case shows the gender, age, height and weight of the patient, where available, and the date of the review. Medications, including any pharmacist comments, diagnoses including any available comments and pathology if provided, are shown. Pathology is ordered by date from oldest to newest.

Case List Case Summary Help Log Out

Female, aged 72 years height: 146 cm weight: 63 kg

Review date: 2008-06-10

Medications

Medication	Directions	Comments
Senokot 7.5mg Tab	2 n	Every night
Panadol 500mg Tab	2 n	Occasionally
Pulmicort 400mcg Turbhal	1 bd	
Naprosyn SR 750mg Tab	1 daily pm	
Nexium 20mg Tab	1 d	
PVA Tears 14mg/mL Eye Drops	1-2 tds prn	
Diamicron MR 30mg Tab	1 m	
Diaformin 1g Tab	1 bd cc	
Simvabell 80mg Tab	1 n at 8pm	
Coversyl Plus LD 2.5mg/0.625mg Tablet	1 m	

Diagnoses

Diagnosis	Comments
hypertension	
osteoarthritis	
type 2 diabetes	
hypercholesterolaemia	
dry eyes	
gout	
shortness of breath	
allergy	aspirin, ciprofloxacin, flucloxacillin, gemfibrozil, rosiglitazone, roxithromycin
dyspepsia	nocturnal
numbness in finger(s)	
smoking (tobacco)	ex-smoker

Pathology

Date	Item	Value	Reference
2008-04-15	Blood pressure	123/85	mmHg
2008-04-16	Pulse	84	60-90 bpm
2008-04-17	Albumin:creatinine ratio	2.1	0.1-2.3 mg/mmol
2008-04-18	Total cholesterol (fasting)	3.8	< 4.0 mmol/L
2008-04-19	Triglycerides	1.8	< 2.0 mmol/L
2008-04-20	HDL cholesterol	1.6	> 1.0mmol/L
2008-04-21	LDL cholesterol	1.4	< 2.5 mmol/L
2008-04-22	Glycosylated Hb (HbA1c) - Diabetic	7.6	< 7.0%

Some medication brands may not be available in 2012, e.g. Diamicron 30mg has been discontinued. If you move the mouse slowly over the medication name the generic name will be displayed.

Toward the bottom of the screen are four tabs named Source 1, Source 2, Source 3 and Source 4.

Source 1 Source 2 Source 3 Source 4

Each source represents either commercial software for identifying DRPs (two tabs), HMR pharmacists or an automated prescribing guideline.

Figure 75: A portion of the help page

Appendix 12 MRM user survey information sheet

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What is your opinion of Medication Review Mentor's ability to detect drug-related problems?

We would like you to complete a survey based on your own experience using Medscope's Medication Review Mentor (MRM) software. MRM combines patient data with artificial intelligence computer algorithms to identify drug-related problems (DRPs) and provide recommendations.

Assessing the ease of use and perceived usefulness of the software will help researchers determine how much confidence is placed in the findings of MRM. Particularly, how much trust is (or can be) placed in artificial intelligence software, and whether such software may be misused either through overreliance or even under reliance on the DRPs identified and recommendations made by MRM.

You will be required to complete questions concerning your medicines review background and MRM specific questions of data entry, ease of use, perceived usefulness and perception of value. The survey will be available through a website.

There are no foreseeable risks associated with your participation in this study. You are free to withdraw at any time and do not need to provide an explanation. All information will be treated confidentially and stored securely on the University of Tasmania Health Science Server. Information will only be accessed by investigators and will be securely destroyed after five years. Study results may be published in a thesis and in scientific journals. You will not be personally identified in any publication.

The assessment will need to be completed by end of May 2013.

This research project is being conducted as partial fulfilment of a PhD for Colin Curtain under the supervision of Professor Gregory Peterson, Dr Ivan Bindoff and Dr Juanita Westbury.

If you are interested in participating in this project or have further questions please contact Colin Curtain at the School of Pharmacy, University of Tasmania on 03 6226 1096, or by email: colin.curtain@utas.edu.au. This information sheet is for you to keep. You will be deemed to have provided consent to this study by undertaking and completing the web-based survey.

Thank you,

Colin Curtain (PhD candidate)
Professor Gregory Peterson (supervisor)
Dr Ivan Bindoff (supervisor)
Dr Juanita Westbury (supervisor)
Unit for Medications Outcomes Research and Education
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Appendix 13 MRM user survey

Screenshots showing the complete web-based MRM user survey. Questions marked with a red asterisk were mandatory.

