**DETECTING ADVERSE DRUG REACTIONS IN THE NURSING HOME SETTING
USING A CLINICAL EVENT MONITOR**

by

Steven Mark Handler

BS in Neuroscience, University of Pittsburgh, 1993

MD in Medicine, University of Medicine and Dentistry of New Jersey, 1997

Certificate in Health Services Research, University of Pittsburgh, 2002

MS in Biomedical Informatics, University of Pittsburgh, 2004

Submitted to the Graduate Faculty of

the School of Medicine in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2010

UNIVERSITY OF PITTSBURGH

SCHOOL OF MEDICINE

This dissertation was presented

by

Steven Mark Handler

It was defended on

January 6th, 2010

and approved by:

Dr. Shyam Visweswaran, Assistant Professor of Medicine,

Department of Biomedical Informatics

Dr. Wendy W. Chapman, Assistant Professor of Medicine,

Department of Biomedical Informatics

Dr. Joseph T. Hanlon, Professor of Medicine, Department of Medicine,

Division of Geriatric Medicine

Dr. Nicholas G. Castle, Professor, Department of Health Policy and Management, Graduate

School of Public Health

Dissertation Advisor and Committee Chair: Dr. Michael J. Becich, Professor of Medicine,

Department of Biomedical Informatics

DETECTING ADVERSE DRUG REACTIONS IN THE NURSING HOME SETTING USING A CLINICAL EVENT MONITOR

Steven Mark Handler MD, MS, PhD

University of Pittsburgh, 2010

Adverse drug reactions (ADRs) are the most clinically significant and costly medication-related problems in nursing homes (NH), and are associated with an estimated 93,000 deaths a year and as much as $4 billion of excess healthcare expenditures. Current ADR detection and management strategies that rely on pharmacist retrospective chart reviews (i.e., usual care) are inadequate. Active medication monitoring systems, such as clinical event monitors, are recommended by many safety organizations as an alternative to detect and manage ADRs. These systems have been shown to be less expensive, faster, and identify ADRs not normally detected by clinicians in the hospital setting. The main research goal of this dissertation is to review the rationale for the development and subsequent evaluation of an active medication monitoring system to automate the detection of ADRs in the NH setting. This dissertation includes three parts and each part has its own emphasis and methodology centered on the main topic of better understanding of how to detect ADRs in the NH setting.

The first paper describes a systematic review of pharmacy and laboratory signals used by clinical event monitors to detect ADRs in hospitalized adult patients. The second paper describes the development of a consensus list of agreed upon laboratory, pharmacy, and Minimum Data Set signals that can be used by a clinical event monitor to detect potential ADRs. The third paper describes the implementation and pharmacist evaluation of a clinical event monitor using the signals developed by consensus.

The findings in the papers described will help us to better understand, design, and evaluate active medication monitoring systems to automate the detection of ADRs in the NH setting. Future research is needed to determine if NH patients managed by physicians who receive active medication monitoring alerts have more ADRs detected, have a faster ADR management response time, and result in more cost-savings from a societal perspective, compared to usual care.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENTS

I would like to express my deepest appreciation to my dissertation advisor, Michael J. Becich, MD, PhD, for his dedication in helping me achieve the long-standing goal of obtaining a Doctorate in Biomedical Informatics. I greatly appreciate the expertise, guidance, mentorship, and opinions provided by Joseph T. Hanlon, PharmD, MS, who has helped develop my research, writing, career development, and personal skills. I am also grateful to the rest of my dissertation committee, including Shyam Visweswaran, MD, PhD, Nicholas G. Castle, PhD, and Wendy W. Chapman, PhD, for their dedication to my educational objectives. I would like to thank Stephanie A. Studenski, MD, MPH and Subashan Perera, PhD, for their keen intellect, insight, and suggestions on how to improve the quality of my research.

I cannot thank my family enough for their dedication, understanding, and support of my decision to pursue biomedical informatics research to improve the quality of care for vulnerable older adults. To my wife Denise, you of course deserve a special mention. Without you believing in me and recognizing that my charge in life is to help older adults through the development and dissemination of innovative technology, I would not have been able to accomplish what I have done to date or complete this dissertation.

Finally, I would like to recognize the funding agencies and grant support that have provided me with the protected time and resources to carry out my ideas including: NIH grants KL2RR024154 from the National Center for Research Resources (NCRR), a component of the

1.0   INTRODUCTION

1.1   MEDICATION USE IN NURSING HOMES

Medications are commonly prescribed to nursing home (NH) residents with the goals of curing or palliating disease and improving quality of life.[1] Nursing home residents are prescribed more medications than patients in any other medical setting because of the number and severity of chronic comorbid medical conditions. Using data from 1997, nursing home residents take an average of 8.8 medications per day (7.6 regularly scheduled and 1.2 as needed) and nearly one-third were prescribed ≥9 medications (the Centers for Medicare & Medicaid definition of polypharmacy).[2] Using the most recently available data, the number of NH residents who are prescribed ≥9 medications has increased to 60.9%, as of 2005.[3] Medication-related problems are a frequent consequence of polypharmacy.

1.2   MEDICATION-RELATED PROBLEMS IN NURSING HOMES

The terms adverse drug event and adverse drug reaction are often used interchangeably. Although interrelated, these terms represent distinct and measurable phenomena. The definition, terminology, and measurement of adverse drug events (ADEs) and adverse drug reactions

(ADRs) in this proposal will follow the World Health Organization's model [4-5] and the model of

Naranjo et al. [6], depicted graphically below (Figure 1).

```
┌─────────────────┐        ┌─────────────────┐        ┌─────────────────┐
│  Adverse Event  │═══════▷│ Adverse Drug Event│═══════▷│Adverse Drug Reaction│
│      (AE)       │        │      (ADE)      │        │      (ADR)      │
└─────────────────┘        └─────────────────┘        └─────────────────┘
```
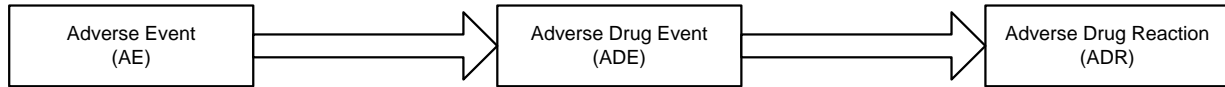
Figure 1. World Health Organization/Naranjo Model of Adverse Drug Reactions.