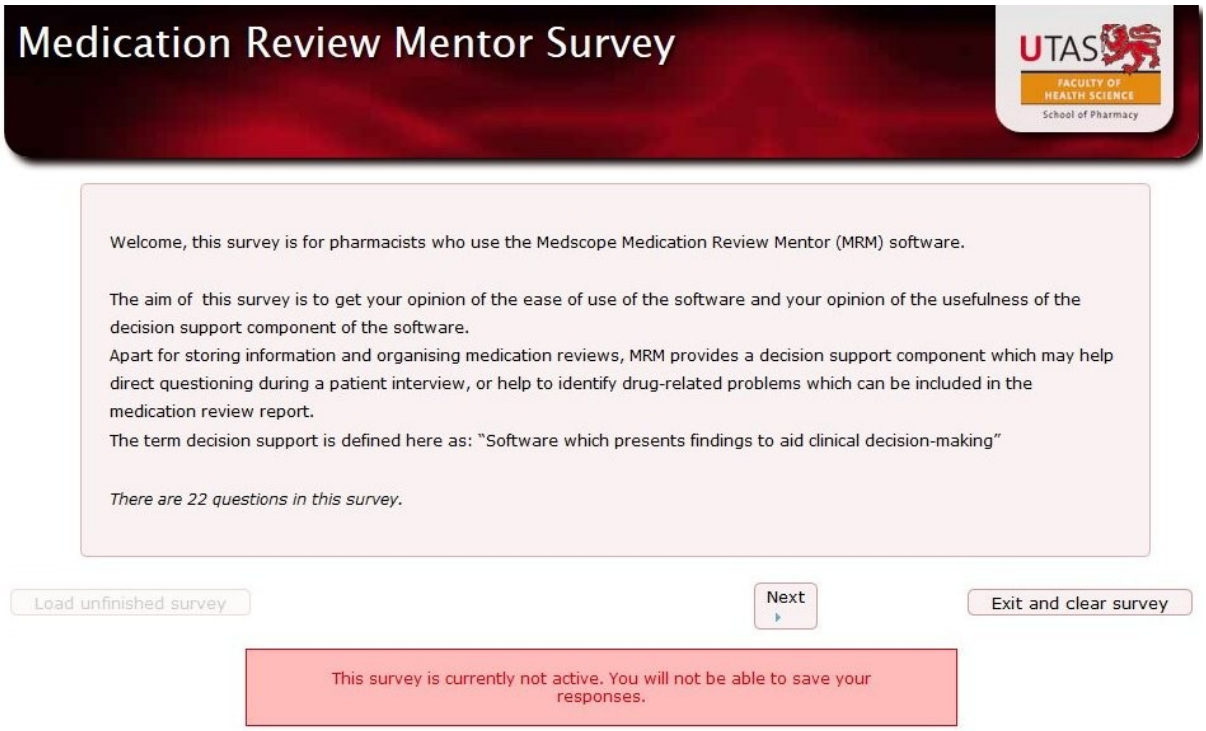


Figure 76: MRM survey - introduction screen

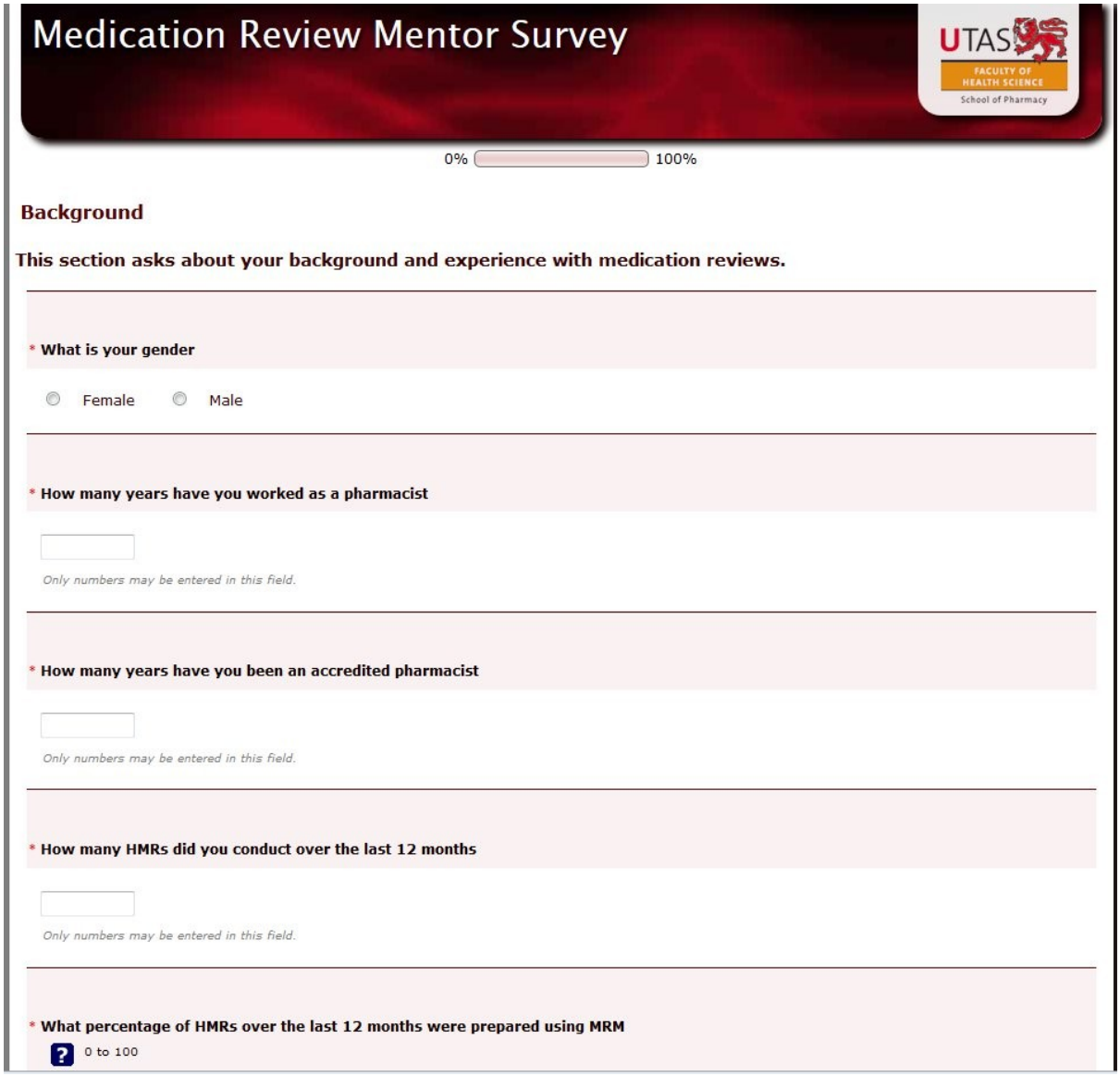


Figure 77: MRM survey - pharmacist background 1

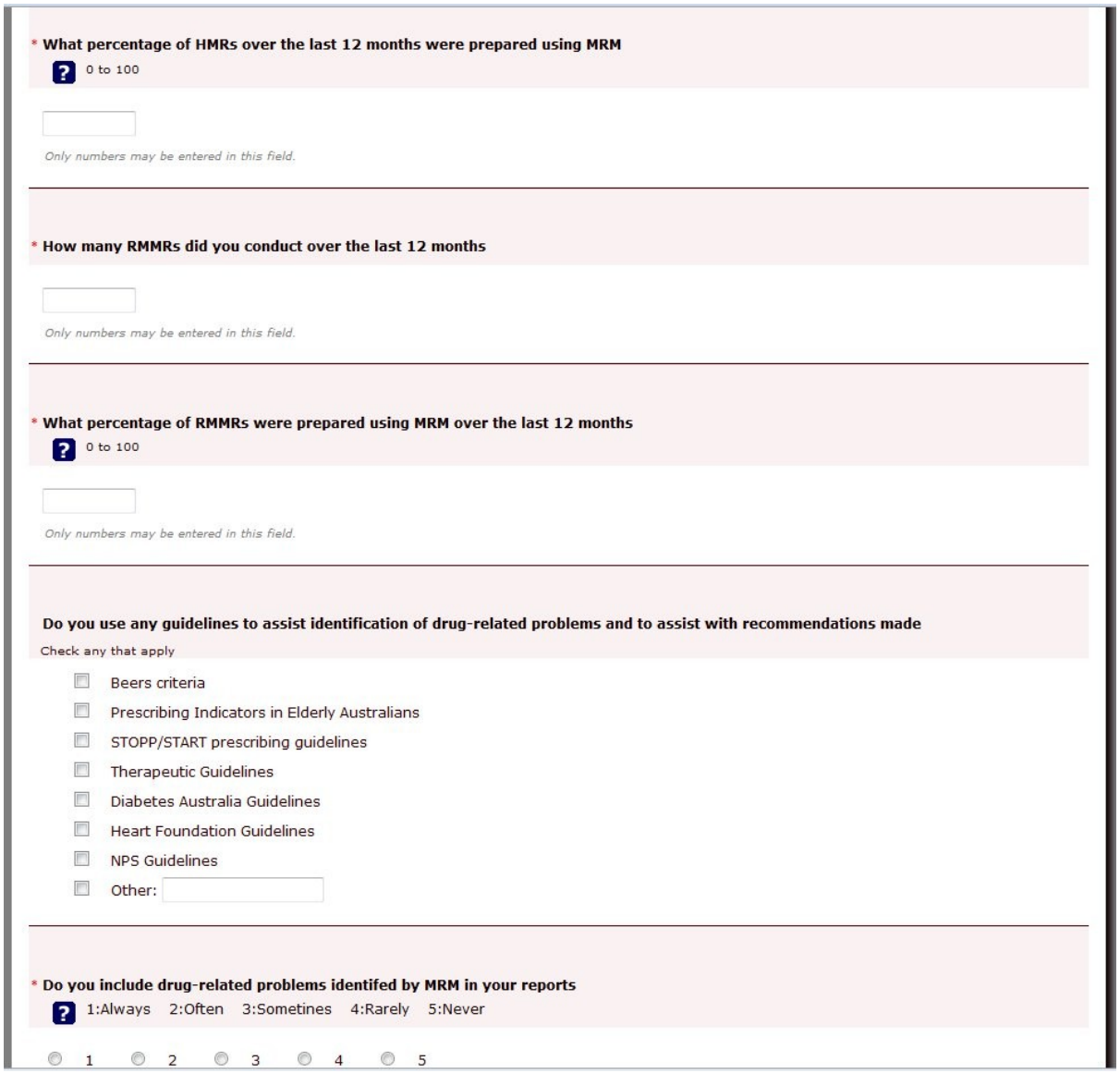


Figure 78: MRM survey - pharmacist background 2

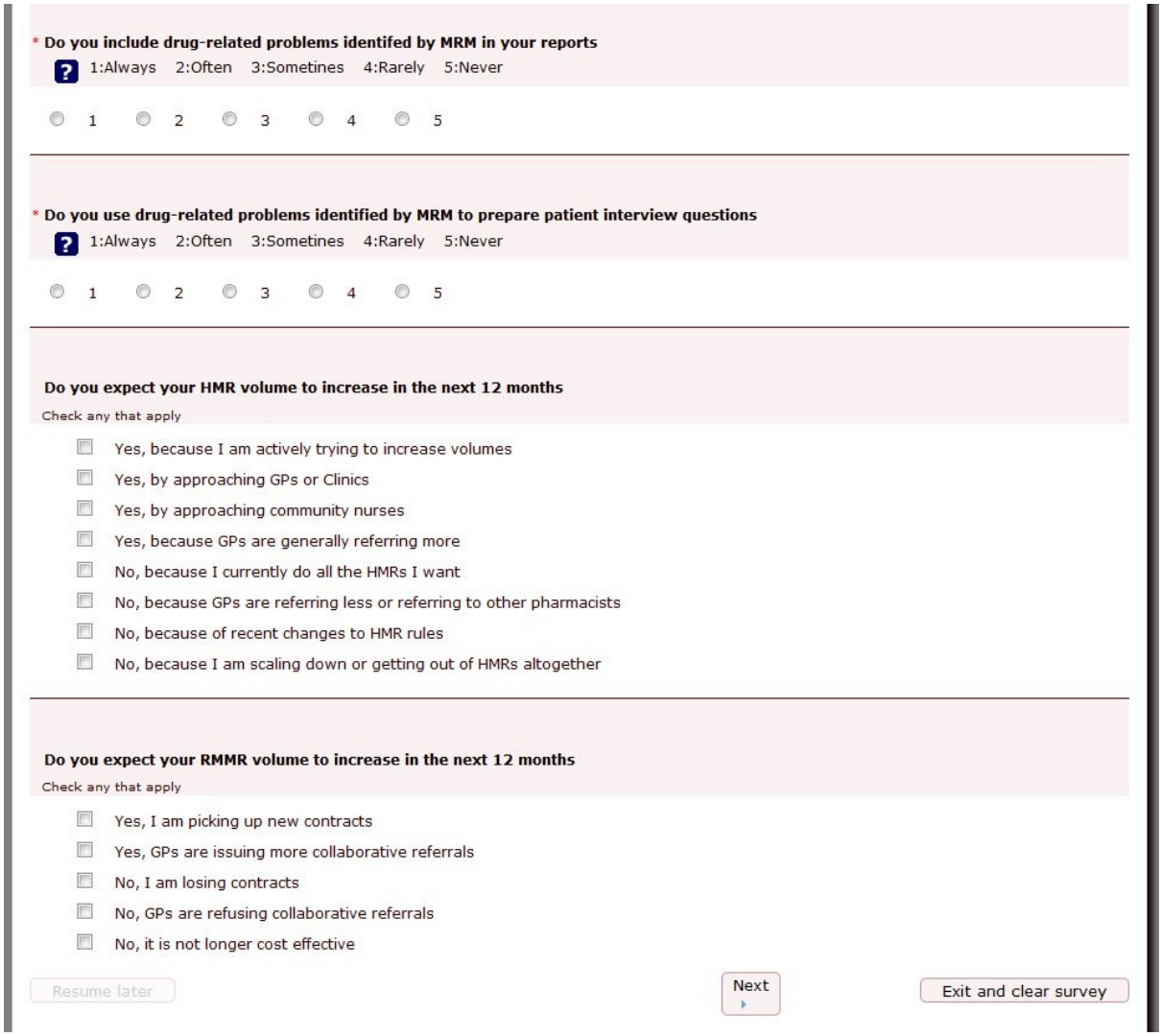


Figure 79: MRM survey - pharmacist background 3

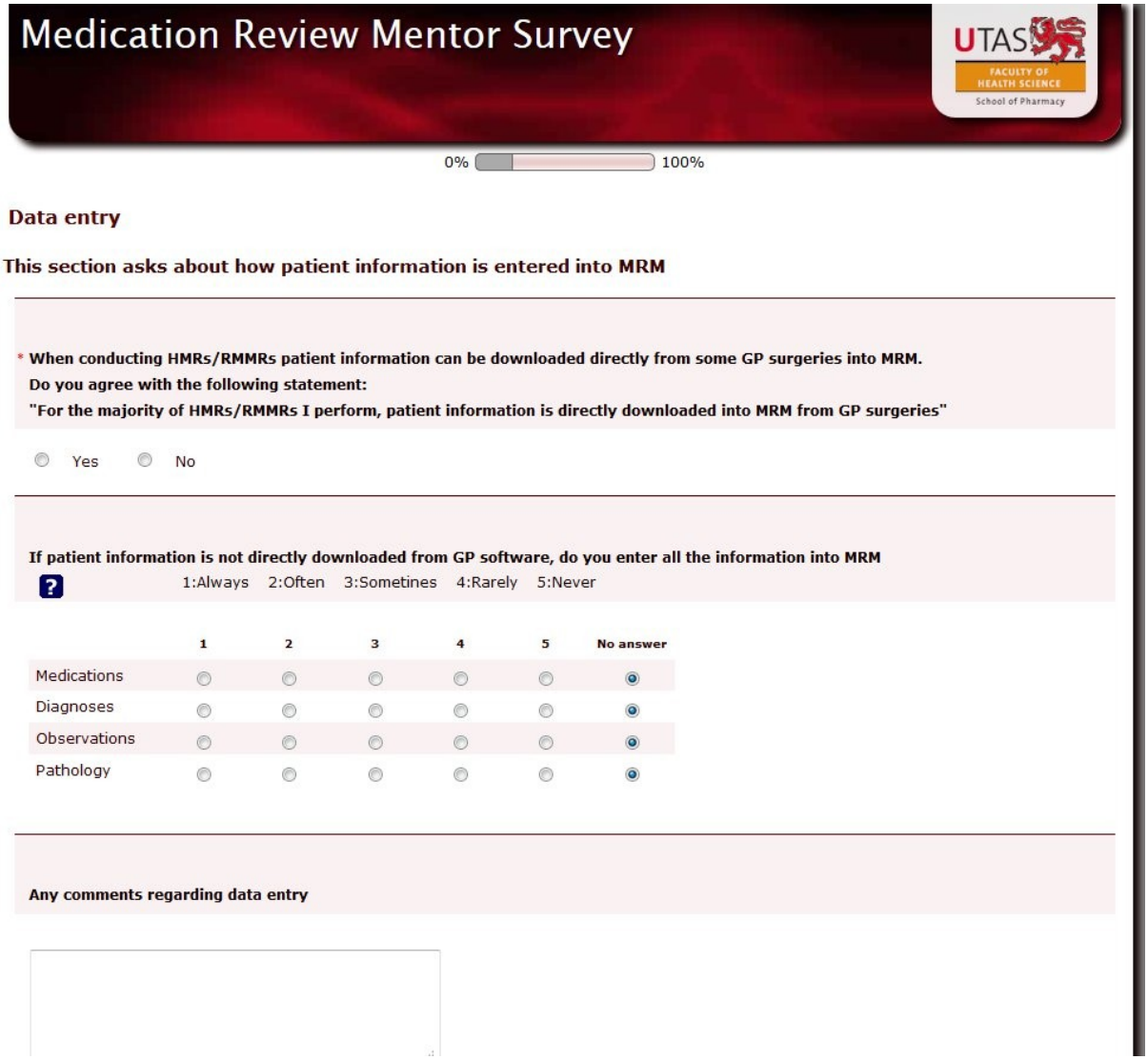


Figure 80: MRM survey - data entry

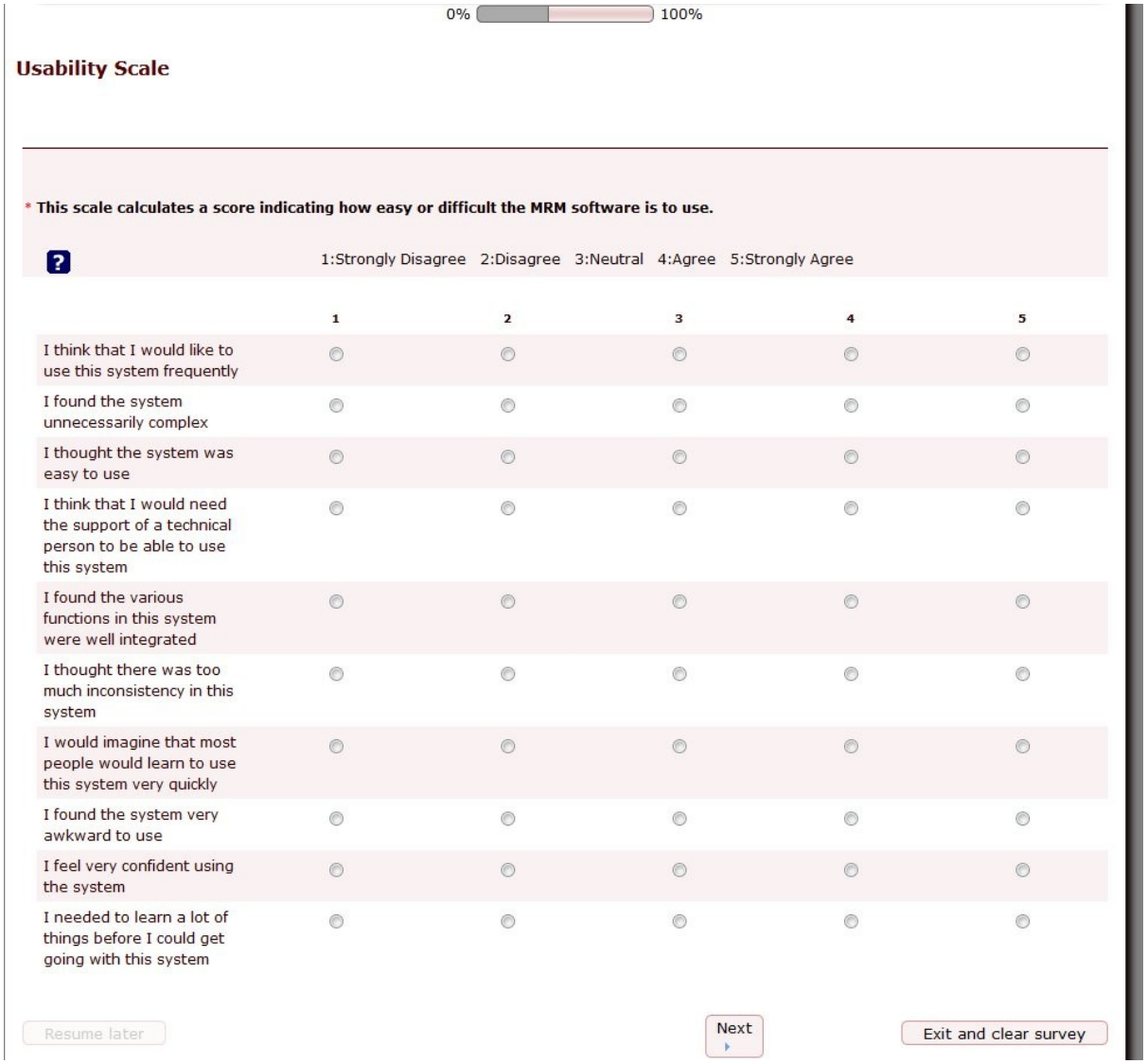


Figure 81: MRM survey - SUS

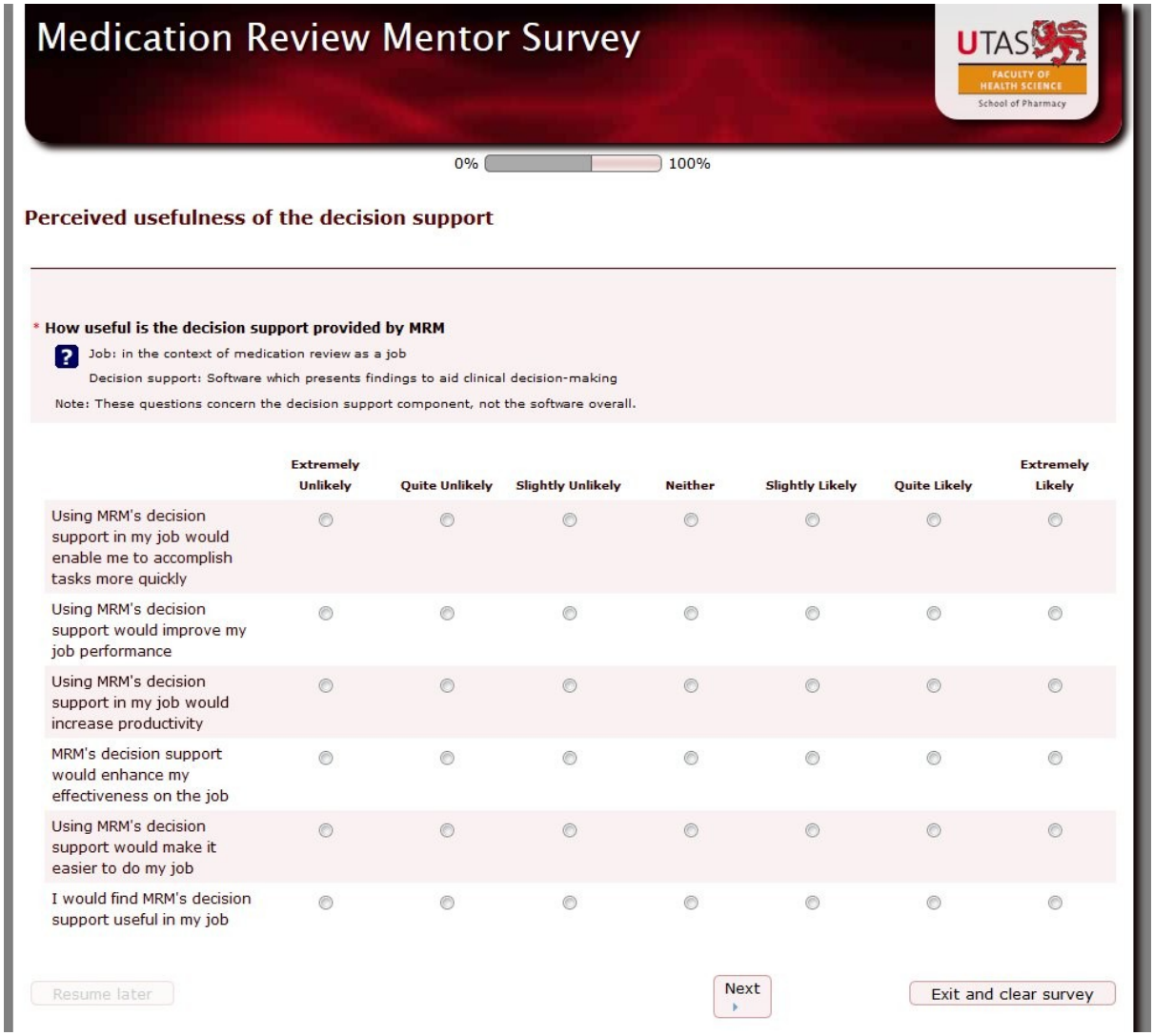


Figure 82: MRM survey - perceived usefulness

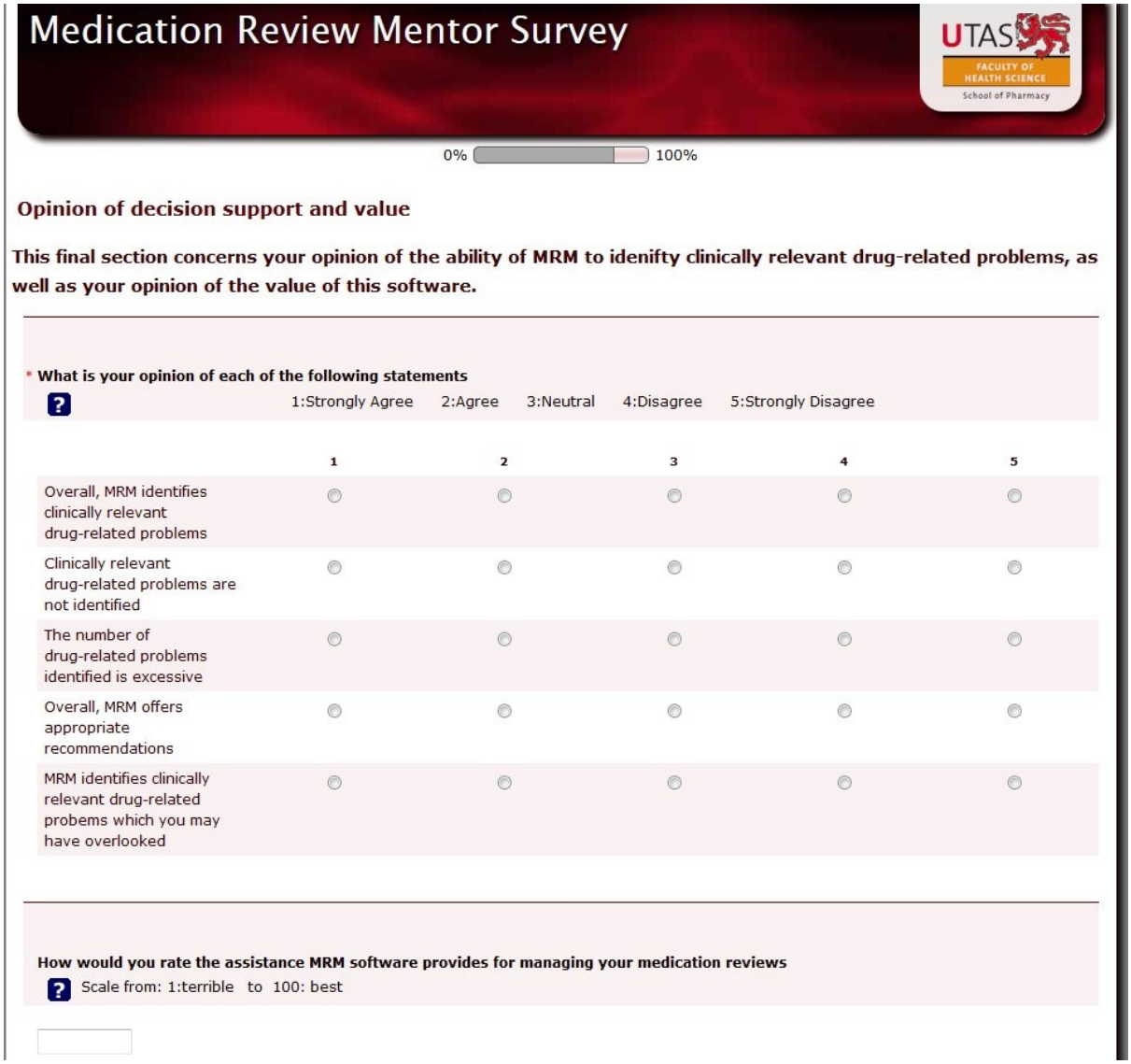


Figure 83: MRM survey - opinion of decision support

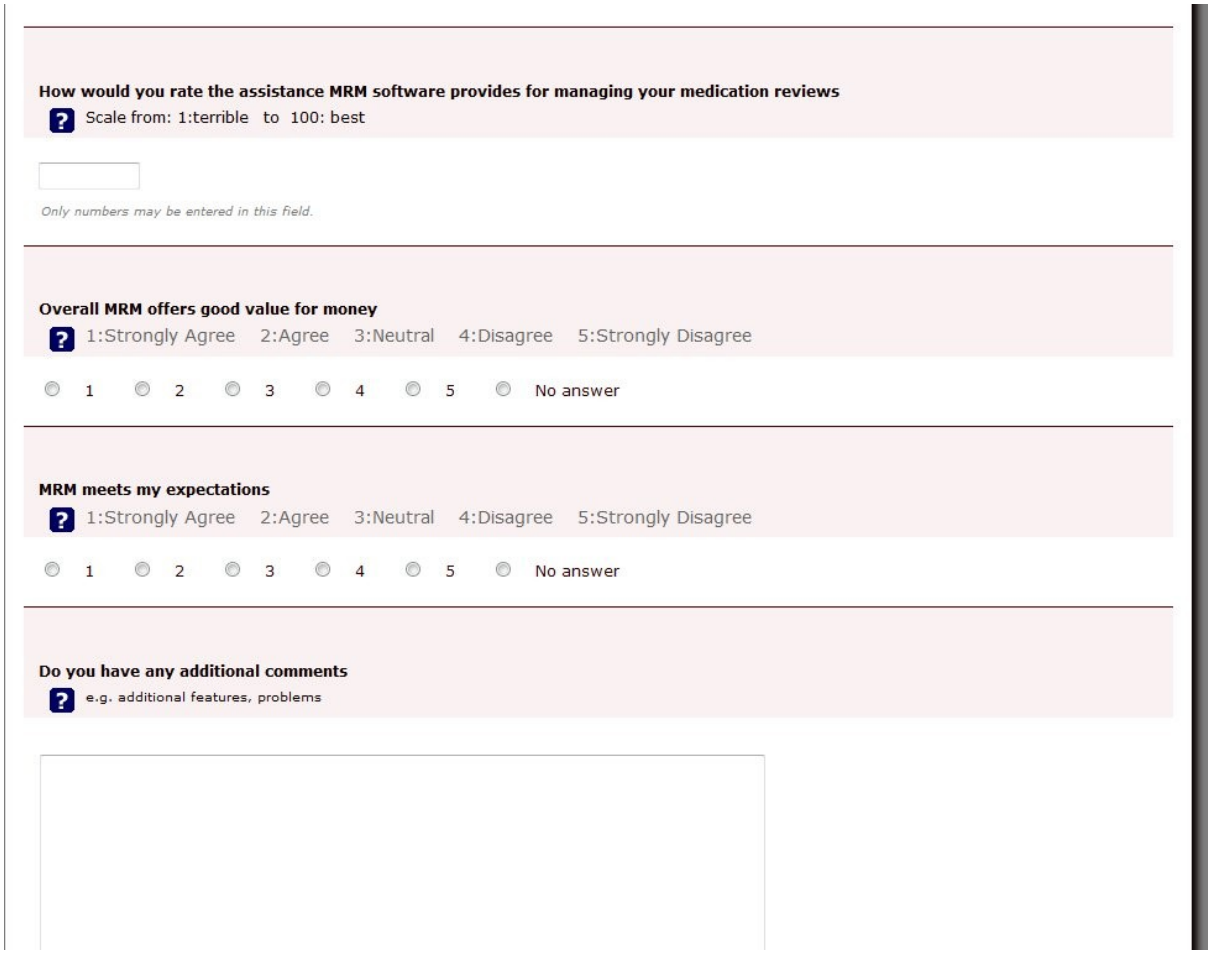


Figure 84: MRM survey - opinion of software value

Appendix 14 Descriptive classifications by source

Table 62: Frequency of descriptive classifications by DRP source

Classification	Beers03	Beers12	MRM	Pharmacist	PIEA	STOPP/ START
ACEI cough			11	12		
AF requires aspirin or warfarin			4	5	40	28
Airway disease un(der)treated			64	17		5
Allopurinol and reduced renal function			15	8		
Amiodarone or other antiarrythmic prescribed	11	39				
Analgesia optimisation with regular paracetamol needed			59	77		
Antibiotic no indication				2		
Anticholinergic use not elsewhere specified	78	65	37	33	33	14
Anticholinergics and cognitive impairment	12	12		4	6	17
Anticholinergics and constipation	47	14	22	7		48
Anticoagulant toxicity			22	13		
Antidiabetic drug no indication			15	5		
Antigout medication (might) not indicated			76	13		
Antilipidaemic drug no indication			56	1		
Antiplatelet not indicated			60	4		150
Aspirin high dose not indicated	3			2		2
Aspirin or thiazide contraindicated in gout			21			13
Asthma moderate/severe requires inhaled corticosteroid			15	4	1	31
Beta-blocker for hypertension			4	2		
Bleeding disorder and antiplatelet or anticoagulant	1					4
Bleeding risk interacting drugs			26	31	55	23
Calcium channel blocker and constipation		13		4		39
Calcium channel blocker and peripheral oedema			20	17		
Calcium channel blocker and reflux			120	1		
Can reduce daily drug frequency			6	8		
Cardiovascular disease/risk requires antiplatelet			70	26	39	30
Cardiovascular disease/risk requires statin			44	14	177	42
Cardiovascular drug no indication			89	8		
Clopidogrel and aspirin interaction			16	13		
Combine medications into combination product			3	10		
Compliance - Confusion about therapy				*29*		
Compliance - using too little medication				*113*		
Compliance - using too much medication				*9*		
Constipation un(der)treated			33	9		
COPD and using benzodiazepines	15				38	
COPD/Asthma and using a beta blocker			34	6	45	4
Cost of therapy concern				*4*		
Current therapy insufficient			48	32	12	5
Depression un(der)treated			92	9		17
Dextropropoxyphene prescribed	7		8	2		

Classification	Beers03	Beers12	MRM	Pharmacist	PIEA	STOPP/ START
Diabetes and CV risks or renal disease requires ACEI or ARB (CCB)			36	4	1	1
Diabetes and taking medication that affects glucose levels				12	42	
Diabetes monitoring required			41	8	5	
Diabetes undertreated (HBA1c or BSLs high)			36	17		
Difficulty using dosage form				*35*		
Digoxin dose over 125mcg or considered too high	7	19	17	17		2
Digoxin monitoring required			38	3		
Digoxin toxicity			8			
Documentation insufficient				*5*		
Drug causing dyspepsia with PPI			25	1	270	
Duration of therapy may be excessive			10	16		
Eligible for DVA funded DAA				*34*		
Epilepsy and medication affecting seizure threshold		2	1	1		
Falls risk/history and sedatives/antihypertensives/other	13	51	6	15	21	25
Family history disease risk, preventative therapy indicated				2		
Fluoxetine prescribed	7					
Glaucoma untreated			13	2		
Glibenclamide prescribed		2	1	1	2	2
GORD drug no indication			115	19		
Haematology monitoiring required			11	12		
Heart disease un(der)treated			47	13		10
Heart failure and concurrent verapamil or diltiazem		13	11	3	11	11
Heart failure or hypertension and using high sodium or salt retaining drugs	2		13		37	
Heart failure or IHD requires beta-blocker				5	114	24
Heart failure requires ACEI or ARB			12	3	20	20
Hexamine prescribed (poor renal clearance)				1	1	
Hydralazine monitoring required			3	2		
Hyperkalaemia (or risk of) and medication			46	29		
Hyperlipidaemia under/untreated			83	31		
Hypertension under/untreated				38	18	20
Hyponatremia drug toxicity			17	5		
INR outside therapeutic range			10	2	15	
Iron and constipation	7		3	2		
Iron no indication			11	2		
Lifestyle issues - overweight				5		
Lipid monitoring required			1	14		
Lithium monitoring required			1	1		
Medication expired				*15*		
Medication monitoring - calcium intake			22			
Medication monitoring - Potassium			25	9		
Medication regimen complicated				2		
Metformin dose high with renal			35	12	8	

Classification	Beers03	Beers12	MRM	Pharmacist	PIEA	STOPP/ START
impairment						
Methyldopa prescribed	2	5	2			
Mineral oil laxative prescribed	3	3		2		
Nitrate free period required			2	3		
Nitrofurantoin prescribed	3		3	2		
NSAID combined with ACEI or ARB, diuretic - triple whammy			22	24	54	
NSAID not recommended (CV/HF/bleed/other)	4	39	59	28	77	84
NSAID used with (risk of) renal failure		9	1	6	87	9
NSAID without acid suppressant			35			
Oestrogens and thromboembolism or cancer risk	3	5	5			6
Opioid constipation may require laxative or increased lax therapy			61	13	5	2
Opioid sedation			25			
Osteoporosis (or risk) may require calcium and or vitamin D			137	117		50
Osteoporosis (or risk) requires antiosteoporotic			7	1	53	32
Other cardiovascular drug toxicity				44		
Other disease/symptoms untreated			2	30		67
Other DRP MRM			8			
Other DRP pharmacist				48		
Other drug disease contraindication	3	5	54	13	4	4
Other drug interaction			62	59		2
Other drug no indication			35	34		14
Other monitoring (lab) required			3	27		
Other monitoring (non-lab) required			13	2		
Other PIM	8	18				
Other toxicity - drug suspected			11	64		
Pain un(der)treated			5	28		13
Parkinsonism and antipsychotics or metoclopramide	3	16	14	4		3
Patient disease management education provided/required				19		
Patient drug education provided/required			27	17		
Pioglitazone in HF		1	1	3		
PPI and clopidogrel interaction			1			
PPI high dose			69	24		15
Quinine prescribed			19	11		
Renal impairment and using or check for renally excreted drugs			122	48		
Rosiglitazone prescribed		3	11	6		
Sedatives long-acting or sedative long term	75	51	55	31	68	56
Serotonergic drugs interaction			2	4	5	
Short acting nitrate required			28	5		
Skin disease un(der)treated				16		
Smoking cessation education required/provided				5		
Statin myopathy risk			8	29	96	
Statin toxicity			15	4		

Classification	Beers03	Beers12	MRM	Pharmacist	PIEA	STOPP/ START
Stimulant laxative long term use	60			7		
Therapeutic dose too high		2	28	13		
Therapeutic dose too low			13	27		
Therapy duplication			2	27		29
Thyroid function monitoring required			11	7		
Timing of dose inappropriate				14		
Vaccination required (Flu, pneumonia)				18		
Vitamin no indication			1	6		
Vitamin B12 and or folate deficiency possible			83	66		
Warfarin and aspirin interaction			4	7		4
Weight loss un(der)treated				3		
Totals	**374**	**387**	**2854**	**1680**	**1460**	**977**

Table 63: Frequency of distinct classifications by source, limited to 100 test cases

Description	Beers03	Beers12	MRM	MRX	Pharmacist	PIEA	STOPP / START
ACEI cough			3		2		
AF requires aspirin or warfarin						3	2
Airway disease un(der)treated			8		2		
Allopurinol and reduced renal function			4		4		
Amiodarone or other antiarrhythmic prescribed	2	8		2			
Analgesia optimisation with regular paracetamol needed			10		17		
Anticholinergic use not elsewhere specified	10	7	7	75	6	6	3
Anticholinergics and cognitive impairment	3	2		76			
Anticholinergics and constipation	6	3	3				8
Anticoagulant toxicity			2		3		
Antidiabetic drug no indication			1		1		
Antigout medication (might) not indicated			16		5		
Antilipidaemic drug no indication			9				
Antiplatelet not indicated			10		1		22
Aspirin high dose not indicated					1		
Aspirin or thiazide contraindicated in gout			7				4
Asthma moderate/severe requires inhaled corticosteroid			2				4
Beta-blocker for hypertension			1				
Bleeding risk interacting drugs			3		2	9	4
Calcium channel blocker and constipation		2			1		4
Calcium channel blocker and peripheral oedema			2		2		
Calcium channel blocker and reflux			19				
Can reduce daily drug frequency			1		3		

Description	Beers03	Beers12	MRM	MRX	Pharmacist	PIEA	STOPP / START
Cardiovascular disease/risk requires antiplatelet			10		3	4	5
Cardiovascular disease/risk requires statin			8		1	23	4
Cardiovascular drug no indication			15		1		
Clopidogrel and aspirin interaction			4		3		
Combine medications into combination product			2		2		
Compliance - Confusion about therapy					*3*		
Compliance - using too little medication					*18*		
Compliance - using too much medication					*3*		
Constipation un(der)treated			2		3		
COPD and using benzodiazepines	3					6	
COPD/Asthma and using a beta blocker			7			6	2
Current therapy insufficient			10		4	1	1
Depression un(der)treated			12				1
Diabetes and CV risks or renal disease requires ACEI or ARB (CCB)			6		1		
Diabetes and taking medication that affects glucose levels					1	10	
Diabetes monitoring required			6		4	3	
Diabetes undertreated (HBA1c or BSLs high)			6		1		
Difficulty using dosage form					*5*		
Digoxin dose over 125mcg or considered too high	4	8	9		7		2
Digoxin monitoring required			6		2		
Digoxin toxicity			3				
Drug causing dyspepsia with PPI			7			48	
Duration of therapy may be excessive			2		3		
Eligible for DVA funded DAA					*6*		
Falls risk/history and sedatives/antihypertensives/other	3	12	1	100	1	5	5
Fluoxetine prescribed	2			2			
Glaucoma untreated			4		2		
Glibenclamide prescribed		1	1			1	1
GORD drug no indication			17		2		
Haematology monitoiring required			2		5		
Heart disease un(der)treated			7		3		2
Heart failure and concurrent verapamil or diltiazem	1						
Heart failure or hypertension and using high sodium or salt retaining drugs			2			5	
Heart failure or IHD requires beta-blocker					2	17	6

Description	Beers03	Beers12	MRM	MRX	Pharmacist	PIEA	STOPP / START
Heart failure requires ACEI or ARB			3		1	4	4
Hyperkalaemia (or risk of) and medication			7		4		
Hyperlipidaemia under/untreated			19		8		
Hypertension under/untreated					7	1	5
Hyponatremia drug toxicity			2		1		
Medication monitoring – calcium intake			5				
Medication monitoring - cognitive				91			
Medication monitoring - communication/social problems				100			
Medication monitoring - dehydration				55			
Medication monitoring - nutritional status or dental care				91			
Medication monitoring - Potassium			4				
Medication monitoring - pressure ulcers				60			
Medication monitoring - urinary incontinence				90			
Medication monitoring - visual disturbance				68			
Metformin dose high with renal impairment			7			3	
Nitrate free period required			1		3		
NSAID combined with ACEI or ARB, diuretic - triple whammy			2		3	8	
NSAID not recommended (CV/HF/bleed/other)		4	6	1	6	14	18
NSAID used with renal failure (or risks of)		2	1		1	15	2
NSAID without acid suppressant			4				
Oestrogens and thromboembolism or cancer risk				1			1
Opioid constipation may require laxative or increased lax therapy			10		2	1	
Opioid sedation			3				
Osteoporosis (or risk) may require calcium and or vitamin D			28		16		11
Osteoporosis (or risk) requires antiosteoporotic			2		1	12	3
Other cardiovascular drug toxicity					11		
Other disease/symptoms untreated					4		8
Other DRP pharmacist					7		
Other drug disease contraindication		1	12	60	2	1	
Other drug interaction			15		12		
Other drug no indication			6		5		3
Other monitoring (lab) required			2		9		
Other monitoring (non-lab)			2		1		

Description	Beers03	Beers12	MRM	MRX	Pharmacist	PIEA	STOPP / START
required							
Other PIM		3		2			
Other toxicity - drug suspected			1		12		
Pain un(der)treated					2		1
Parkinsonism and antipsychotics or metoclopramide		2	2		2		
Patient disease management education provided/required					2		
Patient drug education provided/required			4		3		
PPI high dose			16		5		3
Quinine prescribed			5		5		
Renal impairment and using or check for renally excreted drugs			18		9		
Rosiglitazone prescribed		1	2		1		
Sedatives long-acting or sedative long term	11	11	9	6	2	11	11
Serotonergic drugs interaction			1			1	
Short acting nitrate required			8		2		
Skin disease un(der)treated					2		
Smoking cessation education required/provided					1		
Statin myopathy risk			2		6	23	
Statin toxicity			1				
Stimulant laxative long term use	9				2		
Therapeutic dose too high			5		1		
Therapeutic dose too low			2		5		
Therapy duplication					4		5
Thyroid function monitoring required			2		4		
Timing of dose inappropriate					3		
Vaccination required (Flu, pneumonia)					3		
Vitamin no indication					2		
Vitamin B12 and or folate deficiency possible			15		12		1
Warfarin and aspirin interaction			1				1
Weight loss un(der)treated					1		

In both tables italicised classifications were pharmacist-only identified *compliance* or *non-classifiable*. These were excluded from the analysis. In both tables the bold classifications *other DRP – MRM* and *other DRP – pharmacist* were also not included in analysis, they were too difficult to classify in any meaningful way.

Appendix 15 Descriptive classifications common to MRM and pharmacists in 570 cases

Table 64: Classifications found by MRM and pharmacists (570 cases aged 65 and older)

Classification	Total cases MRM found	Total cases pharmacist found	Total number of cases found in common	Total Cases	Overlap percent of total cases
Osteoporosis (or risk) may require calcium and or vitamin D	137	117	49	205	23.9%
Renal impairment and using or check for renally excreted drugs	122	48	24	146	16.4%
Vitamin B12 and or folate deficiency possible	83	66	16	133	12.0%
Analgesia optimisation with regular paracetamol needed	59	77	5	131	3.8%
GORD drug no indication	115	19	7	127	5.5%
Calcium channel blocker and reflux	120	1	1	120	0.8%
Other drug interaction	62	59	5	116	4.3%
Depression un(der)treated	92	9	5	96	5.2%
Hyperlipidaemia under/untreated	83	31	20	94	21.3%
PPI high dose	69	24	7	86	8.1%
Cardiovascular disease/risk requires antiplatelet	70	26	16	80	20.0%
Antigout medication (might) not be indicated	76	13	11	78	14.1%
Current therapy insufficient	48	32	2	78	2.6%
Airway disease un(der)treated	64	17	6	75	8.0%
Other toxicity - drug suspected	11	64	3	72	4.2%
NSAID not recommended (CV/HF/bleed/other)	59	28	17	70	24.3%
Sedatives long-acting or sedative long term	55	31	18	68	26.5%
Other drug no indication	35	34	1	68	1.5%
Opioid constipation may require laxative or increased lax therapy	61	13	7	67	10.4%
Hyperkalaemia (or risk of) and medication	46	29	10	65	15.4%
Anticholinergic use not elsewhere specified	37	33	7	63	11.1%
Antiplatelet not indicated	60	4	3	61	4.9%

Descriptive classifications common to MRM and pharmacists in 570 cases

Classification	Total cases MRM found	Total cases pharmacist found	Total number of cases found in common	Total Cases	Overlap percent of total cases
Heart disease un(der)treated	47	13	2	58	3.4%
Antilipidaemic drug no indication	56	1	1	56	1.8%
Cardiovascular disease/risk requires statin	44	14	5	53	9.4%
Bleeding risk interacting drugs	26	31	5	52	9.6%
Diabetes monitoring required	41	8	1	48	2.1%
Diabetes undertreated (HBA1c or BSLs high)	36	17	9	44	20.5%
Metformin dose high with renal impairment	35	12	5	42	11.9%
Constipation un(der)treated	33	9	2	40	5.0%
Digoxin monitoring required	38	3	1	40	2.5%
COPD/Asthma and using a beta blocker	34	6	3	37	8.1%
NSAID combined with ACEI or ARB, diuretic - triple whammy	22	24	9	37	24.3%
Diabetes and CV risks or renal disease requires ACEI or ARB or CCB	36	4	3	37	8.1%
Medication monitoring - Potassium	25	9	1	33	3.0%
Short acting nitrate required	28	5	2	31	6.5%
Statin myopathy risk	8	29	7	30	23.3%
Calcium channel blocker and peripheral oedema	20	17	8	29	27.6%
Anticoagulant toxicity	22	13	7	28	25.0%
Digoxin dose over 125mcg or considered too high	17	17	9	25	36.0%
Anticholinergics and constipation	22	7	4	25	16.0%
Clopidogrel and aspirin interaction	16	13	5	24	20.8%
Haematology monitoring required	11	12	1	22	4.5%
Hyponatremia drug toxicity	17	5	1	21	4.8%
Quinine prescribed	19	11	10	20	50.0%
Antidiabetic drug no indication	15	5	1	19	5.3%
Asthma moderate/severe requires inhaled corticosteroid	15	4	1	18	5.6%

Descriptive classifications common to MRM and pharmacists in 570 cases

Classification	Total cases MRM found	Total cases pharmacist found	Total number of cases found in common	Total Cases	Overlap percent of total cases
Allopurinol and reduced renal function	15	8	5	18	27.8%
ACEI cough	11	12	7	16	43.8%
Heart failure requires ACEI or ARB	12	3	1	14	7.1%
Thyroid function monitoring required	11	7	4	14	28.6%
Glaucoma untreated	13	2	2	13	15.4%
Combine medications into combination product	3	10	1	12	8.3%
Iron no indication	11	2	1	12	8.3%
Heart failure and concurrent verapamil or diltiazem	11	3	3	11	27.3%
Rosiglitazone prescribed and (risk of) HF	11	6	6	11	54.5%
INR outside therapeutic range	10	2	1	11	9.1%
Warfarin and aspirin interaction	4	7	2	9	22.2%
Dextropropoxyphene prescribed	8	2	2	8	25.0%
Osteoporosis (or risk) requires antiosteoporotic	7	1	1	7	14.3%
Vitamin no indication	1	6	1	6	16.7%
Serotonergic drugs interaction	2	4	1	5	20.0%
Nitrate free period required	2	3	1	4	25.0%
Hydralazine monitoring required	3	2	1	4	25.0%
Iron and constipation	3	2	2	3	66.7%
Nitrofurantoin prescribed	3	2	2	3	66.7%
Pioglitazone in HF	1	3	1	3	33.3%
Lithium monitoring required	1	1	1	1	100.0%

Appendix 16 Descriptive classifications common to MRM and pharmacists in 100 test cases

Table 65: Overlap of common classifications between MRM and pharmacists (100 test cases)

Descriptive classification	Total cases MRM found	Total cases pharmacists found	Total cases found in common	Total Cases	Overlap percent of total cases
Osteoporosis (or risk) may require calcium and or vitamin D	28	16	8	36	22.2%
Analgesia optimisation with regular paracetamol needed	10	17	1	26	3.8%
Vitamin B12 and or folate deficiency possible	15	12	1	26	3.8%
Hyperlipidaemia under/untreated	19	8	6	21	28.6%
PPI high dose	16	5	1	20	5.0%
Renal impairment and using or check for renally excreted drugs	18	9	7	20	35.0%
Antigout medication (might) not indicated	16	5	4	17	23.5%
Digoxin dose over 125mcg or considered too high	9	7	4	12	33.3%
Opioid constipation may require laxative or increased lax therapy	10	2	1	11	9.1%
Antiplatelet not indicated	10	1	1	10	10.0%
NSAID not recommended (CV/HF/bleed/other)	6	6	2	10	20.0%
Sedatives long-acting or sedative long term	9	2	2	9	22.2%
Hyperkalaemia (or risk of) and medication	7	4	2	9	22.2%
Short acting nitrate required	8	2	1	9	11.1%
Heart disease un(der)treated	7	3	1	9	11.1%
Diabetes monitoring required	6	4	1	9	11.1%
Statin myopathy risk	2	6	1	7	14.3%
Digoxin monitoring required	6	2	1	7	14.3%
Quinine prescribed	5	5	4	6	66.7%
Haematology monitoring required	2	5	1	6	16.7%
Clopidogrel and aspirin interaction	4	3	1	6	16.7%
Allopurinol and reduced renal function	4	4	3	5	60.0%
Bleeding risk interacting drugs	3	2	1	4	25.0%
NSAID combined with ACEI or ARB, diuretic - triple whammy	2	3	1	4	25.0%

Descriptive classifications common to MRM and pharmacists in 100 test cases

Descriptive classification	Total cases MRM found	Total cases pharmacists found	Total cases found in common	Total Cases	Overlap percent of total cases
ACEI cough	3	2	1	4	25.0%
Glaucoma untreated	4	2	2	4	50.0%
Thyroid function monitoring required	2	4	2	4	50.0%
Anticoagulant toxicity	2	3	1	4	25.0%
Combine medications into combination product	2	2	1	3	33.3%
Nitrate free period required	1	3	1	3	33.3%
Calcium channel blocker and peripheral oedema	2	2	2	2	100.0%
Rosiglitazone prescribed and (risk of) HF	2	1	1	2	50.0%
Hyponatremia drug toxicity	2	1	1	2	50.0%
Osteoporosis (or risk) requires antiosteoporotic	2	1	1	2	50.0%