Adverse events (AEs) are negative patient events that are expressed as symptoms, signs or

laboratory abnormalities.[6]   When a relationship between the adverse event and a drug is

suspected and plausible, then an ADE is assumed. When an ADE is determined to be causally

related to a drug, then an ADR is assumed. Thus, an ADR will be defined as a unintended or

noxious responses to a drug given in a dosage intended for prophylaxis, diagnosis, or therapy.[4-5]

In essence, the model delineates differing levels of certainty about the relationship of an adverse

patient event to a drug. In our studies we will be using ADRs as the endpoint for all analyses.

1.3   PUBLIC HEALTH SIGNIFICANCE AND IMPACT OF ADVERSE DRUG

EVENTS IN NURSING HOMES

Institutionalized elderly experience ADEs at a rate as high as 10.8 events per 100-patient months,

often as a result of polypharmacy, multiple comorbid illness, and difficulty with monitoring

prescribed medications.[7-8] This translates into approximately 135 ADEs each year in an average

size NH (bed size of 105) or approximately 2 million events a year among all U.S. NH patients.

ADEs represent the most clinically significant and costly medication-related problems in NHs

and are associated with 93,000 deaths a year and in as much as $4 billion of excess healthcare

expenditures.[8-9] Excess healthcare expenditures associated with ADEs are usually a result of increased physician visits, ordering of additional medications or diagnostic studies, and the evaluation and management of patients in the emergency department or hospital setting.[10-11] The frequency of ADEs will likely increase as the U.S. population ages and the demand for NH services increases from the current 1.6 million people receiving care in one of more than 16,000 NHs to over 3 million people by 2030.[12-13]

1.4 EPIDEMIOLOGY OF ADVERSE DRUG EVENTS IN NURSING HOMES

Investigators have conducted epidemiological studies to attempt to identify a uniform set of patient-level risk factors for the development of ADEs in NHs in order to focus detection and prevention efforts on high-risk individuals.[10-11, 14-18] These studies evaluated the effects of age, gender, time since admission, number of comorbid conditions, and number and type of prescribed medications. Only the presence of polypharmacy (not uniformly defined throughout the studies) has consistently been found to increase the likelihood of developing an ADE. The lack of easily identifiable patient characteristics has limited the development and implementation of efforts to detect and prevent ADEs in the NH.[19]

1.5 SYSTEMS ANALYSIS OF ADVERSE DRUG EVENTS IN NURSING HOMES

A systems analysis is the interdisciplinary part of science, dealing with analysis of sets of interacting entities, the systems, often prior to their automation as computer systems, and the

interactions within those systems.[20-22] A systems analysis of ADEs suggest that as many as half of these events are preventable and that they are frequently a direct result of medication errors.[7] Medication errors are commonly defined as errors occurring in the medication use process (e.g., prescribing, order communication, dispensing, administration, and monitoring).[23] Data about preventable ADEs in NHs suggest that most (70-80%) are associated with *monitoring*, rather than *prescribing* errors.[10-11] Monitoring errors generally refer to inadequate laboratory evaluation of drug therapies or a delayed or failed response to signs or symptoms of drug toxicity or laboratory evidence of toxicity. Based on the results of these and other studies,[24-27] the term *suboptimal medication monitoring* has recently been introduced to explain a common pathway of systems failures that underlie monitoring errors causing ADEs in older adults.[28]

1.6 LIMITATIONS OF CURRENT METHODS FOR DETECTING ADVERSE DRUG EVENTS

Manual ADE detection techniques, including voluntary reporting through ADE, medication error or incident reports, direct observation of medication passes, and retrospective chart reviews have formed the foundation for the body of research underlying our current understanding of ADEs in the NH setting. Although retrospective manual chart review is considered to be the criterion standard for ADE detection, it is time-consuming, costly, and impractical for routine clinical use.[29-32]

Manual chart review is also the primary ADE case-finding technique for consultant pharmacists, who have a federal mandate to conduct monthly medication regimen reviews in NHs (i.e., *usual care*) and report their findings to the appropriate attending physician.[33]

4

Consultant pharmacist services have been required in NHs since 1974.[34] The Centers for Medicare and Medicaid Services outlines the expectations of the NH's consultant pharmacist in Appendix PP of the State Operations Manual that are used to guide and set minimal standards during annual state surveys. The State Operations Manual mandates that the drug regimen of each patient must be reviewed at least once a month by a licensed consultant pharmacist who must report the presence of ADEs and recommend that a medication should be stopped, changed, or monitored more closely by the attending physician.[35] The State Operations Manual further suggests that the reports made by a consultant pharmacist be acted on by the attending physician within 30 days.

A significant limitation of pharmacist-conducted monthly medication regimen reviews is their retrospective nature, which has not been shown to improve clinical outcomes.[36-37] Retrospective chart reviews do not provide the attending physician with real-time notification of ADEs, and could result in notification delays of up to 30 days .[19] Moreover, in a recent study, although attending physicians rated the two most important functions of consultant pharmacists as helping the NH comply with state and federal regulations, and monitoring the safety of all prescribed medication, physicians also rated these two functions as most in need of improvement.[38]

1.7   ACTIVE MEDICATION MONITORING SYSTEMS FOR DETECTING ADVERSE DRUG EVENTS ARE RECOMMENDED

The Institute of Medicine and other patient safety organizations recommend that all healthcare settings assess the safety of medication use through active monitoring systems within a culture of

safety.[19, 35, 39-44] Nevertheless, the majority of health information technology interventions to improve patient safety with respect to medications have focused on enhancing *prescribing* through the use of with CPOE (computerized provider order entry) with CDS (clinical decision support).[45-48] These CPOE with CDS interventions have had varying degrees of success in detecting and reducing ADEs in diverse clinical settings, including NHs.[8, 49] Active medication monitoring systems are particularly needed to detect ADEs in priority populations such as institutionalized elderly. This is because of long-standing concern about the quality of their pharmaceutical care, presence of polypharmacy, and the limited ability of the NH workforce to monitor prescribed medications effectively due to an insufficient healthcare personnel, high staff turnover, and a poorly developed safety culture.[2, 50-54]