Appendix 17 Prescribing guidelines mapped to descriptive classifications

Table 66: Prescribing guidelines mapped to descriptive classifications

Classification	Prescribing Criteria	Rule	Criterion
AF requires aspirin or warfarin	START	A01	Warfarin in the presence of chronic atrial fibrillation
	START	A02	Aspirin in the presence of chronic atrial fibrillation where warfarin is contraindicated but not aspirin
	PIEA	9	Patient with AF is taking an oral anticoagulant
Airway disease un(der)treated	STOPP	D02	Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate to severe chronic obstructive pulmonary disease (unnecessary exposure to long-term side effects of systemic steroids)
Amiodarone or other antiarrythmic prescribed	Beers		Antiarrhythmic drugs: amiodarone, flecainide, procainamide, quinidine, sotalol
Anticholinergic use not elsewhere specified	STOPP	B02	Tricyclic antidepressant with glaucoma (likely to exacerbate glaucoma)
	STOPP	B03	Tricyclic antidepressant with cardiac conductive abnormalities (pro-arrhythmic effects)
	STOPP	B06	Tricyclic antidepressant with prostatism or history of urinary retention (risk of urinary retention)
	STOPP	D03	Nebulised ipratropium with glaucoma (may exacerbate glaucoma)
	STOPP	F02	Antimuscarinic drugs with chronic glaucoma (risk of acute exacerbation of glaucoma)
	STOPP	F04	Antimuscarinic drugs with chronic prostatism (risk of urinary retention)
	PIEA	32	Patient is not taking more than one medication with anticholinergic activity (q)
	Beers		Anticholinergics and first-generation antihistamines: diphenhydramine, cyproheptadine, promethazine, dexchlorpheniramine, doxylamine, triprolidine
	Beers		Antiparkinson agents: belladonna, trihexylphenidyl
	Beers		Belladonna alkaloids, dicyclomine, hyoscyamine, propantheline, hyoscine
	Beers		TCAs: amitriptyline, clomipramine, doxepine > 6mg/d, imipramine, trimipramine
Anticholinergics and cognitive impairment	STOPP	B01	Tricyclic antidepressant with dementia (risk of worsening cognitive impairment)
	STOPP	B13	Prolonged use, more than 1 week, of first-generation antihistamines (risk of sedation and anticholinergic effects)
	PIEA	31	Patient with dementia is not receiving anticholinergic medication (q)
	Beers		Dementia or cognitive impairment: anticholinergics, benzodiazepines, H2-receptor antagonists,
Anticholinergics and constipation	STOPP	B04	Tricyclic antidepressant with constipation (likely to worsen constipation)
	STOPP	B05	Tricyclic antidepressant with opiate or calcium channel blocker (risk of severe constipation)
	STOPP	C05	Anticholinergic antispasmodic drugs with chronic constipation (risk of exacerbation of constipation)
	STOPP	F03	Antimuscarinic drugs with chronic constipation (risk of exacerbation of constipation)
	Beers		Chronic constipation: *oxybutinin, solifenacin, tolterodine*, diltiazem, verapamil, *dexchlorpheniramine, clemastine, cyproheptadine, diphenhydramine, doxylamine, promethazine, triprolidine, antipsychotics, belladonna alkaloids, hyoscyamine, propantheline, hyoscine, TCAs, orphenadrine*

Classification	Prescribing Criteria	Rule	Criterion
Antiplatelet not indicated	STOPP	A13	Aspirin with no history of coronary, cerebral or peripheral vascular symptoms or occlusive event (not indicated)
Aspirin high dose not indicated	STOPP	A12	Aspirin at dose > 150mg/day (increased bleeding risk, no evidence for increased efficacy)
Aspirin or thiazide contraindicated in gout	STOPP	A04	Thiazide diuretic with a history of gout (may exacerbate gout)
Asthma moderate/severe requires inhaled corticosteroid	START	B01	Regular inhaled corticosteroid or anticholinergic agent for mild-to-moderate asthma or COPD
	PIEA	35	Patient with asthma using an inhaled LABA is also using an inhaled corticosteroid
Bleeding disorder and antiplatelet or anticoagulant	STOPP	A11	Aspirin with a past history of peptic ulcer disease without histamine H2-receptor antagonist or proton pump inhibitor (risk of bleeding)
	STOPP	A17	Aspirin, clopidogrel, dipyridamole or warfarin with concurrent bleeding disorder (high risk of bleeding)
Bleeding risk interacting drugs	STOPP	E05	Warfarin and NSAID together (risk of gastrointestinal bleeding)
	PIEA	29	Patient taking an SSRI is not concurrently taking medications known to increase the risk of gastrointestinal bleeding (o)
Calcium channel blocker and constipation	STOPP	A08	Calcium channel blockers with chronic constipation (may exacerbate constipation)
	Beers		Chronic constipation: oxybutinin, solifenacin, tolterodine, *diltiazem, verapamil*, dexchlorpheniramine, clemastine, cyproheptadine, diphenhydramine, doxylamine, promethazine, triprolidine, antipsychotics, belladonna alkaloids, hyoscyamine, propantheline, hyoscine, TCAs, orphenadrine
Cardiovascular disease (or risk) requires statin	START	A05	Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, where the patients functional status remains independent for activities of daily living and life expectancy is greater than 5 years
	START	F04	Statin therapy in diabetes mellitus if coexisting major cardiovascular risk factors present
	START	F03	Antiplatelet therapy in diabetes mellitus with coexisting major cardiovascular risk factors (hypertension, hypercholesterolaemia, smoking history)
	PIEA	2	Patient at high risk of a cardiovascular event (b) is taking an HMG-CoA reductase inhibitor (statin)
Cardiovascular disease(or risk) requires antiplatelet	START	A03	Aspirin or clopidogrel with a documented history of atherosclerotic coronary, cerebral or peripheral vascular disease in patients with sinus rhythm
	PIEA	4	Patient with IHD or a history of MI is taking an antiplatelet agent unless taking an oral anticoagulant (c)
	PIEA	11	Patient with a history of non-haemorrhagic stroke or TIA is taking an antiplatelet agent unless taking an anticoagulant (c)
	PIEA	16	Patient with diabetes at high risk of a cardiovascular event (b) is taking an antiplatelet agent unless taking an anticoagulant (c)
COPD and using benzodiazepines	PIEA	34	Patient with COPD is not taking benzodiazepines
COPD/Asthma and using a beta blocker	STOPP	A05	Non-cardioselective beta-blocker with chronic obstructive pulmonary disease (risk of increased bronchospasm)
	PIEA	37	Patient with asthma is not taking a medication that may worsen asthma (s)
Current therapy insufficient	STOPP	A03	Loop diuretic as first-line monotherapy for hypertension (safer, more effective alternatives available)
	STOPP	F05	Alpha-blockers in males with frequent incontinence (one or more incontinence episodes daily) (risk of urinary frequency and worsening of incontinence)
	PIEA	38	Female patient with recurrent UTIs has been prescribed intravaginal estrogen
Depression un(der)treated	START	C02	Antidepressant drug in the presence of moderate/severe depressive symptoms lasting at least three months

Classification	Prescribing Criteria	Rule	Criterion
Diabetes and CV risks or renal disease requires ACEI or ARB or CCB	START	F02	ACE inhibitor or angiotensin receptor blocker in diabetes with nephropathy (overt urinalysis proteinuria or microalbuminuria more than 30mg/24 hours)
	PIEA	15	Patient with type 2 diabetes and hypertension and albuminuria is taking an ACE inhibitor or ARB
Diabetes and taking medication that affects glucose levels	PIEA	17	Patient with diabetes is not taking a medication that may increase or decrease blood glucose concentrations (h)
Diabetes monitoring required	PIEA	18	Patient with diabetes has had an HbA1c measurement within the previous 6 months
Digoxin dose over 125mcg or considered too high	STOPP	A01	Digoxin at long term dose >125ug/day with impaired renal function. Serum creatinine > 150umol/L (increased risk of toxicity)
	Beers		Digoxin > 125mcg/day
Drug causing dyspepsia with PPI	PIEA	33	Patient taking a PPI is not taking a medication that may cause dyspepsia
Epilepsy and medication affecting seizure threshold	Beers		Seizures or epilepsy: bupropion, chlorpromazine, clozapine, olanzapine, thioridazine, thiothixene, tramadol
Falls risk/history and sedatives/antihypertensives/other	STOPP	H01	In this patient with a history of falls, benzodiazepines (sedative, may cause reduced sensorium, impair balance)
	STOPP	H02	In this patient with a history of falls, neuroleptic drugs (may cause gait dyspraxia, parkinsonism)
	STOPP	H03	In this patient with a history of falls, first-generation antihistamines (sedative, may impair sensorium)
	STOPP	H04	In this patient with a history of falls, vasodilator drugs with persistent postural hypotension (> 20mmHg drop in systolic blood pressure) (risk of syncope, falls)
	STOPP	H05	Long term opiates in those with recurrent falls (risk of drowsiness, postural hypotension, vertigo)
	PIEA	28	Patient with a history of falls is not taking psychotropic medications (n)
	Beers		Falls history or fractures: Anticonvulsants, antipsychotics, benzodiazepines, zalepion, zolpidem, TCAs, SSRIs
Glibenclamide prescribed	STOPP	G01	Glibenclamide or chlorpropamide with type 2 diabetes mellitus (risk of prolonged hypoglycaemia)
	PIEA	20	Patient taking metformin for diabetes is not concurrently taking glibenclamide
	Beers		Sulphonylureas long acting: glibenclamide, chlorpropamide
Heart disease un(der)treated	START	A07	Angiotensin converting enzyme inhibitor following acute myocardial infarction
Heart failure and concurrent verapamil or diltiazem	STOPP	A07	Use of diltiazem or verapamil with NYHA class III or IV heart failure (may worsen heart failure)
	Beers		Heart failure: NSAIDS, COX2, diltiazem, verapamil, pioglitazone, rosiglitazone
Heart failure or hypertension and using high sodium or salt retaining drugs	PIEA	7	Patient with heart failure is not taking medications that may exacerbate heart failure (d)
	PIEA	8	Patient with heart failure or hypertension is not taking high sodium-containing medications (e)
Heart failure or IHD requires beta-blocker	START	A08	Beta-blocker with chronic stable angina
	PIEA	3	Patient with IHD or a history of MI is taking a beta-blocker
	PIEA	5	Patient with heart failure is taking a beta-blocker
Heart failure requires ACEI or ARB	START	A06	Angiotensin converting enzyme inhibitor with chronic heart failure
	PIEA	6	Patient with heart failure is taking an ACE inhibitor or ARB
Hexamine prescribed (poor renal clearance)	PIEA	40	Patient with a creatinine clearance <50ml/min is not receiving methenamine (hexamine) for UTI prophylaxis
Hypertension un(der)treated	START	A04	Antihypertensive therapy where systolic blood pressure consistently >160mmHg
	PIEA	1	Patient taking an antihypertensive is at their target blood pressure (a)
INR outside therapeutic range	PIEA	10	Patient with AF taking an anticoagulant has an INR between 2 and 3
Metformin dose high with renal impairment	PIEA	19	Patient taking metformin for diabetes has had the dose adjusted for creatinine clearance

Classification	Prescribing Criteria	Rule	Criterion
Methyldopa or clonidine prescribed	Beers		Alpha blockers central: clonidine, methyldopa
Mineral oil laxative prescribed	Beers		Mineral oil, oral
NSAID combined with ACEI or ARB, diuretic - triple whammy	PIEA	25	Patient is not concurrently taking an ACE inhibitor or ARB, diuretic and NSAID (excluding low-dose aspirin)
NSAID not recommended (CV/HF/bleed/other)	STOPP	E02	NSAID with moderate to severe hypertension (risk of exacerbation of hypertension)
	STOPP	E03	NSAID with heart failure (risk of exacerbation of heart failure)
	STOPP	E04	Long term use of NSAID (> 3 months) for symptom relief of mild osteoarthritis (simple analgesics preferable and usually as effective for pain relief)
	STOPP	E08	Long term NSAID or colchicine for chronic treatment of gout where there was no contraindication to allopurinol (allopurinol first-choice prophylactic drug in gout)
	PIEA	7	Patient with heart failure is not taking medications that may exacerbate heart failure (d)
	PIEA	13	Patient with cardiovascular disease is not taking and NSAID
	Beers		NSAIDs non-COX selective: Aspirin>325mg, diclofenac, diflunisal, ibuprofen, ketoprofen, mefenamic acid, meloxicam, naproxen, piroxicam, sulindac
	Beers		Indomethacin, ketorolac
	Beers		Heart failure: *NSAIDS, COX2*, diltiazem, verapamil, pioglitazone, rosiglitazone
NSAID used with renal failure (or risks of)	STOPP	E06	NSAID with chronic renal failure (risk of deterioration of renal function)
	PIEA	24	Patient with risk factors for impaired renal function (L) is not taking an NSAID
	Beers		Chronic kidney disease: NSAIDs, triamterene
Oestrogens and thromboembolism or cancer risk	STOPP	G03	Estrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence)
	STOPP	G04	Estrogens without progestogen in patients with intact uterus (risk of endometrial cancer)
	Beers		Estrogens with or without progestins, except topical
Opioid constipation may require laxative or increased lax therapy	STOPP	I02	Regular opiates for > 2 weeks in those with chronic constipation without concurrent laxative use (risk of severe constipation)
	PIEA	23	Patient taking an opioid (k) is taking prophylactic treatment for constipation
Osteoporosis (or risk) may require calcium and or vitamin D	START	E03	Calcium and vitamin D supplement in patients with known osteoporosis (previous fragility fracture, acquired dorsal kyphosis)
Osteoporosis (or risk) requires antiosteoporotic	START	E02	Biphosphonates in patients taking maintenance corticosteroid therapy
	PIEA	44	Patient with osteoporosis is receiving anti-osteoporotic medication (w)
Other disease/symptoms untreated	START	F01	Metformin with type 2 diabetes with or without metabolic syndrome (in absence of renal impairment)
	START	D02	Fiber supplement for chronic, symptomatic diverticular disease with constipation
Other drug disease contraindication	STOPP	I03	Long term opiates in those with dementia unless for palliative care or management of moderate/severe chronic pain syndrome (risk of exacerbation of cognitive impairment)
	PIEA	7	Patient with heart failure is not taking medications that may exacerbate heart failure (d)
	Beers		Antipsychotics first and second for behavioural dementia problems: chlorpromazine, fluphenazine, haloperidol, thioridazine, thiothixene, trifluoperazine, triflupromazine, aripiprazole, asenapine, clozapine, olanzapine, paliperidone, quetiapine, risperdone
	Beers		Dementia or cognitive impairment: anticholinergics, benzodiazepines, H2-receptor antagonists,
Other drug interaction	STOPP	A06	Beta-blocker in combination with verapamil (risk of symptomatic heart failure)

Prescribing guidelines mapped to descriptive classifications

Classification	Prescribing Criteria	Rule	Criterion
Other drug no indication	STOPP	A02	Loop diuretic for dependent ankle edema only i.e. no clinical signs of heart failure (no evidence of efficacy, compression hosiery usually more appropriate)
Other PIM	Beers		Alpha-blockers: doxazosin, prazosin, terazosin
	Beers		Nifedipine immediate release
Pain un(der)treated	STOPP	E07	Long term corticosteroids (> 3 months) as monotherapy for rheumatoid or osteoarthritis (risk of major systemic corticosteroid side-effects)
	STOPP	E08	Long term NSAID or colchicine for chronic treatment of gout where there was no contraindication to allopurinol (allopurinol first-choice prophylactic drug in gout)
Parkinsonism and antipsychotics or metoclopramide	STOPP	C03	Prochlorperazine (Stemetil) or metoclopramide with parkinsonism (risk of exacerbating parkinsonism)
	Beers		Metoclopramide avoid except for gastroparesis
	Beers		Parkinson's disease: *antipsychotics* except quetiapine and clozapine, *metoclopramide*, prochlorperazine, promethazine
Pioglitazone and HF	Beers		Heart failure: NSAIDS, COX2, diltiazem, verapamil, *pioglitazone*, rosiglitazone
PPI high dose	STOPP	C04	Proton pump inhibitor for peptic ulcer disease at full therapeutic dosage for more than 8 weeks (dose reduction or earlier discontinuation indicated)
Rosiglitazone and HF	Beers		Heart failure: NSAIDS, COX2, diltiazem, verapamil, pioglitazone, *rosiglitazone*
Sedatives long-acting or sedative long term	STOPP	B07	Long term, more than 1 month, long-acting benzodiazepines (risk of prolonged sedation, confusion, impaired balance, falls)
	PIEA	26	Patient with sleep disturbance or anxiety has not been taking benzodiazepines for >4 weeks
	Beers		Benzodiazepines: all. Avoid except for: seizures, generalized anxiety disorders
	Beers		Non-benzodiazepine hypnotics: eszopiclone, zolpidem, zalepion
Serotonergic drugs interaction	PIEA	30	Patient taking an SSRI is not concurrently taking other medications that may contribute to serotonin toxicity (p)
Statin myopathy risk	PIEA	12	Patient with risk factors for myopathy (f) is not taking >= 40mg/day of simvastatin or atorvastatin
Therapeutic dose too high	Beers		Spironolactone > 25mg/d
Therapy duplication	STOPP	J	Any duplicate drug classes (optimisation of monotherapy within a single drug class should be observed prior to considering a new class of drug)
Warfarin and aspirin interaction	STOPP	A09	Use of aspirin and warfarin in combination without histamine H2-receptor antagonist (except cimetidine because of interaction with warfarin) or proton pump inhibitor (high risk of gastrointestinal bleeding)

Appendix 18 Expert panel qualitative codes

Codes contain the following abbreviations: gen generic, mrm = MRM, mrx = MRX, ph = pharmacist, stopp = STOPP, drps = DRPs.