1.8   ACTIVE MEDICATION MONITORING SYSTEMS ARE OPTIMAL FOR DETECTING ADVERSE DRUGE EVENTS

Computerized clinical event monitors, a type of active medication monitoring system, can detect ADEs via the processing of signals for laboratory test results and pharmacy orders.[31, 55-56] Compared with manual methods of ADE detection, hospital studies indicate that clinical event monitors, which provide feedback to healthcare professionals based on information available in electronic format, are less expensive, faster, and can identify ADEs not normally detected by clinicians.[30, 57-61] Clinical event monitor systems have also been shown in certain studies to prevent the development, progression, or mitigate the seriousness of ADEs by promoting the early detection and appropriate response to events in evolution in the hospital and ambulatory care settings.[32, 62-68] Despite the proven benefits of clinical event monitors on improving

healthcare quality and efficiency while reducing cost, few healthcare organizations have implemented and formally evaluated them.[41-42, 49, 69]   When used, these active medication monitoring systems have been implemented in non-standardized ways that make it difficult to reproduce findings and compare their effectiveness across patients and healthcare settings.[39, 70] This lack of generalizability contributes to the suboptimal detection and management of ADEs in U.S. hospitals and ambulatory care settings.[71]

1.9   BARRIERS TO USING ACTIVE MEDICATION MONITORING SYSTEMS IN NURSING HOMES

Studies have been conducted to assess the adoption and barriers to implementing health information technology such as active medication monitoring systems in a variety of clinical settings including NHs.[72-73]   These studies suggest that NHs are the farthest behind in the adoption of health information technology. Moreover, when health information technology is available, it is used primarily for state or federal payment and certification requirements. There is minimal use of clinical health information technology applications, and when used, these systems are usually not integrated. Nevertheless, almost all NHs generate laboratory, pharmacy, and Minimum Data Set data (MDS; a standardized summary assessment instrument required for all NH patients) in electronic format as a byproduct of other work processes. Studies to assess barriers to the use of health information technology in the NH setting[74-75] have concluded that multiple stakeholders would incur the costs of implementing and maintaining these systems, but that these costs would likely not be fully aligned with their benefits. In addition to concerns about cost, other barriers include difficulty in finding health information technology producers

7

that meet their needs, lack of evidence that health information technology will have a positive impact on quality of care and operational efficiencies (e.g., alert burden), and lack of the hardware or technical support to access and use the electronic data that they generate.[76-77]

1.10   SUMMARY AND OBJECTIVE OF DISSERTATION

ADEs among NH patients are common and costly problems that are likely to increase substantially as the U.S. NH population grows. A lack of easily identifiable patient-specific risk factors makes it difficult to routinely detect these events. Systems analyses of ADEs suggest that suboptimal medication monitoring is the most common pathway underlying these events in the NH.   Current strategies that rely on voluntary reporting, such as incident reports, direct observation of medication passes, and retrospective chart review are time-consuming, costly, and impractical for routine clinical use.   Several prominent quality improvement organizations recommend active medication monitoring systems as a potential solution to improving medication safety.   Active medication monitoring systems are particularly needed to detect ADRs in priority populations such as institutionalized elderly because of the long-standing concern about the quality of their pharmaceutical care. Although NHs have yet to adopt a significant amount of health information technology, the majority generate laboratory, pharmacy, and Minimum Data Set data in electronic format that can be used by active medication monitoring systems such as clinical event monitors to automate the detection of ADEs. The main research goal of this dissertation is to review the rationale for the development and subsequent evaluation of an active medication monitoring system to automate the detection of ADRs in the NH setting.

1.11   CONTRIBUTION OF DISSERTATION

In a comprehensive review of medication-related adverse events in nursing homes, Handler et al. reported that there was substantial variability in the incidence of ADEs, ranging from 1.19 to 7.26 per 100 resident-months.[7] The authors concluded that the variability in the incidence of ADEs was most likely due to the lack of uniformity in case-finding techniques. In particular, Gurwitz et al.[11] reported the highest incidence rate, which was greater than four times higher than the rate in their previous study.[10] The significant increase in the incidence of ADEs was attributed to the investigators using a previously developed clinical event monitor system that had been developed for use in the hospital setting.

The overall goal of my research has been to expand on our previous knowledge by developing and testing a clinical event monitor system specifically designed for detecting ADRs in the NH setting. The first step was to conduct a systematic review of hospital-based clinical event monitor systems to better understand the universe of signals used to detect ADEs and how to calculate and compare their respective performance characteristics using positive predictive values. The second step was to develop NH-specific signals for ADR detection by conducting a modified Delphi survey of experts in geriatrics. The third step was to assess the performance characteristic of a NH-specific clinical event monitor system that uses the signals derived by expert consensus. To the best of my knowledge, no previous research has been published on the development of a consensus list of signals and/or the evaluation of an active medication monitoring system to automate the detection of ADRs in the NH setting.

1.12   ORGANIZATION OF DISSERTATION

The remainder of the dissertation is divided into four chapters including three papers (chapters 2, 3, and 4), followed by a summary of findings, their significance, and direction of future research. Each paper has its own method centered on the theme of development and evaluation of an active medication monitoring system to automate the detection of ADRs in the NH setting. The first paper describes a systematic review of pharmacy and laboratory signals used by clinical event monitors to detect ADEs in hospitalized adults. This paper has been published in the Journal of the American Medical Informatics Society.[60] The second paper describes the development of a consensus list of agreed upon laboratory, pharmacy, and Minimum Data Set signals that can be used by a clinical event monitor to detect potential ADRs. This paper has been published in the Journal of the American Geriatrics Society.[78] The third paper describes the implementation and pharmacist evaluation of a clinical event monitor using the signals developed by consensus. This paper has been published in the American Medical Informatics Association Annual Symposium Proceedings.[79]

2.0   A SYSTEMATIC REVIEW OF THE PERFORMANCE CHARACTERISTICS OF CLINICAL EVENT MONITOR SIGNALS USED TO DETECT ADVERSE DRUG EVENTS IN THE HOSPITAL SETTING

2.1   ABSTRACT

2.1.1   Objective

Despite demonstrated benefits, few healthcare organizations have implemented clinical event monitors to detect adverse drug events (ADEs). The objective of this study was to conduct a systematic review of pharmacy and laboratory signals used by clinical event monitors to detect ADEs in hospitalized adults.

2.1.2   Design

We performed a comprehensive search of MEDLINE, CINHAL, and EMBASE to identify studies published between 1985 and 2006. Studies were included if they: described a clinical event monitor to detect ADEs in an adult hospital setting; described laboratory or pharmacy ADE signals; and provided positive predictive values (PPVs) or information to allow the calculation of PPVs for individual ADE signals.