Table 67: Qualitative codes and frequency

Qualitative code	Code categories	Code frequency
gen_treatment_goal_symptomatic_only	Generic issues	4
gen_wrongly_assigned	Generic issues	1
mrm_good_recommendations	mrm_positive	3
mrm_good_review	mrm_positive	6
mrm_lose_impact	mrm_negative	1
mrm_need_to_collate_drps	mrm_negative	7
mrm_no_patient_context	mrm_negative, patient_context_no	4
mrm_no_recommendations_made	mrm_neutral	2
mrm_not_relevant	mrm_negative, patient_context_no	3
mrm_poor_recommendations	mrm_negative	1
mrm_relevant	mrm_positive, patient_context_yes	3
mrm_repetitive	mrm_negative, repetition	8
mrm_uncertain		1
mrx_alert_fatigue	mrx_negative	1
mrx_correct_but_unsatisfactory	mrx_negative	2
mrx_excessive_drps	mrx_negative	4
mrx_generic_advice_litle_use	mrx_negative	19
mrx_good_as_pre-screen	mrx_positive	2
mrx_hate_or_similar	mrx_negative, negative_emotion	14
mrx_just_a_list	mrx_negative	9
mrx_no_patient_context	mrx_negative, patient_context_no	31
mrx_not_relevant	mrx_negative, patient_context_no	25
mrx_relevant	mrx_positive, patient_context_yes	3
mrx_repetitive	mrx_negative, repetition	3
mrx_tedious	mrx_negative	1
mrx_time_cost	mrx_negative	1
mrx_unhelpful	mrx_negative	20
ph_benzod_weaning_not_suggested	pharm_negative	1
ph_dont_like_dogmatic_approach	pharm_negative	1
ph_not_all_good_drps	pharm_negative	4
ph_not_thorough	pharm_negative	7
ph_relevant	pharm_positive, patient_context_yes	2
ph_too_many_drps	pharm_negative	1
ph_uncertain		1
stopp_drps_too_generic	stopp_negative	1
stopp_identified_no_drps		14
stopp_no_patient_context	stopp_negative, patient_context_no	5
stopp_not_relevant	stopp_negative, patient_context_no	2
stopp_not_thorough	stopp_negative	6
stopp_relevant	stopp_positive, patient_context_yes	1
stopp_repetitive	stopp_negative, repetition	3
stopp_uncertain		5

Appendix 19 MRX care areas

Table 68: Details of DRPs identified by MRX

Problem	Problem description	Monitoring indicators
Activities	The use of psychoactive medications may result in reduced activity participation.	Of special interest are problematic changes that may be related to the use of psychoactive medications, such as a recent decline in: • Cognition • Communication • Function • Mood • Behavior
Activities of Daily Living – Functional Status	Adverse medication effects, such as confusion, muscle weakness (asthenia) and inability to coordinate voluntary muscle movements or unsteady gait (ataxia), may interfere with ADL performance and contribute to functional decline.	Medication effects that may affect function: • Asthenia (muscle weakness) • Ataxia • Unsteady gait • Confusion
Anticholinergic	The use of multiple medications with anticholinergic properties in older individuals may be particularly problematic because of the cumulative effects.	• Are any medications with anticholinergic effects potentially inappropriate medications? If so, are there safer alternatives? • Is the patient experiencing any of the following anticholinergic side effects: • Dry mouth, skin or eyes • Urinary retention or difficulty urinating (especially in men) • Constipation • Rapid heart beat • Blurred vision • Clumsiness, unsteadiness • Dizziness • Drowsiness during the day • Lethargy, fatigue • Distress, nervousness • Memory problems • Confusion/disorientation • Restlessness, irritability • Hallucinations
Behavioural Symptoms	Medication side effects may cause or contribute to behavioral symptoms.	Medication side effects that can cause or contribute to behavioural symptoms: • Delirium/delusions • Agitation, difficulty sleeping • Hypersexuality, socially inappropriate behavior • Impaired impulse control
Cognitive Loss/Dementia	Older adults are more likely than younger persons to develop cognitive impairment as a result of taking medications. Medications can impair cognitive function by interfering with learning, memory, and attention; wakefulness and alertness; and orientation and reality awareness. Drug-induced cognitive impairment	Indicators of cognitive impairment: • Short-term memory problem (C0700) • Long-term memory problem (C0800) • Memory/recall ability (C0900) • Difficulty in making decisions; exercising poor judgment in decision-making (C1000) • Difficulty making self understood (B0700)

Problem	Problem description	Monitoring indicators
	can manifest as delirium and dementia. Drugs with anticholinergic properties have a major impact on learning, memory, and attention. • CNS depressant drugs have a major impact on wakefulness and alertness. • Drugs with a high potential to cause confusion have a major impact on orientation and reality awareness.	• Difficulty understanding others (B0800) Neuro-cognitive effects of medications: • Memory loss/impairment • Forgetfulness • Sleep disruption • Impaired alertness • Disorientation • Inattentiveness, impaired concentration (C1300A) • Daytime drowsiness, sleepiness (C1300C) • Confusion • Hallucination (E0100A) • Behavioral disturbances (E0200)
Communication	Some medications may cause or contribute to communication deficits. Ototoxicity (ear damage) can occur during aminoglycoside antibiotic therapy, which can be manifest as high-frequency hearing loss, tinnitus (ringing in the ears), vertigo, dizziness, or nausea. Hearing loss may occur in patients receiving high-dose and/or long-term aspirin therapy; these effects are early manifestations of salicylate toxicity. Psychoactive medications and some Parkinson's medications may cause expressive communication problems, such as changes/difficulties in speech and voice production, finding appropriate words, transmitting coherent statements, describing objects and events.	Signs/symptoms of ototoxicity: • New onset hearing problem (B0200) • High-frequency hearing loss • Tinnitus (ringing in the ears) • Vertigo • Dizziness • Nausea Indicators of expressive communication problem: • Problem with voice production, low volume (B0600) • Unclear speech - slurred or mumbled words (B0600-1) • Impaired ability to make self understood (B0700) • Difficulty putting sentence together (C1300B)
Dehydration/Fluid Maintenance	Medications that increase urine output or cause fluid loss may contribute to dehydration.	Symptoms of dehydration: • Dizziness on sitting or standing • Confusion or change in mental status (delirium) (C1600) • Lethargy • Recent decrease in urine volume or more concentrated urine than usual • Decreased skin turgor • Dry mouth, dry mucous membranes • Constipation • Fever
Delirium	Delirium is a serious condition that can be caused by medical issues/conditions, such as adverse medication effects, infection or dehydration. Delirium typically develops rapidly, over a few days or even hours. Drugs are the most common reversible cause of delirium in older adults, particularly anticholinergic drugs. Recent studies suggest that the total burden of anticholinergic drugs may determine development of delirium rather than any single agen t.	Signs/symptoms of delirium include • Inattention (C1300A)-easily distracted, out of touch or difficulty following what was said. • Disorganized thinking (C1300B)-rambling or irrelevant conversation, unclear or illogical flow of ideas, unpredictable switching from subject to subject. • Altered level of consciousness (C1300C)-e.g., vigilant (startled easily to any sound or touch); lethargic (repeatedly dozed off when being asked questions but responded to voice or touch); stuporous (very difficult to arouse and keep aroused); comatose (could not be

Problem	Problem description	Monitoring indicators
		aroused). • Psychomotor retardation (C1300D)- Unusually decreased level of activity, such as sluggishness, staring into space, staying in one position, moving very slowly. • Acute change in mental status (C1600) • Mental function varies over the course of the day • Sleep disturbances (D0500C) - up and awake at night/asleep during day. • Agitation and inappropriate movements, e.g., unsafe climbing out of bed or chair, pulling out tubes (E0500). • Hypoactivity (C0500D) - e.g., low or lack of motor activity, lethargy or sluggish response. • Perceptual disturbances such as hallucinations (seeing or feeling things that are not there E0100A) and delusions (a fixed false belief E0100B).
Dental Care	Having teeth/dentures that function properly is an important requisite for nutritional adequacy. Some medications can cause dry mouth, inflamed gums, mouth pain, or chewing problems, which may interfere with dental hygiene.	Has the patient experienced any of the following symptoms? • Dry mouth • Inflamed gums • Mouth pain • Chewing problems If so, are the symptoms interfering with nutritional intake?
Falls	Certain medications can contribute to the risk for falls by causing problems such as dizziness, drowsiness, low blood pressure, muscle rigidity, impaired balance, tremors, and decreased alertness.	Medication effects that may contribute to the risk for falls: • Decreased alertness • Dizziness (especially when standing or sitting up) • Drowsiness/lethargy • Confusion • Impaired balance • Muscle rigidity • Unsteady gait • Tremors
Mood State	Certain medications may cause depression or contribute to a mood problem.	Indicators of mood problem: • Little interest or pleasure in doing things (D0200A, D0500A) • Feeling or appearing down, depressed or hopeless (D0200B, D0500B) Trouble falling or staying asleep, or sleeping too much (D0200C, D0500C) • Feeling tired or having little energy (D0200D, D0500D) • Poor appetite or overeating (D0200E, D0500E) • Feeling bad about oneself (D0200F, D0500F) • Trouble concentrating on things (D0200G,

Problem	Problem description	Monitoring indicators
		D0500G) • Moving or speaking so slowly that other people have noticed, or the opposite, being more fidgety or restless than usual (D0200H, D0500H) • States that life isn't worth living, wishes for death, or attempts to harm self (D0200I, D0500I) • Being short-tempered, easily annoyed (D0500J
Nutritional Status	Adverse medication effects may affect appetite or the ability to eat.	Medication effects that may affect nutritional status: • Anorexia (loss of appetite) • Swallowing problem (K0100) • Decreased ability to smell or taste food • Abnormal or distortion of sense of taste (dysgeusia) • Mouth pain (odynophagia), stomatitis, oral ulcers, chewing problems • Dry mouth • Gingival hyperplasia (overgrowth of gum tissue) • Weight loss
Potentially Inappropriate Medications (PIMs)	Certain medications or medication classes should generally be avoided in older persons because they are either ineffective or they pose unnecessarily high risk for older persons and a safer alternative is available.	• Is there an indication for the medication? • Is the medication being used to treat an avoidable adverse medication effect? • Is the patient having any side effects from the medication? • Does the medication cause, aggravate or contribute to any geriatric problem? • Is non-drug therapy indicated? • Is there a safer alternative?
Pressure Ulcers	Pressure ulcers have serious consequences for the older person; however, they are one of the most common preventable and treatable conditions among the elderly who have restricted mobility. Some medications can produce or contribute to lessened mobility, worsen incontinence, and lead to or increase confusion, which may increase the risk for pressure ulcers.	Assess for medication effects that can produce or contribute to lessened mobility, worsen incontinence, and lead to or increase confusion.
Psychosocial Well-Being	Medications with side effects, such as incontinence, diarrhea, delirium, sleepiness, etc., may interfere with or inhibit social interactions.	Assess for medication effects that interfere with social interactions.
Psychotropic Medication Use – Antidepressants	Psychotropic medications (prescribed primarily to affect cognition, mood or behavior) are among the most frequently prescribed agents for elderly nursing facility residents. All psychotropic medications have the potential for producing undesirable and potentially serious side effects, including reduced mental functioning, sleep disturbances, and falls; or aggravating problematic signs and symptoms of existing conditions.	Adverse consequences of antidepressants: • Worsening of depression and/or suicidal behavior or thinking (D0350) • Delirium unrelated to medical illness or severe depression (C1600) • Hallucinations (E0100A) • Dizziness • Nausea • Diarrhea • Anxiety (I5700)

Problem	Problem description	Monitoring indicators
		• Nervousness, fidgety or restless • Insomnia • Somnolence • Weight gain • Anorexia or increased appetite • Seizures (I5400) • MAO inhibitors: hypertensive crisis if combined with certain foods, cheese, wine • Tricyclics: Postural hypotension; anticholinergic effects (constipation, dry mouth, blurred vision, urinary retention, etc)
Psychotropic Medication Use – Antipsychotics	Psychotropic medications (prescribed primarily to affect cognition, mood or behavior) are among the most frequently prescribed agents for elderly nursing facility residents. All psychotropic medications have the potential for producing undesirable and potentially serious side effects, including reduced mental functioning, sleep disturbances, and falls; or aggravating problematic signs and symptoms of existing conditions.	Adverse consequences of antipsychotics: • Anticholinergic effects, such as constipation, dry mouth, blurred vision, urinary retention, etc. • Increase in total cholesterol and triglycerides • Akathesia (inability to sit still) • Parkinsonism: any combination of tremors, postural unsteadiness, muscle rigidity, pill-rolling of hands, shuffling gait, etc. • Neuroleptic malignant syndrome: high fever with severe muscular rigidity • Blood sugar elevation • Cardiac arrhythmias (I0300) • Orthostatic hypotension • Cerbrovascular accident or transient ischemic attach (I4500) • Falls (J1700-J1900) • Tardive dyskinesia: persistent involuntary movements such as tongue thrusting, lip movements, chewing or puckering movements, abnormal limb movements, rocking or writhing trunk movements, etc • Lethargy (D0200D) • Excessive sedation • Depression (D0300, D0600, I5800) • Hallucinations (E01
Psychotropic Medication Use – Anxiolytics	Psychotropic medications (prescribed primarily to affect cognition, mood or behavior) are among the most frequently prescribed agents for elderly nursing facility residents. All psychotropic medications have the potential for producing undesirable and potentially serious side effects, including reduced mental functioning, sleep disturbances, and falls; or aggravating problematic signs and symptoms of existing conditions.	Adverse consequences of anxiolytics Sedation manifested by short-term memory loss (C0500, C0700), decline in cognitive abilities, slurred speech (B0600), drowsiness, little/no activity involvement Delirium unrelated to medical illness or severe depression (C1600) Hallucinations (E0100A) Depression (D0300, D0600, I5800) Disturbances of balance, gait, positioning ability (G0100A, G0100C, G0100D, G0300).
Urinary Incontinence	Many medications can affect the bladder and urethra and result in urinary incontinence (UI). For example, diuretics (N0400G) can cause urge incontinence, anticholinergics can lead to overflow incontinence, sedative/hypnotics (N0400B, N0400D) may cause confusion and	Symptoms of urinary incontinence: • Loss of urine when coughing, sneezing, laughing, exercising or lifting something heavy (stress incontinence). • Sudden, intense urge to urinate, followed by an involuntary loss of urine (urge incontinence).

Problem	Problem description	Monitoring indicators
	alter the ability to recognize the urge to void and lead to UI.	• Frequently or constantly dribble urine, feeling that bladder never completely empty, weak stream of urine (overflow incontinence).
Visual Function	Vision problems can be an unwanted side effect of many different medications. Most of these drugs will cause only temporary visual disturbances that disappear with time or once the medication is discontinued.	Vision side effects of medications: • Blurred or double vision • Excessive tearing • Puffy eyelids • Sensitivity to light • Changes in color vision or seeing a yellow or blue tinge • Abnormal eye movements

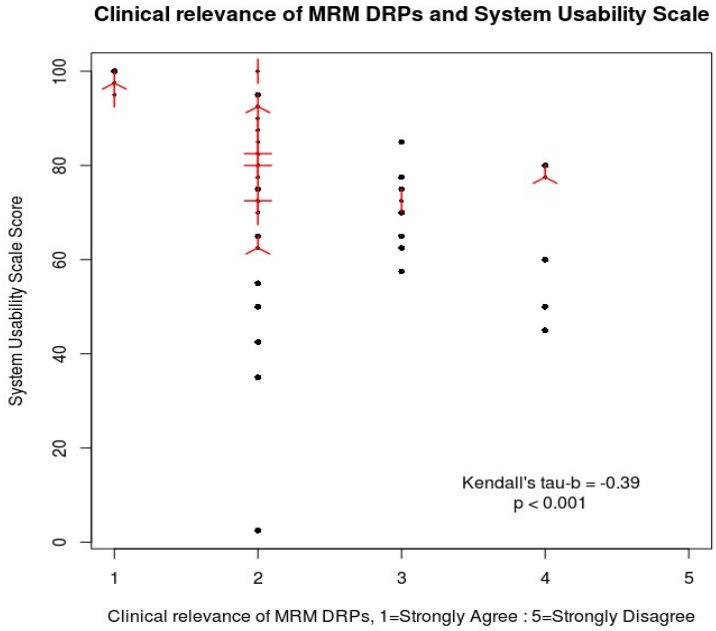
This table show the elderly care areas, descriptions of the problems associated with each care area and monitoring indicators for healthcare professional awareness as displayed in MRX. The alphanumeric codes in brackets are assessment items from the MDS 3.0.[261]

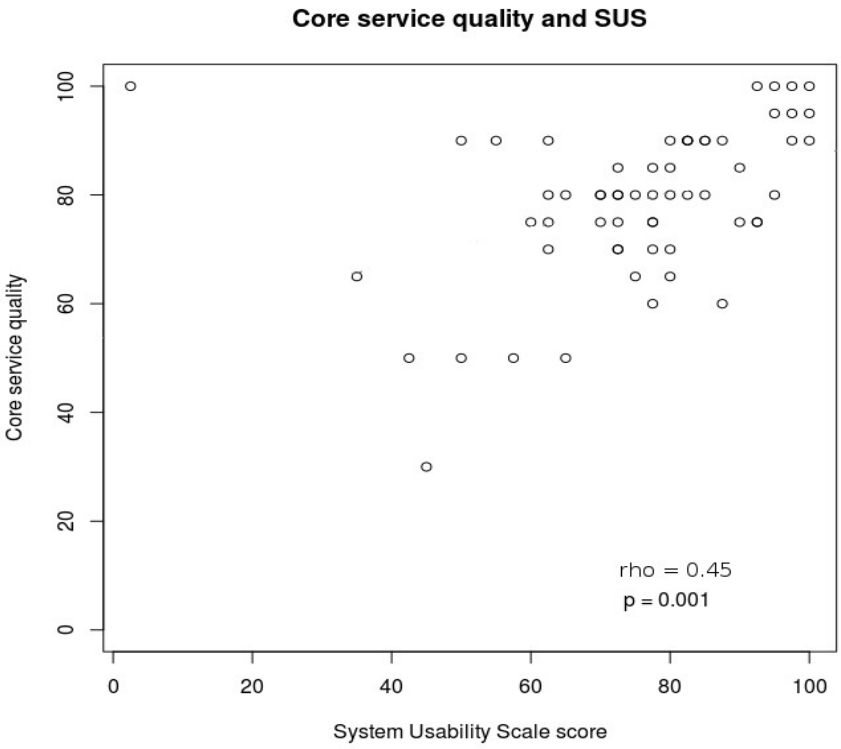
Appendix 20 Correlation plots

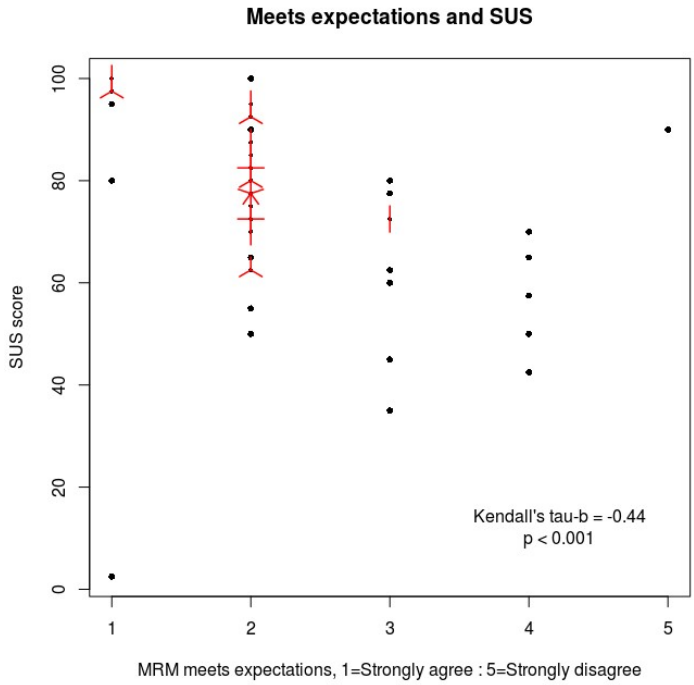
Correlation plots from the pharmacist MRM user survey are shown. Most correlations were performed using Kendall's tau-b. Several correlations were performed using Spearmans's rho correlations. These correlation methods are based on rankings so regression lines are not relevant and not displayed.

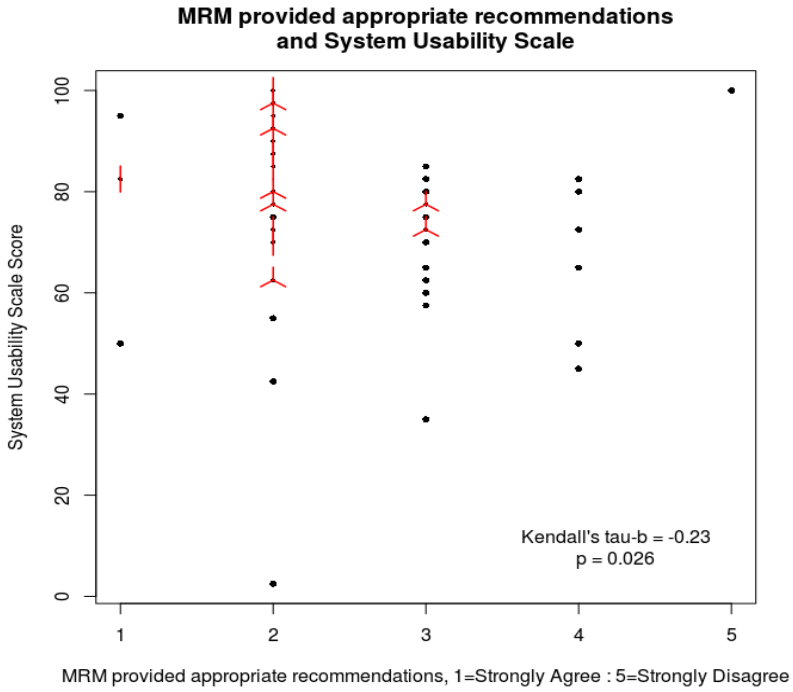
Plots are displayed as sunflower plots, where increased density of values at a single point are represented by additional bars at each point.[324]

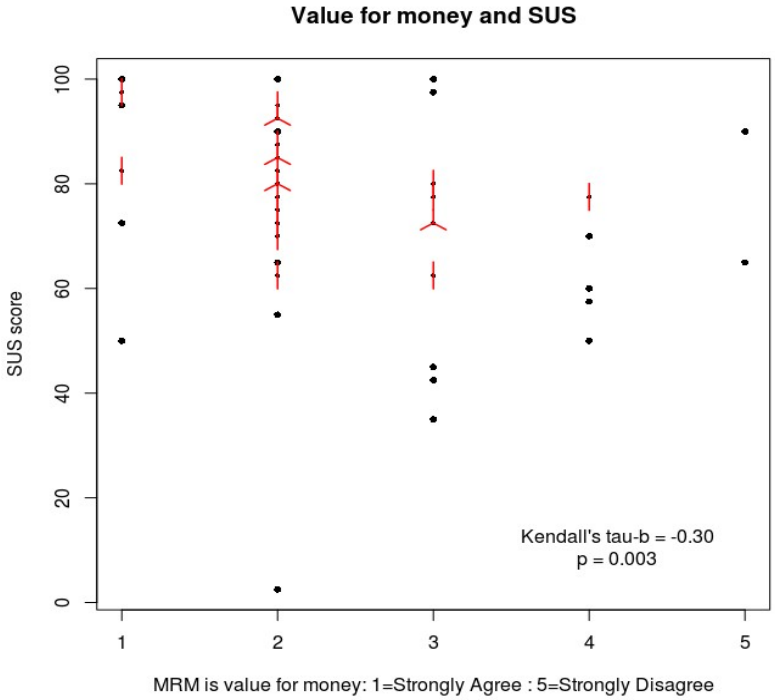
System Usability Scale



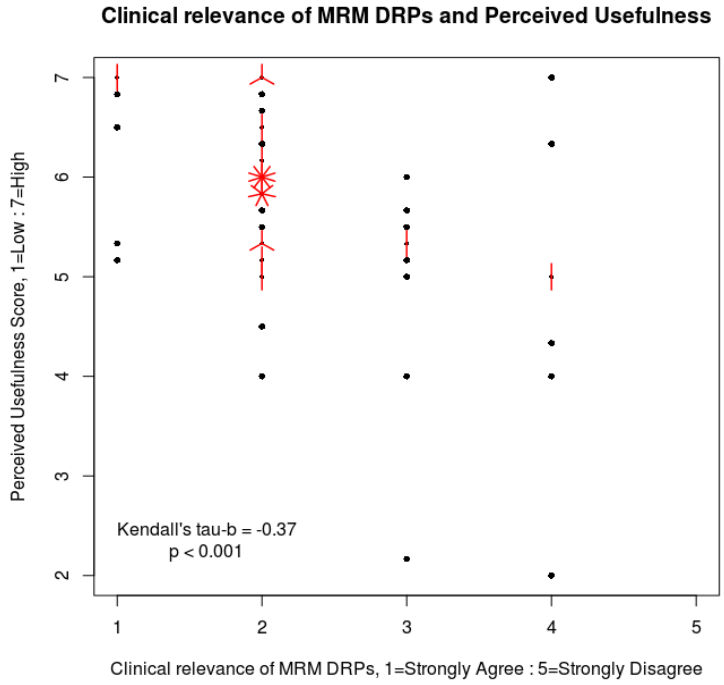

Core service quality and SUS
Core service quality
System Usability Scale score
rho = 0.45
p = 0.001
0
20
40
60
80
100

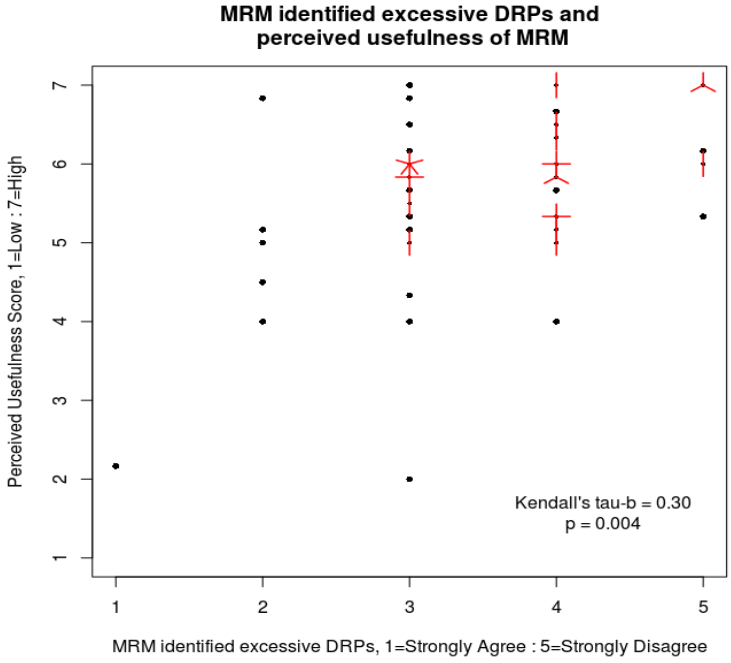

Meets expectations and SUS
SUS score
MRM meets expectations, 1=Strongly agree : 5=Strongly disagree
Kendall's tau-b = -0.44
p < 0.001
0
20
40
60
80
100
1
2
3
4
5

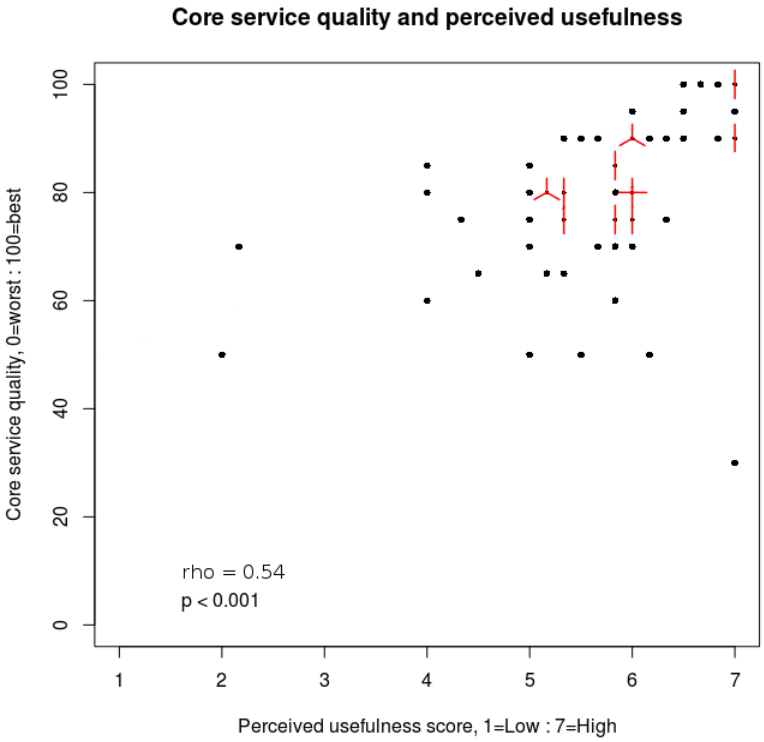

MRM provided appropriate recommendations
and System Usability Scale
System Usability Scale Score
0
20
40
60
80
100
1
2
3
4
5
Kendall's tau-b = -0.23
p = 0.026
MRM provided appropriate recommendations, 1=Strongly Agree : 5=Strongly Disagree

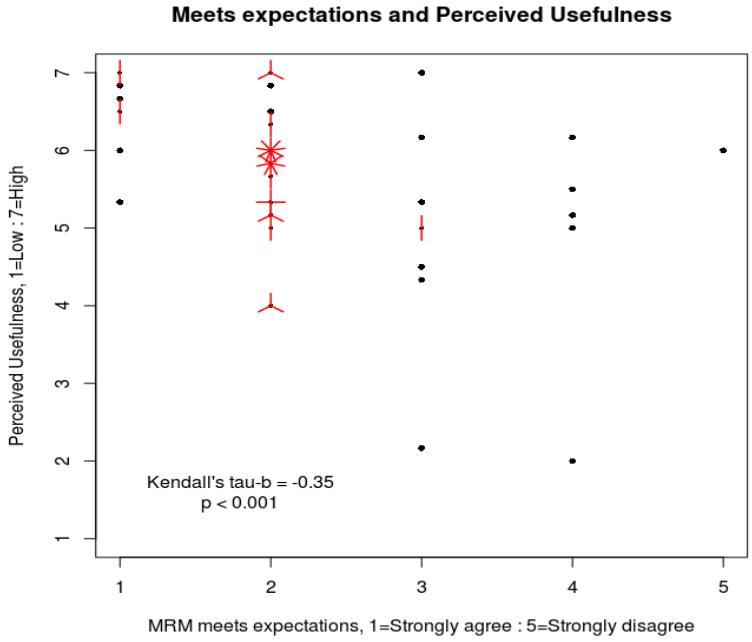

Value for money and SUS
SUS score
0
20
40
60
80
100
1
2
3
4
5
Kendall's tau-b = -0.30
p = 0.003
MRM is value for money: 1=Strongly Agree : 5=Strongly Disagree

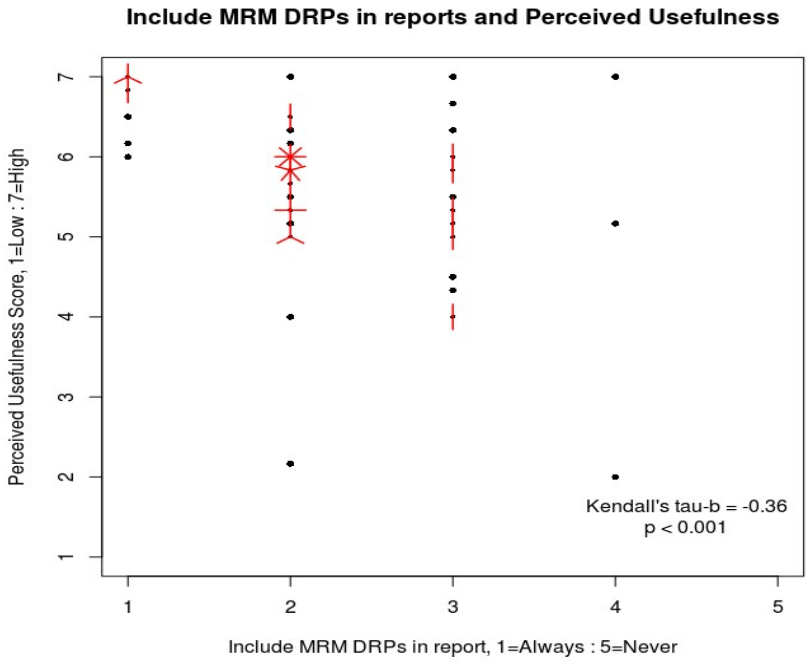
Perceived Usefulness

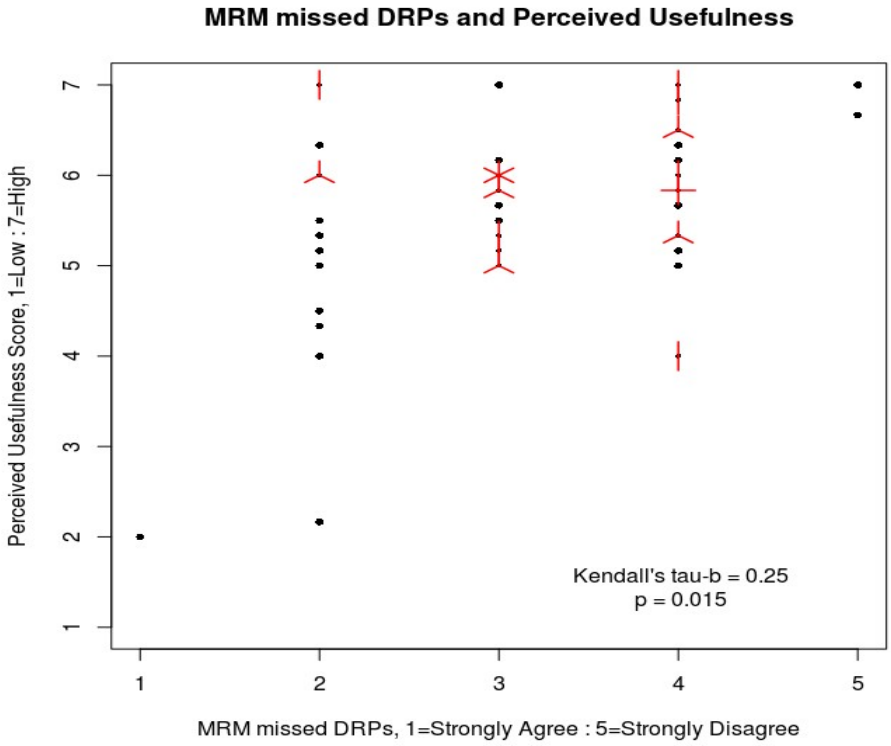


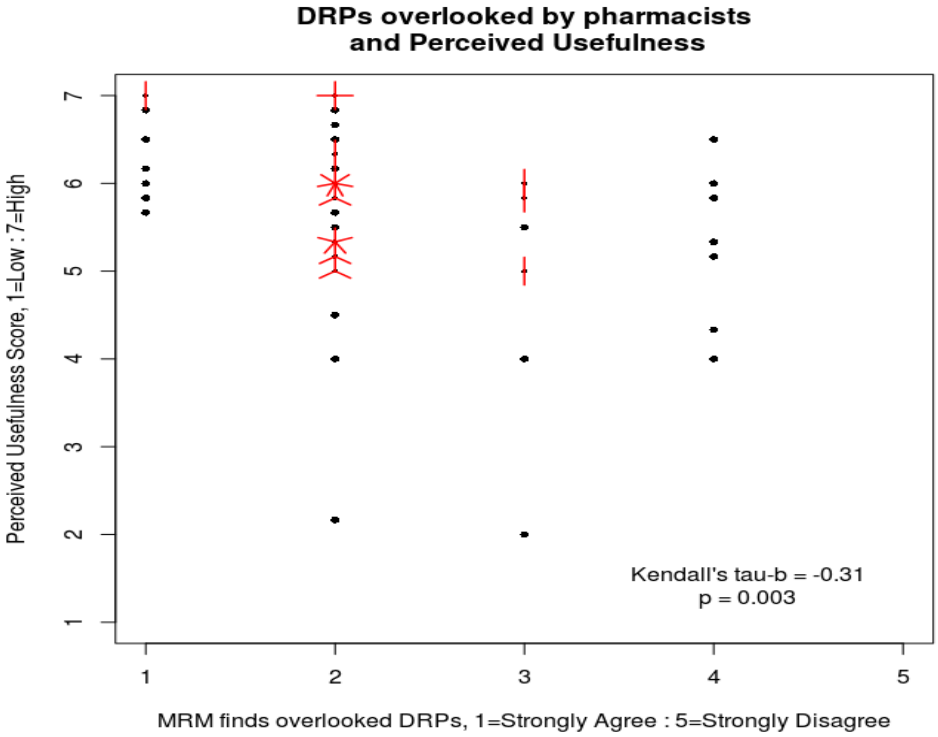


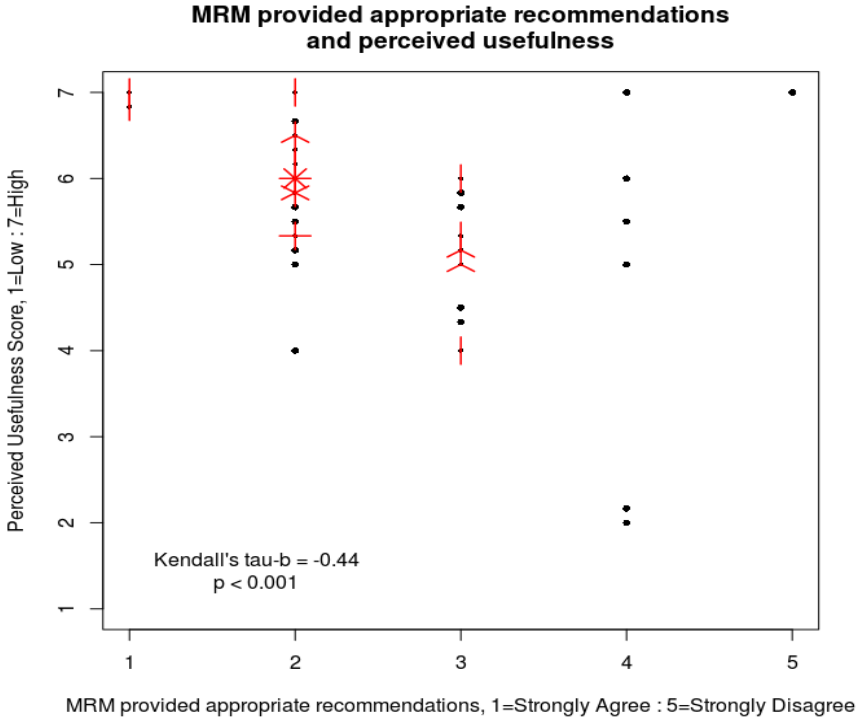

Core service quality and perceived usefulness
Core service quality, 0=worst : 100=best
0
20
40
60
80
100
rho = 0.54
p < 0.001
1
2
3
4
5
6
7
Perceived usefulness score, 1=Low : 7=High

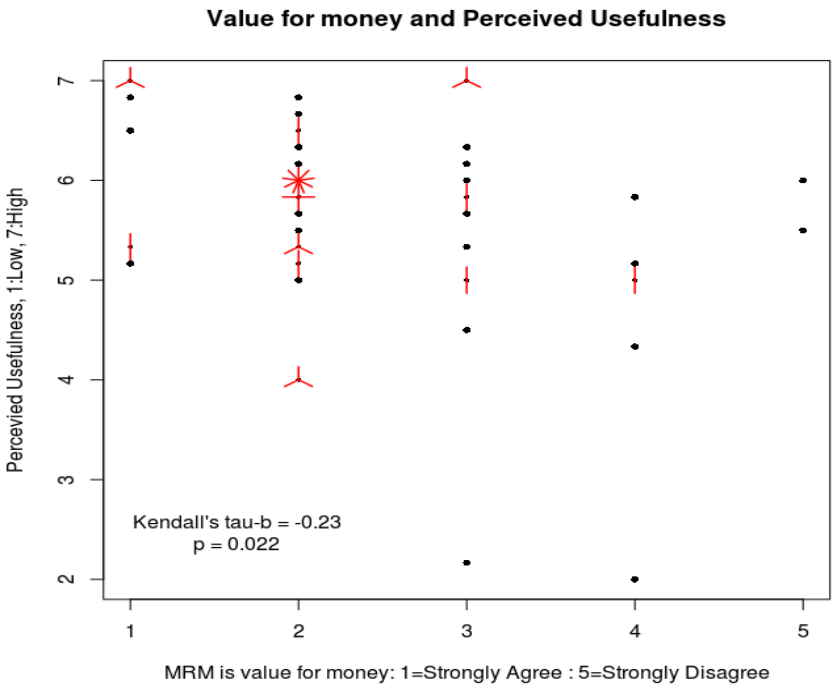

Meets expectations and Perceived Usefulness
Perceived Usefulness, 1=Low : 7=High
1
2
3
4
5
6
7
Kendall's tau-b = -0.35
p < 0.001
1
2
3
4
5
MRM meets expectations, 1=Strongly agree : 5=Strongly disagree