2.1.3   Measurements

We calculated overall estimates of PPVs and 95% confidence intervals (CIs) for signals reported in 2 or more studies and contained no evidence heterogeneity. Results were examined by signal category: medication levels, laboratory tests, or antidotes.

2.1.4   Results

We identified 12 observational studies describing 36 unique ADE signals. Fifteen signals (3 antidotes, 4 medication levels, and 8 laboratory values) contained no evidence of heterogeneity. The pooled PPVs for these individual signals ranged from 0.03 [CI=0.03-0.03] for hypokalemia, to 0.50 [CI=0.39-0.61] for supratherapeutic quinidine level. In general, antidotes (range=0.09-0.11) had the lowest PPVs, followed by laboratory values (0.03-0.27), and medication levels (0.03-0.50).

2.1.5   Conclusion

Results from this study should help clinical information system and computerized decision support producers develop or improve existing clinical event monitors to detect ADEs in their own hospitals by prioritizing those signals with the highest PPVs.

2.2   INTRODUCTION

Clinical decision support (CDS) systems have been shown to improve patient care and treatment outcomes by providing physicians and other healthcare providers with patient-specific information that is intelligently filtered and presented at appropriate times.[71]   Clinical event monitors, one of the most common types of CDS systems, provide feedback through alerts and reminders to healthcare providers when triggered by certain information available in electronic format (i.e., by signals).[80]   Clinical event monitors can be used to detect medication-related problems by processing pharmacy order signals[81-82] and laboratory test result signals,[83] generated by systems with varying levels of automation and sophistication.[30]

The most clinically significant medication-related problems are adverse drug events (ADEs). Various definitions have been proposed and used throughout the literature to describe ADEs. For this paper, we use the Institute of Medicine definition which defines ADEs as "injuries resulting from a medical intervention related to a drug."[7, 39, 84]   ADEs are common and occur in 2.4-5.2 per 100 hospitalized adult patients.[29, 85-87]   A meta-analysis of fatal ADEs suggest that these events are between the fourth and sixth leading cause of death in the U.S.[88] Each ADE is estimated to increase the length of hospital stay by 2.2 days and to increase the hospital cost by $3,244.[89]

Compared with manual methods of ADE detection (e.g., chart review or voluntary reporting), clinical event monitors are less expensive and faster, and they often identify ADEs not normally detected by clinicians during the course of routine hospital care.[57, 61, 90-91]   Through the early detection and prevention of ADEs, clinical event monitors can improve the quality of care, while reducing health care costs by as much as $760,000 per year in a teaching hospital.[62, 92-94]   Despite the potential benefits of clinical event monitors and the fact that several prominent

national organizations have recommended their use to detect ADEs,[41-42] few healthcare systems have implemented them.[49] Moreover, when they have implemented them, they have done so in non-standardized ways that make it difficult to compare and synthesize the results.[23, 70] The lack of generalizability of results in turn contributes to the problems and suboptimal performance of hospitals in the U.S. healthcare system.[71]

To begin to address these concerns and to help clinical information system and CDS producers develop, select, or improve, systems to detect ADEs, we conducted a systematic review of individual pharmacy and laboratory signals that are currently used by clinical event monitors to detect ADEs in the adult hospital setting. When possible, we calculated the positive predictive values (PPVs) of individual signals.

2.3   METHODS

2.3.1   Study Identification and Eligibility

Before we implemented our literature search, we established criteria for inclusion and exclusion of studies. We included studies that met the following four criteria: their results were published between January 1, 1985, and July 1, 2006; they described a clinical event monitoring system to detect ADEs in an adult hospital setting; they described laboratory or pharmacy ADE signals; and they provided PPVs or information to allow the calculation of PPVs for individual ADE signals. We excluded studies if they focused on ADE prevention rather than detection (e.g., if they focused on computerized physician order entry systems) as this has recently been reviewed elsewhere.[95] We also excluded studies if they described non-laboratory or non-pharmacy ADE

14

signals, including signals to monitor physiologic data (e.g., blood pressure or heart rate) or administrative data (e.g., diagnostic or procedural codes [ICD-9 or CPT]), or if they described free-text search strategies to detect potential ADEs. Because of concerns that non–peer-reviewed data might introduce bias into our systematic review,[96-97] we also excluded studies in which data was presented as an abstract, poster presentation, or editorial.

2.3.2   Information Sources and Search Strategy

We searched OVID MEDLINE, OVID CINHAL, and EMBASE for articles published in all languages between January 1, 1985, and July 1, 2006. In OVID, we searched for the following medical subject headings (MeSH) keywords, and text words: adverse drug event, adverse drug reaction, adverse drug reaction reporting systems, clinical event monitor, clinical decisions support systems, clinical laboratory information systems, clinical pharmacy information system, computer generated signals, decision support system, drug monitoring, medication errors, and physiologic monitoring. In EMBASE, we searched for the above terms plus the following EMTREE keywords: computer assisted drug therapy and drug surveillance program. We supplemented the computerized search by reviewing the reference lists of all articles selected for inclusion.

2.3.3   Study Selection, Data Extraction and Review Criteria

Two reviewers (SH and RA) independently assessed each article for eligibility criteria, with adjudication by a third reviewer (JH) in cases of disagreement. While reviewing each study that met the eligibility criteria, the same two authors (SH and RA) used standardized forms to

15

independently extract and record: hospital characteristics (e.g., teaching or community hospital, number of beds); patient characteristics (e.g., number of patients included); the signals monitored by the hospitals; and, data necessary to record or calculate positive predictive values. To collect the necessary data to calculate a PPV, we reviewed the data from each signal in the individual included studies. For every signal in an included study, we recorded the number of times that a specific signal fired and the number of times that a health professional determined that the signal represented an ADE. Study authors were contacted by email for data clarification when necessary.

Signals from each of the studies that met eligibility criteria were included and combined if they measured the same parameter (e.g., digoxin level, serum potassium level, or use of vitamin K) independent of the reference interval or dosage used in the particular study. Signals were then grouped into one of three categories: antidote signals (triggered by administration of medications given to counteract the effects of a poison, toxin, or other agent with toxic effects), medication level signals (triggered by elevated, or supratherapeutic, drug levels), and laboratory result signals (triggered by abnormal values in blood tests).