Include MRM DRPs in reports and Perceived Usefulness
Perceived Usefulness Score, 1=Low : 7=High
Include MRM DRPs in report, 1=Always : 5=Never
Kendall's tau-b = -0.36
p < 0.001

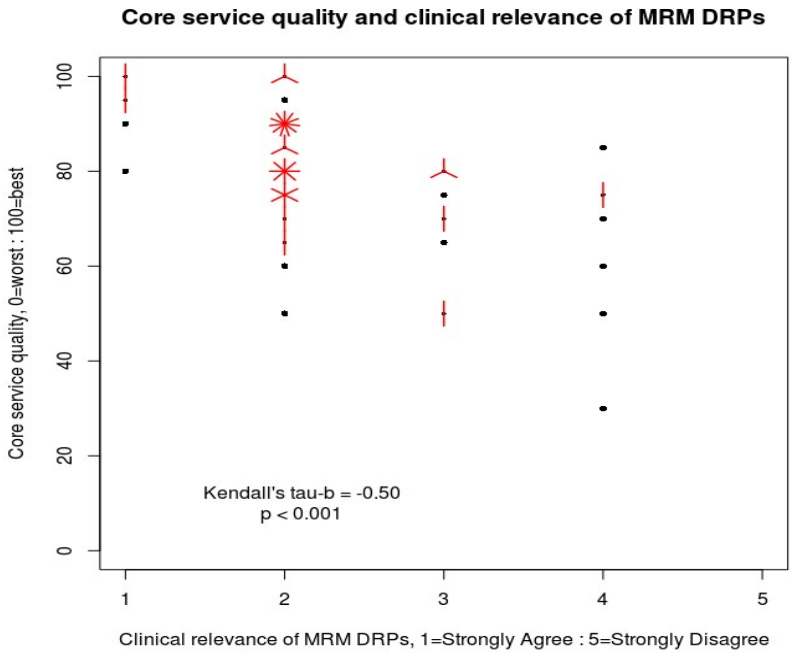

MRM missed DRPs and Perceived Usefulness
Perceived Usefulness Score, 1=Low : 7=High
MRM missed DRPs, 1=Strongly Agree : 5=Strongly Disagree
Kendall's tau-b = 0.25
p = 0.015

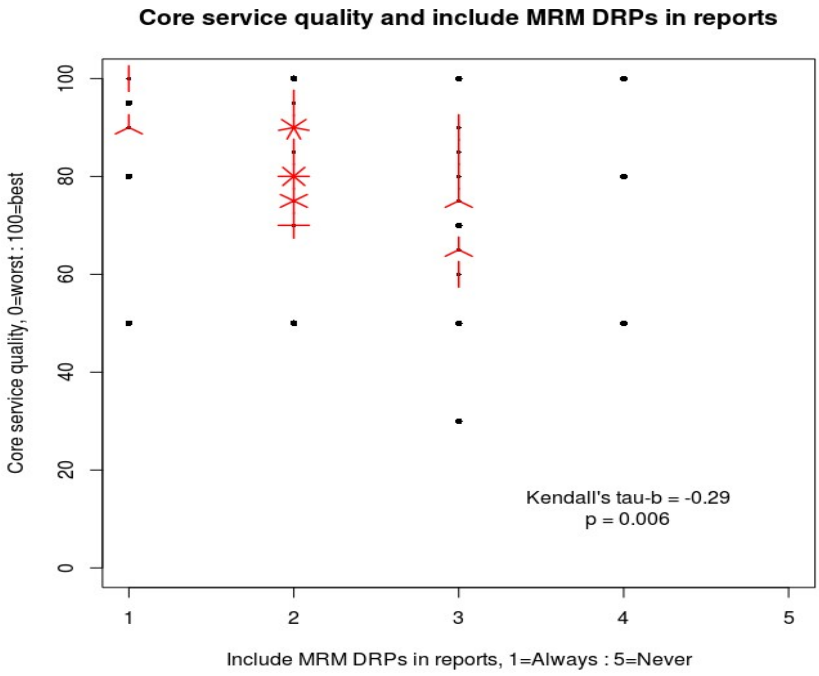

DRPs overlooked by pharmacists
and Perceived Usefulness
Perceived Usefulness Score, 1=Low : 7=High
1
2
3
4
5
6
7
Kendall's tau-b = -0.31
p = 0.003
1
2
3
4
5
MRM finds overlooked DRPs, 1=Strongly Agree : 5=Strongly Disagree

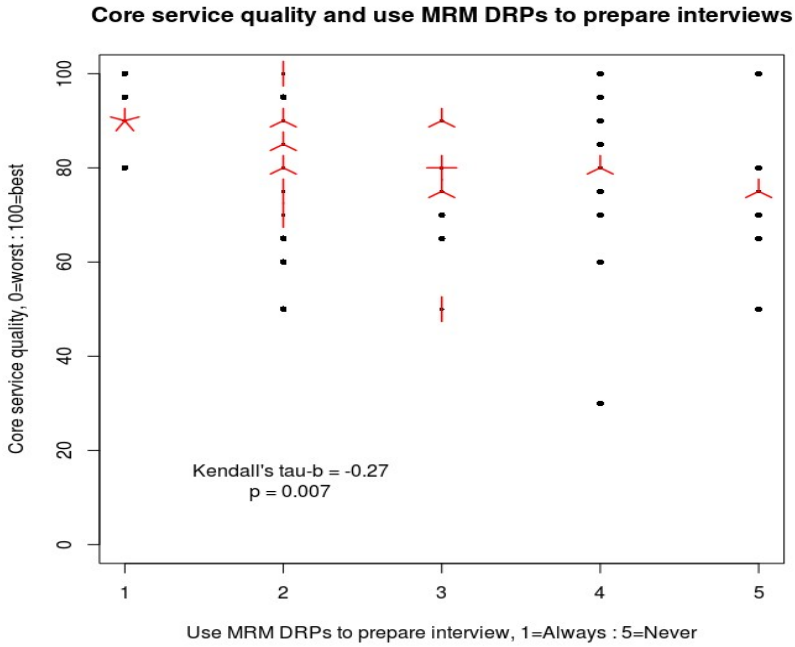

MRM provided appropriate recommendations
and perceived usefulness
Perceived Usefulness Score, 1=Low : 7=High
1
2
3
4
5
6
7
Kendall's tau-b = -0.44
p < 0.001
1
2
3
4
5
MRM provided appropriate recommendations, 1=Strongly Agree : 5=Strongly Disagree

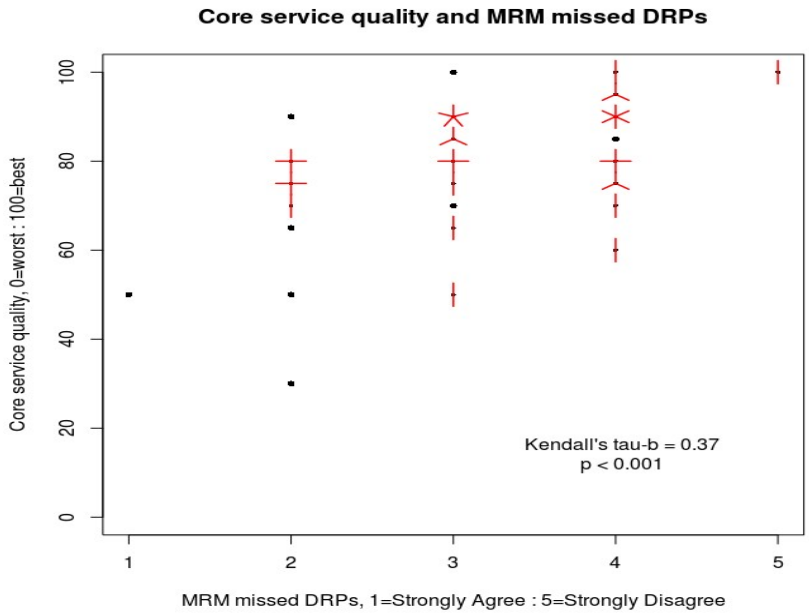


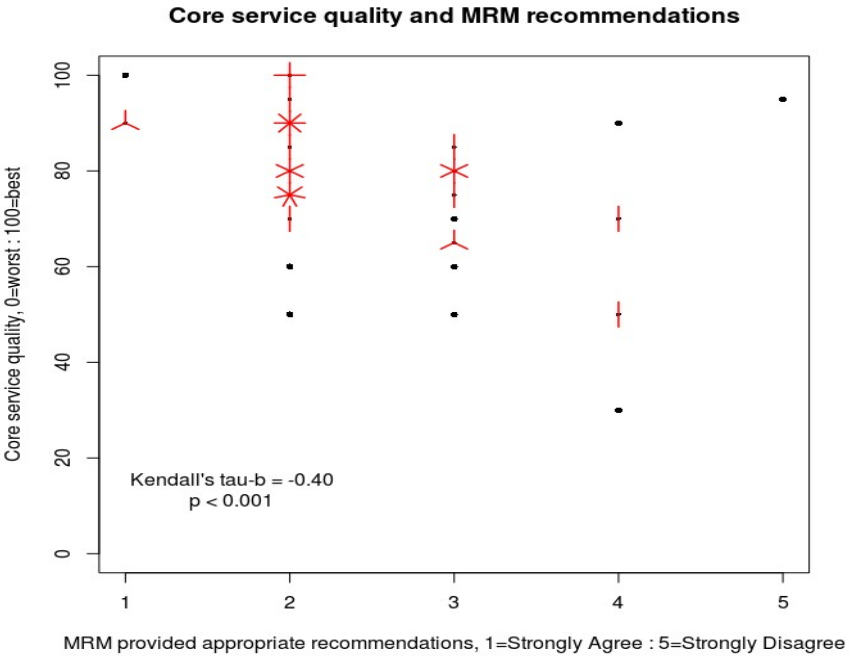
Core service quality (meets expectations)

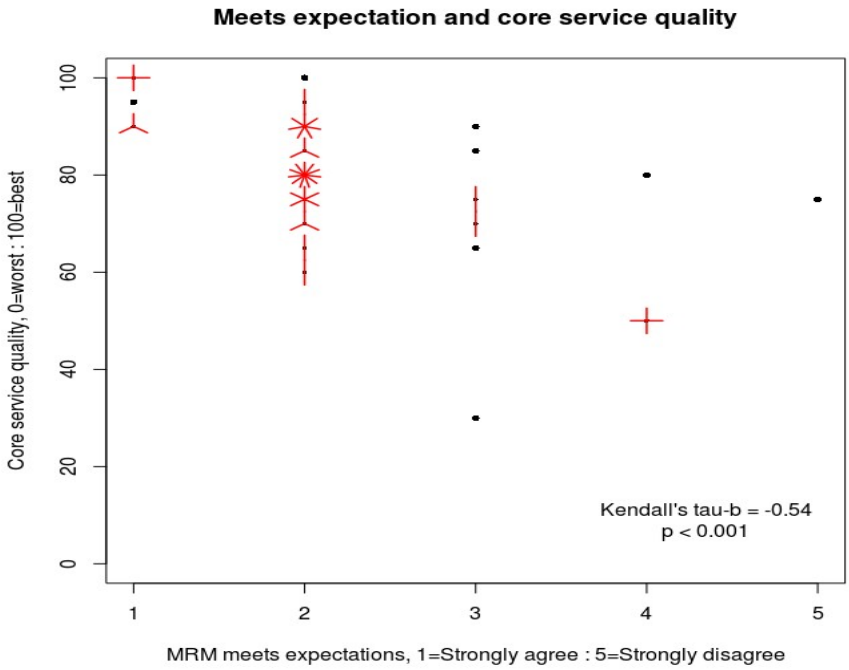


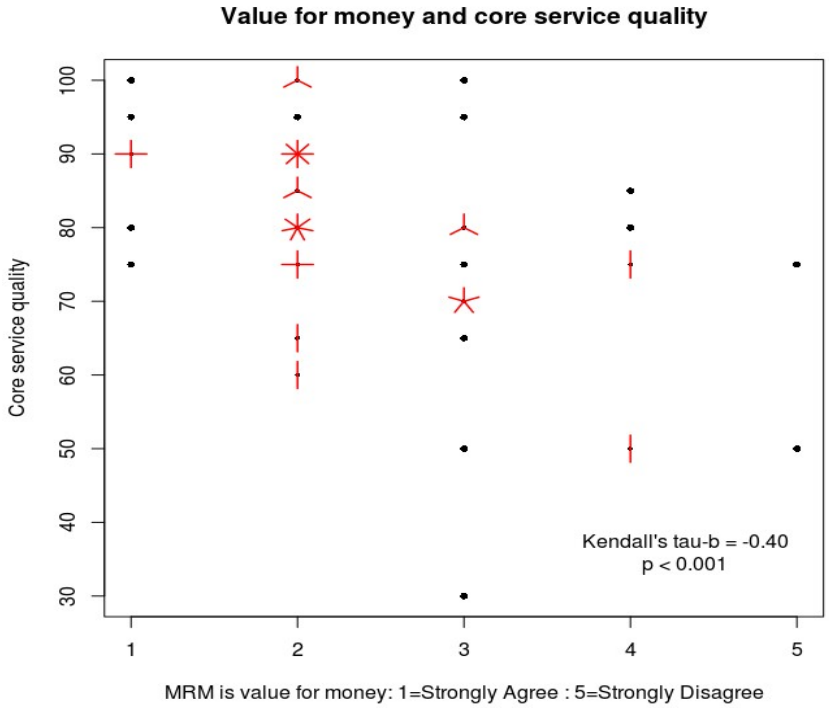

Core service and include MRM DRPs in reports
Core service quality, 0=worst : 100=best
0
20
40
60
80
100
1
2
3
4
5
Kendall's tau-b = -0.29
p = 0.006
Include MRM DRPs in reports, 1=Always : 5=Never


Core service quality and use MRM DRPs to prepare interviews
Core service quality, 0=worst : 100=best
0
20
40
60
80
100
1
2
3
4
5
Kendall's tau-b = -0.27
p = 0.007
Use MRM DRPs to prepare interview, 1=Always : 5=Never


Core service quality and MRM missed DRPs
Core service quality, 0=worst : 100=best
0
20
40
60
80
100
1
2
3
4
5
Kendall's tau-b = 0.37
p < 0.001
MRM missed DRPs, 1=Strongly Agree : 5=Strongly Disagree

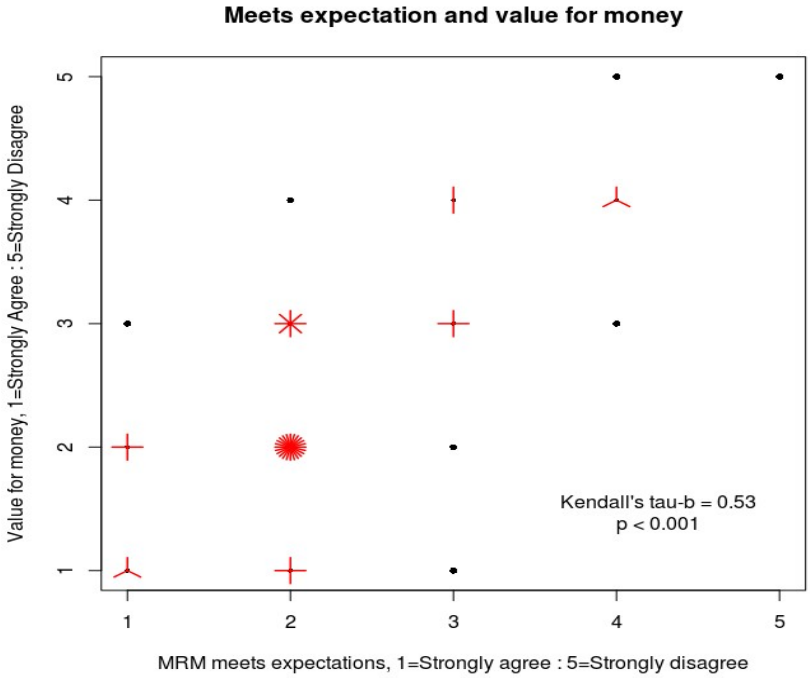

Core service quality and MRM recommendations
Core service quality, 0=worst : 100=best
0
20
40
60
80
100
1
2
3
4
5
Kendall's tau-b = -0.40
p < 0.001
MRM provided appropriate recommendations, 1=Strongly Agree : 5=Strongly Disagree

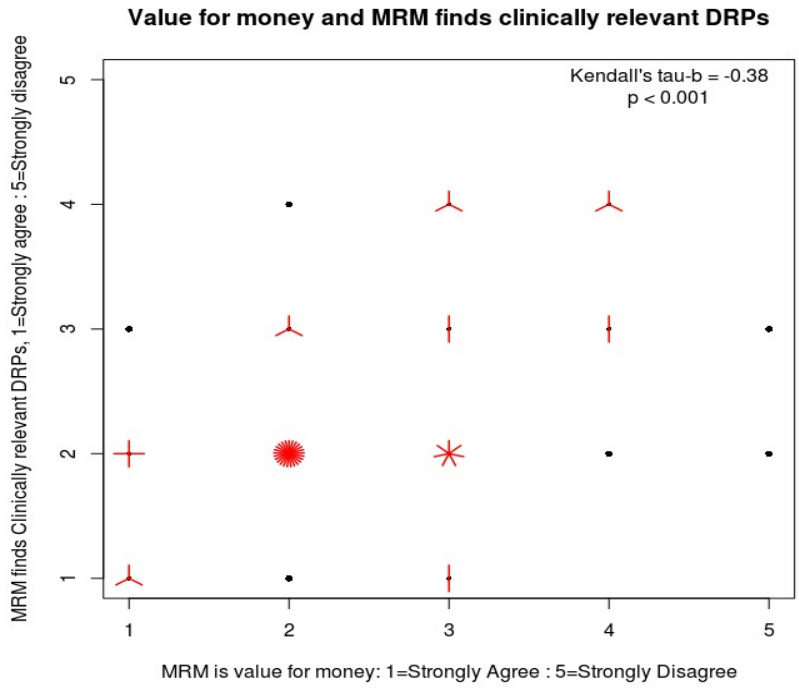


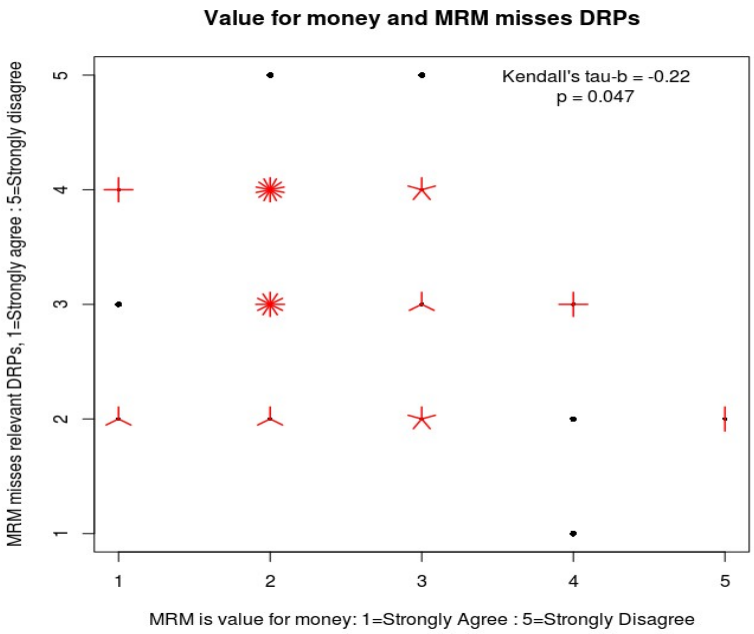


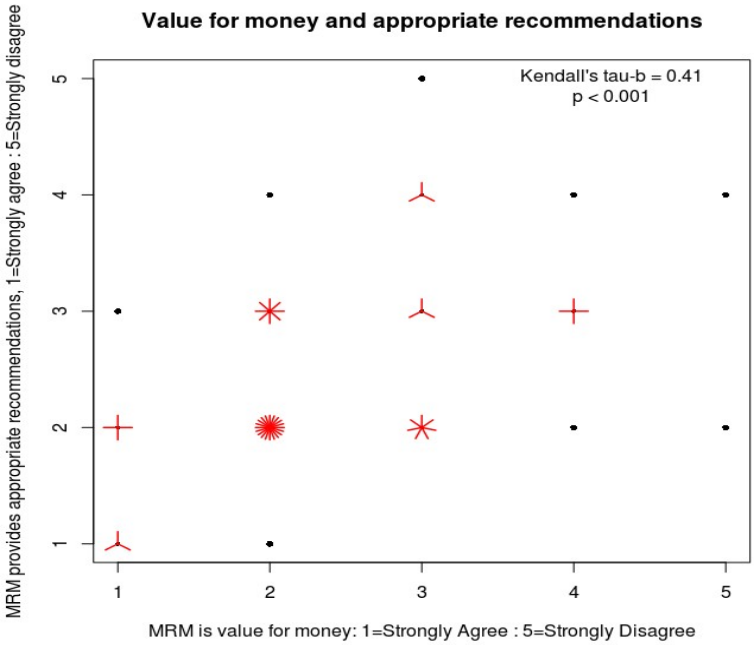
Value for money

Plots included previously.