2.3.4 Quantitative Data Synthesis and Statistical Analysis

To calculate a study-specific PPV for each signal, we divided the number of times that a signal fired and an ADE was confirmed (i.e., the number of true-positives), by the number of times the signal fired with or without an ADE being confirmed (i.e., the sum of true-positives and false-positives). PPVs were chosen as the performance characteristic of interest since the majority of studies conducted a targeted verification of signal firings and did not include a corollary gold-standard measure, such as an independently conducted chart review looking for the presence of

16

ADEs. As a result, the sensitivity and specificity of individual signals used to detect ADEs could not be calculated.

To determine the appropriateness of computing a pooled PPV, we compared the individual study-specific PPVs using the chi-square test for homogeneity of proportions.[98] For those signals which there was no evidence of heterogeneity (p>0.05) we calculated an overall estimate of pooled PPVs and corresponding 95% confidence intervals (CIs). We used a generalized estimating equations (GEE) model by combining the PPVs for signals reported in at least two studies. This model included an exchangeable correlation structure to account for within-study correlation, using the total number of signal firings in each study as the weighing factor.[99-101] We also examined the sensitivity of the overall PPV estimates using a fixed effects model recommended in the meta-analytic literature.[102]

To determine whether certain studies were heavily influencing the overall PPV estimate for each signal, we performed an influence analysis in which we excluded studies, one at a time, and reestimated the overall PPVs. We also examined the cumulative effect on the overall PPV estimate by adding studies, one at a time, ordered by year of publication, and hospital bed size. If there were any publication bias, it would most likely be caused by the greater probability of publication of studies with a larger number of firings or of studies with a smaller number of firings but a greater PPV. We examined this possibility by visually inspecting a scatter plot of the PPV and the square root of the number of signals (which is proportional to the reciprocal of the standard error) and testing for a significant linear trend between them. If we found a lack of data points near the origin or a statistically significant negative linear trend, we would consider it to be evidence of publication bias.[103] We conducted all statistical analyses with either SAS

version 8.2 for Windows (SAS Institute, Inc., Cary, NC) or Stata version 9.0 for Windows (StataCorp, LP, College Station, TX).

2.4   RESULTS

Of the 6649 titles that were initially identified, 4243 were from MEDLINE, 859 were from CINHAL, and 1547 were from EMBASE. After removing duplicates and going through a thorough screening process (Figure 2), we identified 12 observational studies that met our eligibility criteria.[56-57, 64, 66, 68, 104-111]   Table 1 lists the 12 studies and the characteristics of the study sites. All but two of the studies were conducted in teaching hospitals.

```
┌──────────────────────────────────────────────┐
│ Titles identified for title review (n = 6649) │
└──────────────────────────────────────────────┘
                    │
                    ├──────────────────►┌────────────────────────────────┐
                    │                   │ Rejected as duplicates (n = 250)│
                    │                   └────────────────────────────────┘
                    ▼
┌──────────────────────────────────────────────────┐
│ Unique titles identified for title review (n = 6399) │
└──────────────────────────────────────────────────┘
                    │
                    ├──────────────────►┌─────────────────────────────────┐
                    │                   │ Rejected on title review (n = 5417)│
                    │                   └─────────────────────────────────┘
                    ▼
┌──────────────────────────────────────────────┐
│ Titles considered relevant (n = 982)         │
└──────────────────────────────────────────────┘
                    │
                    ├──────────────────►┌──────────────────────────────────┐
                    │                   │ Rejected on abstract review (n = 628)│
                    │                   └──────────────────────────────────┘
                    ▼
┌──────────────────────────────────────────────┐
│ Articles screened (n= 354)                   │
└──────────────────────────────────────────────┘
                    │
                    ├──────────────────►┌─────────────────────────────────┐
                    │                   │ Rejected on article review (n = 342)│
                    │                   └─────────────────────────────────┘
                    ▼
┌──────────────────────────────────────────────┐
│ Articles included (n =12)                    │
└──────────────────────────────────────────────┘
```
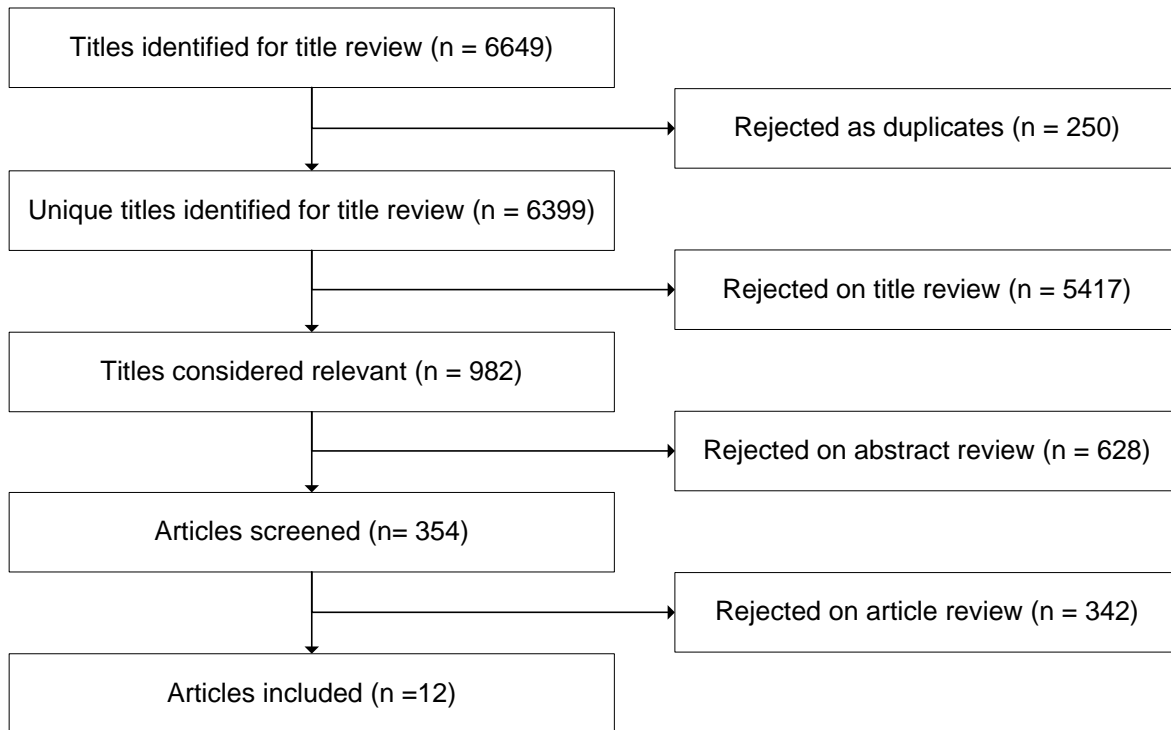
Figure 2. Flow diagram of included and excluded studies.