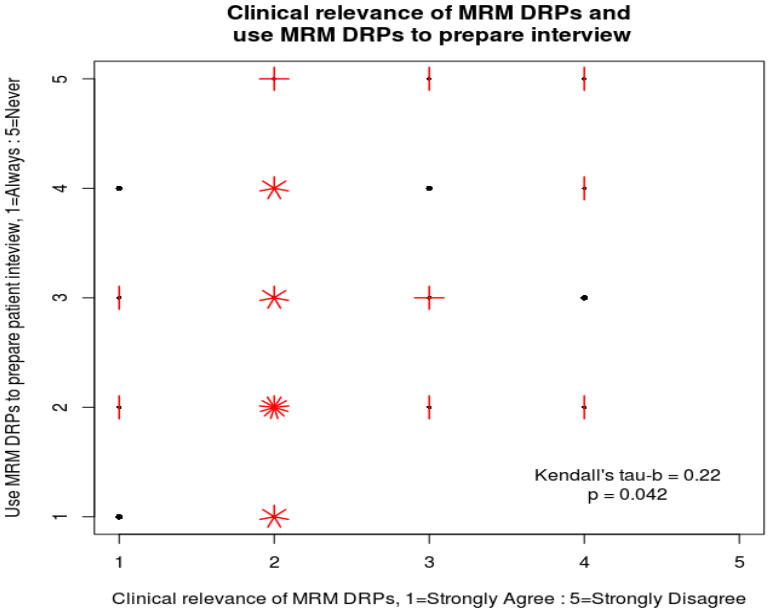


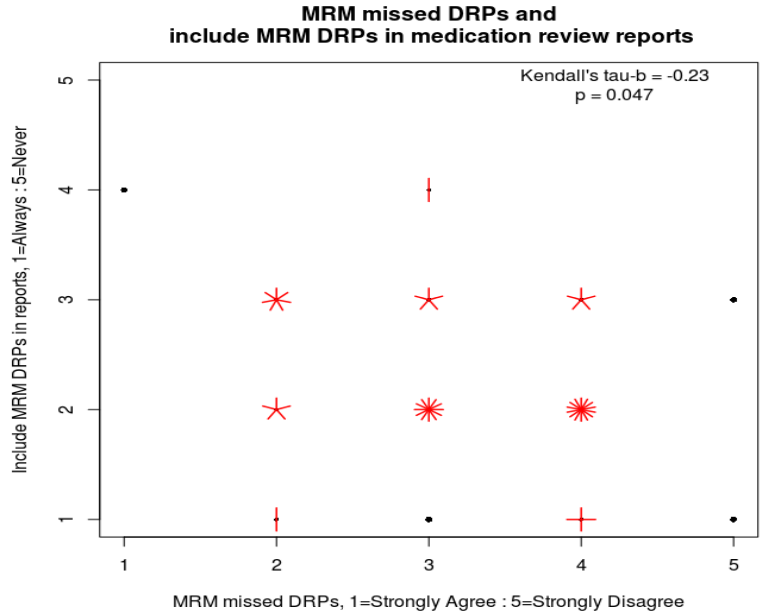


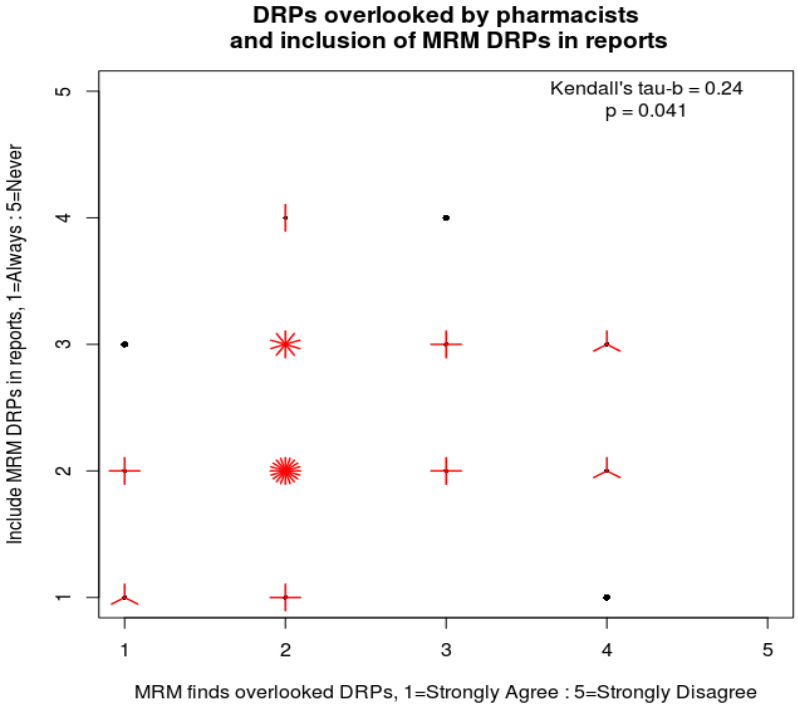

Value for money and MRM misses DRPs
Kendall's tau-b = -0.22
p = 0.047
MRM misses relevant DRPs, 1=Strongly agree : 5=Strongly disagree
MRM is value for money: 1=Strongly Agree : 5=Strongly Disagree

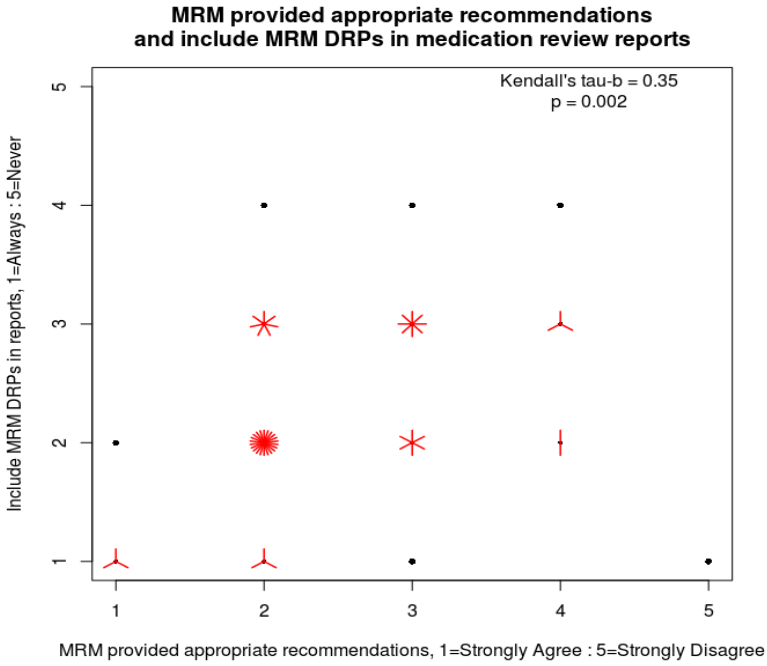

Value for money and appropriate recommendations
Kendall's tau-b = 0.41
p < 0.001
MRM provides appropriate recommendations, 1=Strongly agree : 5=Strongly disagree
MRM is value for money: 1=Strongly Agree : 5=Strongly Disagree

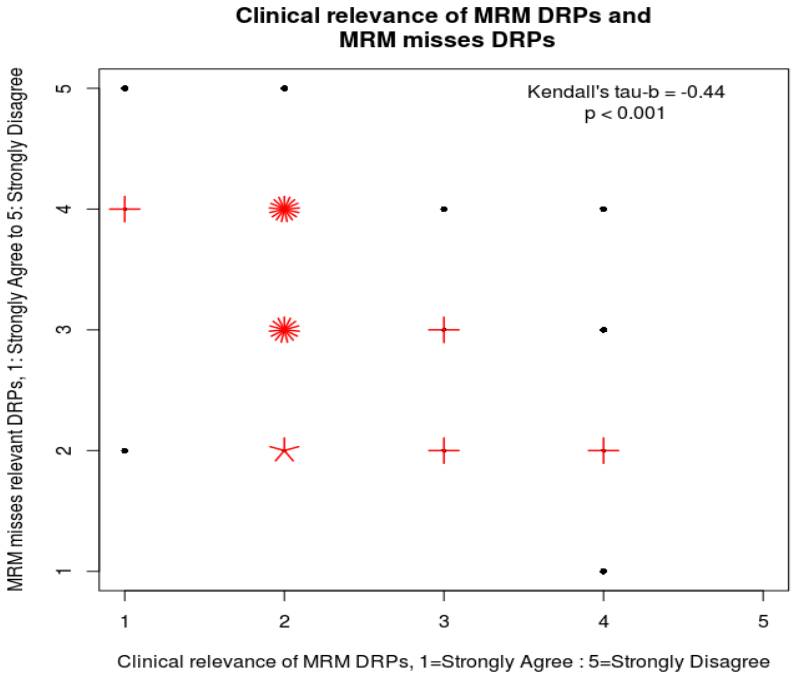
Remainder

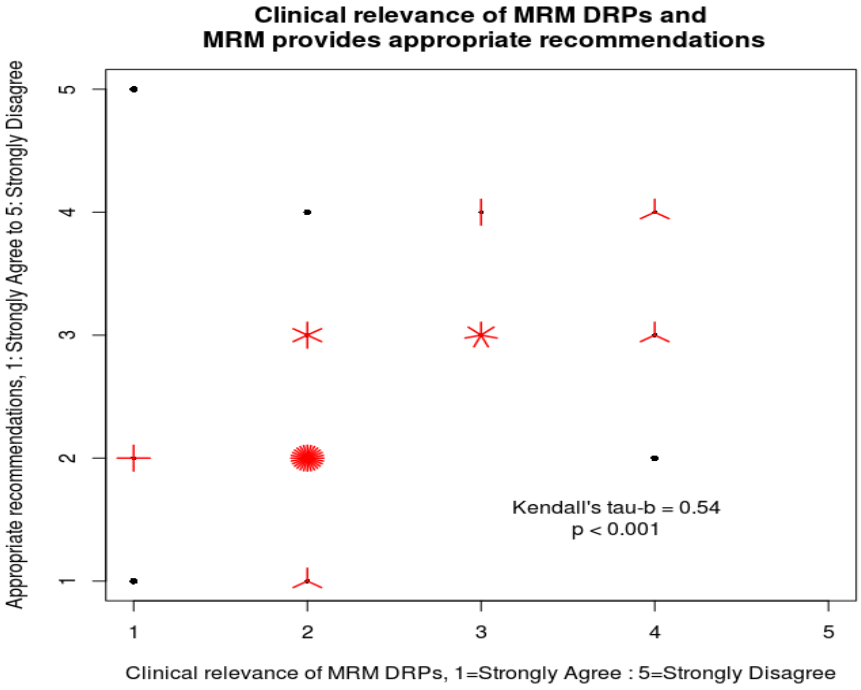

Clinical relevance of MRM DRPs and
use MRM DRPs to prepare interview
Use MRM DRPs to prepare patient inteview, 1=Always : 5=Never
Kendall's tau-b = 0.22
p = 0.042
Clinical relevance of MRM DRPs, 1=Strongly Agree : 5=Strongly Disagree

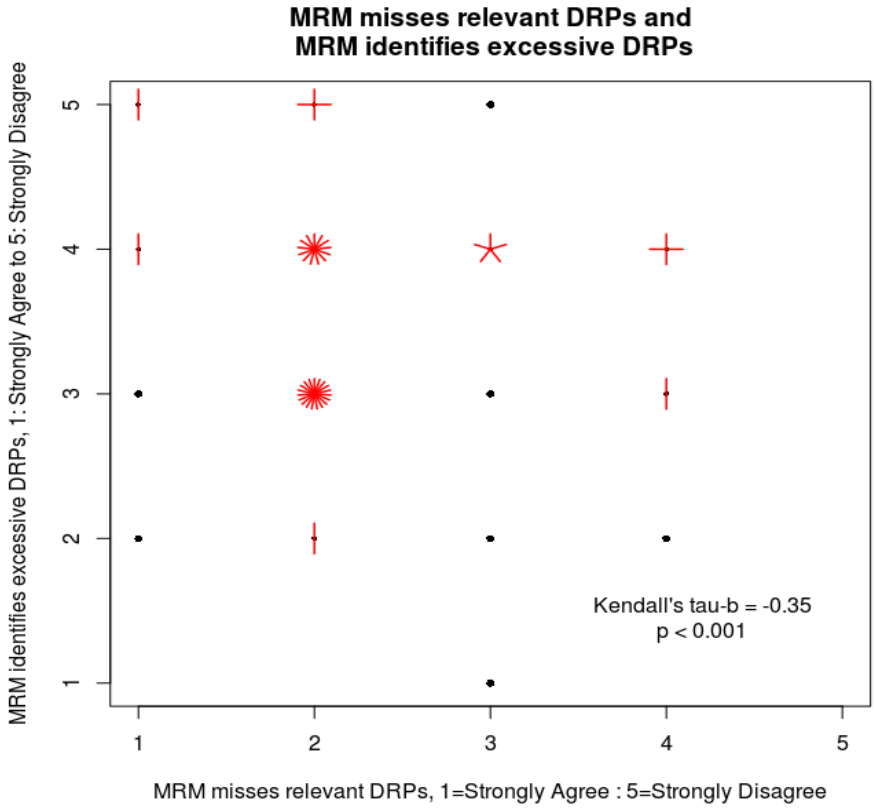

MRM missed DRPs and
include MRM DRPs in medication review reports
Include MRM DRPs in reports, 1=Always : 5=Never
Kendall's tau-b = -0.23
p = 0.047
MRM missed DRPs, 1=Strongly Agree : 5=Strongly Disagree


DRPs overlooked by pharmacists
and inclusion of MRM DRPs in reports
Kendall's tau-b = 0.24
p = 0.041
Include MRM DRPs in reports, 1=Always : 5=Never
MRM finds overlooked DRPs, 1=Strongly Agree : 5=Strongly Disagree
1
2
3
4
5


MRM provided appropriate recommendations
and include MRM DRPs in medication review reports
Kendall's tau-b = 0.35
p = 0.002
Include MRM DRPs in reports, 1=Always : 5=Never
MRM provided appropriate recommendations, 1=Strongly Agree : 5=Strongly Disagree
1
2
3
4
5


Clinical relevance of MRM DRPs and
MRM misses DRPs
Kendall's tau-b = -0.44
p < 0.001
MRM misses relevant DRPs, 1: Strongly Agree to 5: Strongly Disagree
1
2
3
4
5
Clinical relevance of MRM DRPs, 1=Strongly Agree : 5=Strongly Disagree


Clinical relevance of MRM DRPs and
MRM provides appropriate recommendations
Kendall's tau-b = 0.54
p < 0.001
Appropriate recommendations, 1: Strongly Agree to 5: Strongly Disagree
1
2
3
4
5
Clinical relevance of MRM DRPs, 1=Strongly Agree : 5=Strongly Disagree


MRM misses relevant DRPs and
MRM identifies excessive DRPs
MRM identifies excessive DRPs, 1: Strongly Agree to 5: Strongly Disagree
1
2
3
4
5
Kendall's tau-b = -0.35
p < 0.001
MRM misses relevant DRPs, 1=Strongly Agree : 5=Strongly Disagree

Appendix 21 MRM survey qualitative codes

Qualitative code	Code category	Frequency
Satisfied with MRM	Good impressions	8
DRPs or recommendations irrelevant	Bad impressions	6
Time consuming	Time	5
Value for money	Good impressions	5
Incorrectly analysing data	DRPs could be better, Bad impressions	4
Need to edit final report		4
Positive customer service	Good impressions	4
Time saving	Time	4
General could be better	Product needs polish	3
Makes HMRs easier	Good impressions	3
Store my own comments functionality	Needs functionality	3
DRPs missed by MRM	DRPs could be better, Bad impressions	2
Duplicates DRPs and recommendations	DRPs could be better, Bad impressions	2
Finds relevant DRPs	Good impressions	2
Like report template	Good impressions	2
Not value for money for few MRs		2
presentation lacks professionalism	Product needs polish	2
Repeated MRs convenient due to data stored	Good impressions	2
Suggestions for improvement		2
Add DRPs MRM cannot find	DRPs could be better	1
Becomes predictable		1
Better than competitors	Good impressions	1
Cannot rely only on MRM DRPs		1
Direct download functionality needed	Needs functionality	1
DRPs contradictory	DRPs could be better, Bad impressions	1
DRPs need better interactions	DRPs could be better, Bad impressions	1
DRPs not current best practice	DRPs could be better, Bad impressions	1
DRP wording too strong	DRPs could be better, Bad impressions	1
Loss of confidence	DRPs could be better, Bad impressions	1
Med list order by condition functionality	Needs functionality	1
MRM not useful	Bad impressions	1
Navigating software difficult	Bad impressions	1
Need references for recommendations		1
Needs report section for RMMR staff	Needs functionality	1
need standard drug interaction functionality	Needs functionality	1
Negative customer service	Bad impressions	1
No longer use MRM	Bad impressions	1
Not kept up to date	Bad impressions	1
Occasional bugs	Product needs polish	1
Outdated data	Product needs polish	1
Safety net for pharmacist	Good impressions	1
Slower than competitor	Time	1
Spelling and punctuation problems	Product needs polish	1
Update the tutorial	Product needs polish	1
Want electronic form functionality	Needs functionality	1