Table 1. Characteristics of studies included in the systematic review.

Author/Year/Reference	Study Site
Evans et al, 1991 [104]	500-bed tertiary teaching hospital
Azaz-Livshits et al, 1998 [105]	34 bed medical ward in teaching hospital
Jha et al, 1998 [56]	726 bed tertiary teaching hospital
Raschke et al, 1998 [64]	650 bed community teaching hospital
Levy et al, 1999 [57]	34 bed medical ward in teaching hospital
Dormann et al, 2000 [107]	9 bed medical ward in a teaching hospital
Brown et al, 2000 [111]	238 bed Veterans Administration Medical Center
Jha et al, 2001 [108]	726 bed tertiary care teaching hospital
Thuermann et al, 2002 [109]	86 bed neurology department in teaching hospital
Dormann et al, 2004 [110]	29 bed gastroenterology ward in teaching hospital
Silverman et al, 2004 [66]	726 bed tertiary care teaching hospital
Hartis et al, 2005 [68]	1,952 beds in six community hospitals

Of the total of 36 signals that we identified in two or more publications and included in our analysis, 7 were administrations of antidotes, 10 were supratherapeutic medication levels, and 19 were abnormal laboratory test results. Fifteen signals (3 antidotes, 8 laboratory tests, and 4 medication levels) contained no evidence of heterogeneity (p>0.05) and were pooled to calculate overall PPVs and 95% CIs. Naloxone was not included in the analysis because of the 12 studies that met eligibility criteria, only one study provided sufficient information about naloxone to calculate PPVs.[37] Because we could not calculate a pooled PPV (our primary unit of analysis) with the PPV from only one study, naloxone was not included in our systematic review.

Of the antidote signals (Table 2), sodium polystyrene administration, had the lowest pooled PPV 0.09 (95% CI, 0.06–0.13), and metronidazole or vancomycin administration had the highest 0.11 (95% CI, 0.06–0.20).

Table 2. Signals associated with antidotes.

Signal*	Number of Studies	PPV Range	P-value Test for Heterogeneity	Overall Estimate of PPV† (95% CI)	Overall Estimate of PPV‡ (95% CI)
Vitamin K given	3	0.02 – 0.30	< 0.01	-	-
Activated charcoal given	2	0.08 – 0.45	0.03	-	-
Antihistamine (e.g., diphenhydramine or hydroxyzine) given	3	0.03 – 0.14	< 0.01	-	-
Oral metronidazole or vancomycin given	2	0.07 – 0.16	0.06	0.11 (0.06–0.20)	0.10 (0.06 – 0.14)
Antidiarrheal (e.g., loperamide, diphenoxylate, bismuth) given	3	0 – 0.11	0.06	0.09 (0.07–0.13)	0.07 (0.00 – 0.15)
Sodium polystyrene (Kayexalate®) given	3	0.06 – 0.12	0.44	0.09 (0.06–0.13)	0.08 (0.05 – 0.12)

| Oral or topical steroids (e.g., prednisone, prednisolone) given | 2 | 0.04 – 0.09 | < 0.01 | - | - |

* Naloxone not included as data was available from only a single study; †PPV calculated using GEE pooled estimate and CI; ‡PPV calculated using fixed effects pooled estimate and CI

Of the laboratory test result signals (Table 3), hypokalemia had the lowest pooled PPV 0.03 (95% CI, 0.03–0.03), and hypoglycemia had the highest 0.28 (95% CI, 0.24–0.32).

Table 3. Signals associated with laboratory test results.

Signal	Number of Studies	PPV Range	P-value Test for Heterogeneity	Overall Estimate of PPV† (95% CI)	Overall Estimate of PPV‡ (95% CI)
Serum creatinine elevated or increasing	5	0.08 – 0.39	<0.01	-	-
Hypoglycemia (as indicated by low or decreasing glucose)	2	0 – 0.33	0.49	0.27 (0.27–0.27)	0.10 (0.00 – 0.27)
Hyperbilirubinemia (as indicated by high or increasing bilirubin)	4	0.05 – 0.39	< 0.01	-	-
Hyponatremia (as indicated by low or decreasing sodium)	2	0.24 – 0.33	0.72	0.25 (0.23–0.28)	0.25 (0.09 – 0.41)
Blood urea nitrogen (BUN) elevated or increasing	3	0 – 0.30	0.41	0.22 (0.14–0.32)	0.17 (0.08 – 0.26)
Eosinophilia (as indicated by high or increasing eosinophils)	5	0 – 0.62	< 0.01	-	-
Hyperkalemia (as indicated by high or increasing potassium)	5	0 – 0.67	< 0.01	-	-

Alanine aminotransferase (ALT) elevated or increasing	3	0.12 – 0.38	< 0.01	-	-
Anemia (as indicated by a low or decreasing hemoglobin/hematocrit)	5	0.12 – 0.30	0.14	0.19 (0.12–0.29)	0.16 (0.11 – 0.22)
Partial thromboplastin time (PTT) elevated or increasing	3	0.04 – 0.92	< 0.01	-	-
Gamma-Glutamyl Transferase (GGTP) elevated or increasing	4	0.03 – 0.19	0.03	-	-
Alkaline phosphatase (ALP) level elevated or increasing	5	0 – 0.31	< 0.01	-	-
Aspartate aminotransferase (AST) elevated or increasing	4	0.01 – 0.23	< 0.01	-	-
Agranulocytosis or leukopenia (as indicated by low or decreasing white blood cells)	4	0.09 – 0.5	0.15	0.11 (0.07–0.17)	0.10 (0.04 – 0.15)
International normalized ratio (INR) elevated or increasing	4	0.05 – 1.0	< 0.01	-	-

				PPV (95% CI)†	PPV (95% CI)‡
Lactate dehydrogenase (LDH) elevated or increasing	3	0.02 – 0.17	0.06	0.06 (0.02–0.14)	0.03 (0.00 – 0.06)
Thrombocytopenia (as indicated by low or decreasing platelets)	4	0.03 – 0.12	0.01	-	-
Hypocalcemia (as indicated by low or decreasing calcium)	2	0 – 0.11	0.25	0.06 (0.02–0.18)	0.02 (0.00 – 0.08)
Hypokalemia (as indicated by low or decreasing potassium)	2	0 – 0.03	0.86	0.03 (0.03–0.03)	0.03 (0.01 – 0.04)

PPV= positive predictive value; †PPV calculated using GEE pooled estimate and CI; ‡PPV calculated using fixed effects pooled estimate and CI

Of the medication level signals (Table 4), cyclosporine had the lowest pooled PPV 0.03 (95% CI, 0.02–0.06) and quinidine had the highest 0.50 (95% CI, 0.39–0.61). Among the pooled signals considered, the antidote category had the lowest PPVs (range= 0.09-0.11), followed by the laboratory test result category (range= 0.03-0.27), and the medication level category (range= 0.03-0.50).

Table 4. Signals associated with supratherapeutic medication levels.

Signal	Number of Studies	PPV Range	P-value Test for Heterogeneity	Overall Estimate of PPV† (95% CI)	Overall Estimate of PPV‡ (95% CI)
Quinidine	2	0.43 – 0.60	0.56	0.50 (0.39–0.61)	0.50 (0.22 – 0.78)
Phenobarbital	3	0 – 1.0	< 0.01	-	-
Theophylline trough	5	0.25 – 1.0	0.01	-	-
Vancomycin peak or trough levels	3	0.18 – 0.33	0.31	0.26 (0.22–0.32)	0.26 (0.20 – 0.32)
Procainamide	3	0 – 0.42	<0.01	-	-
Lidocaine	3	0.17 – 0.50	0.51	0.19 (0.17–0.21)	0.18 (0.09 – 0.28)
Aminoglycoside antibiotic	3	0.04 – 1.0	< 0.01	-	-
Digoxin	8	0.08 – 1.0	< 0.01	-	-
Phenytoin	7	0.07 – 1.0	< 0.01	-	-
Cyclosporine	2	0 – 0.04	0.29	0.03 (0.02–0.06)	0.03 (0.00 – 0.06)

PPV= positive predictive value; †PPV calculated using GEE pooled estimate and CI; ‡PPV calculated using fixed effects pooled estimate and CI

There were no meaningful differences in overall PPV estimates calculated with GEE models or fixed effects models. The influence analysis suggested that the removal of certain studies affected the PPVs for particular signals. For example, when the Evans et al. study was removed from the analysis of the signal for agranulocytosis or leukopenia, the pooled PPV increased from 0.11 to 0.23.[104] Similarly, when the Theurmann et al. study was removed from the analysis of the anemia signal, the PPV increased from 0.19 to 0.26.[112] No effects were noted on the overall PPV estimates when stratified by study year or bed size.

Some evidence of publication bias was found for the signal agranulocytosis or leukopenia. Specifically, a significant negative association between the number of firings and the PPV ($p<0.05$), suggesting the possibility that smaller studies with lower PPVs may not have been published and may therefore have eluded our systematic review. For the remaining signals, we found no evidence of publication bias.

2.5   DISCUSSION

This systematic review analyzed the performance characteristics of individual pharmacy and laboratory signals that are currently used by clinical event monitors to detect ADEs in the adult hospital setting. Our review of the PPVs of 36 signals from 12 studies published between 1985 and 2006 revealed two important findings.

First, there was evidence of significant between-study heterogeneity for the majority of signals, limiting our ability to pool the PPVs of signals across studies. Of the 36 signals identified in two or more publications, 21 contained evidence of heterogeneity and could therefore not be pooled to calculate overall PPVs. There are at least two plausible explanations

for this heterogeneity. First, it may be due to the use of different reference intervals for therapeutic medication levels and laboratory values in different studies. Second, it may be attributable to the different hospital and/or patient characteristics which affect the underlying prevalence of ADEs. This is particularly important because PPVs are by definition affected by the underlying prevalence of the condition of interest.

The second important finding was that there was significant variability in the PPVs for different individual signals, both across studies and within signal categories (e.g., antidotes, medication levels, and laboratory test results). The overall PPV estimates for the 15 pooled signals in the analysis ranged from 0.03 for hypokalemia to 0.50 for a supratherapeutic quinidine level. Moreover, antidotes had the lowest PPVs, followed by laboratory test results, and medication levels. It is not surprising that PPVs were highest for medication levels. For this category of signal, the prior odds of an ADE are increased, since the underlying assumption is that patients in each case are already receiving the medication of interest and their prescribing clinicians are aware of the possibility of an ADE.[113] In contrast, the other two categories of signals would not necessarily be expected to be associated with an ADE. Laboratory values are often abnormal because of the onset or worsening of medical conditions unrelated to the use of medications. Likewise, the majority of antidotes analyzed in our study can be used to treat multiple medical conditions, only a fraction of which are related to the presence of an ADE.

2.5.1 Limitations and Strengths

Our systematic review has several limitations that deserve mention. First, systematic reviews of effect sizes often limit their selection of studies to those involving randomized controlled trials (RCTs).[114] However, analyzing RCTs is not always feasible or preferable for evaluating the

performance characteristics of individual signals used to detect ADEs.[115-116] For purposes of our analysis, we did not limit our systematic review to RCTs, so we were not able to apply instruments commonly used to assess the quality of RCTs.[117-118] Second, although we found 12 studies that could be included in the overall analysis, we found few studies that covered each ADE signal. This may have limited our ability to identify the dependence of overall PPVs on factors such as facility bed size and to detect publication bias, a problem to which all systematic reviews are susceptible.[119-120] Third, our analysis focused on data that is widely available in electronic format (such as laboratory and pharmacy information) and was thus biased against data that cannot be readily computed. It also excluded some sources of electronic data available to enhance ADE detection, such as administrative data (e.g., ICD-9 and CPT codes), allergy rules, and free-text searching of clinician progress and discharge notes.[31]

Despite these limitations, we believe that our results are important and represent the most comprehensive information available on the performance characteristics of ADE signals in the adult hospital setting. Our analysis employed the "best practice" methods recommended for conducting systematic reviews of the literature.[114] Moreover, in keeping with suggestions of the Roadmap for National Action on Clinical Decision Support, the study was designed to capture, organize, and assess studies available internationally.[71]

2.5.2 Implications

While the benefits of health information technology are clear at least in theory, adapting information systems to healthcare has proven difficult, partly because there are so many non-standardized and independent approaches to creating and representing clinical knowledge and clinical decision support systems.[73, 121] In this regard, our systematic review may provide a

foundation for and influence the future design and implementation of computerized decision support systems used to detect ADEs in the hospital setting. Having comprehensive information on the performance characteristics of individual signals may help hospitals prioritize the signals to be included in their systems to maximize the detection of ADEs and to minimize the number of false-positive alerts (i.e., alert burden), which is a growing problem.[76, 122] To further reduce false-positive alerts, investigators have also begun to integrate data from multiple sources, including pharmacy, laboratory, and demographic data.[123-124] Taking the false-positive rate into account is especially important when large-scale information systems are being developed, since as many as 30% of information system projects fail and a significantly larger number have cost overruns.[125]

The fact that many of the signals to detect ADEs have relatively low PPVs should not impede the adoption of clinical event monitors.[126] In many respects, the monitors can be treated as a type of screening test that allows for early ADE identification and intervention, and thereby reduces morbidity and mortality rates.[127] Indeed, the monitors have been shown to detect ADEs not normally detected by clinicians during the course of routine care, and to decrease the length of time until diagnosis and treatment.[57, 61, 128] Screening tests such as fecal occult blood testing to detect colorectal cancer are recommended despite having PPVs that range from 0.02 to 0.18 in adults over 50 years old, and are thus similar to the ranges of some signals described in our study.[129]

2.5.3   Recommendations for Future Work

Additional studies are needed to improve the performance characteristics of individual ADE signals and clinical decision support systems, apply these systems to other clinical environments,

develop interoperable systems, and perform economic analyses of these systems. Studies have suggested that ADE detection rates can be improved by combing multiple data sources and having a better understanding of the context of the data as they relate to patients' underlying medical conditions.[130-133] Investigators have begun to use clinical decision support systems to detect ADEs in other clinical care settings, such as ambulatory care clinics and nursing homes.[11, 31, 134-135] These systems may be particularly useful in the nursing home setting where patients are frail, have multiple comorbid medical conditions, and take more medications per patient than in any other clinical setting.[2, 11, 136] Since most systems lack standardized methods to export or share ADE algorithms, additional studies are required to develop interoperable systems.[137-138] Additional cost-benefit and cost-effectiveness studies are needed not only to determine the rational selection, optimal use, and potential success of systems used to detect ADEs, but also to determine the costs of developing and maintaining the systems and of responding to true-positive and false-positive alerts.

2.6   CONCLUSIONS

Our systematic review provides the PPVs of pharmacy and laboratory signals used to detect ADEs in the adult hospital setting, and suggests that the PPVs of individual signals vary widely. Our findings should help clinical information system and clinical decision support producers create and modify clinical decision support systems to detect ADEs in their own institutions. Future studies are needed to improve the performance characteristics of individual ADE signals and clinical decision support systems, apply these systems to other clinical environments, develop interoperable systems, and perform economic analyses of the systems.

30

3.0 CONSENSUS LIST OF SIGNALS TO DETECT POTENTIAL ADVERSE DRUG REACTIONS IN NURSING HOMES

3.1 ABSTRACT

3.1.1 OBJECTIVES

To develop a consensus list of agreed upon laboratory, pharmacy, and Minimum Data Set signals that can be used by a computer system in the nursing home to detect potential adverse drug reactions (ADRs).

3.1.2 DESIGN AND SETTING

Literature search for potential ADR signals, followed by an Internet-based, two-round, modified Delphi survey of experts in geriatrics.

3.1.3 PARTICIPANTS

Panel of 13 physicians, 10 pharmacists, and 13 advanced practitioners.

3.1.4   MEASUREMENTS

Mean score and 95% confidence interval (CI) for each of 80 signals rated on a 5-point Likert scale (5=strong agreement with likelihood of indicating potential ADRs). Consensus agreement indicated by a lower-limit 95% CI of ≥ 4.0.

3.1.5   RESULTS

Panelists reached consensus agreement on 40 signals: 15 laboratory/medication combinations, 12 medication concentrations, 10 antidotes, and 3 Resident Assessment Protocols (RAPs). Highest consensus scores (4.6; 95% CI, 4.4–4.9 or 4.4–4.8) were for naloxone when taking opioid analgesics; phytonadione when taking warfarin; dextrose, glucagon, or liquid glucose when taking hypoglycemic agents; medication-induced hypoglycemia; supratherapeutic international normalized ratio when taking warfarin; and triggering the Falls RAP when taking certain medications.

3.1.6   CONCLUSION

A multidisciplinary expert panel was able to reach consensus agreement on a list of signals to detect potential ADRs in nursing home residents. The results of this study can be used to prioritize an initial list of signals to be included in paper or computer-based methods for potential ADR detection.

3.2 INTRODUCTION

Adverse drug reactions (ADRs) are the most frequent medication-related adverse events in the nursing home setting, with an incidence ranging from 1.19 to 7.26 per 100 resident-months.[7] Other types of medication-related adverse events, include therapeutic failures and adverse drug withdrawal events. However, their precise incidence and impact have not been well characterized in the literature.[139] Data from the largest study on adverse drug reactions (ADRs) in nursing homes suggest that over half of the events are preventable, and that 70% are associated with monitoring errors.[10] Although comprehensive chart review is the primary ADR case-finding technique for research, and is considered by some to be the "gold standard,"[30] it is time-consuming, costly, and impractical for routine clinical use.[29] Therefore, alternative surveillance systems are needed in nursing homes to detect and minimize the potential consequences of ADRs.

ADRs can be detected by computerized clinical event monitors via the processing of laboratory test result signals and pharmacy order signals.[31, 55-56] Hospital studies indicate that these automated clinical decision-support systems, which provide feedback to healthcare professionals based on information available in electronic format, are less expensive and much faster to use than manual chart reviews, and can identify events not normally detected by clinicians during the course of routine care.[30, 57] More recently, computerized ADR detection has been examined in the ambulatory and nursing home settings using many of the same pharmacy and laboratory signals used by hospital-based systems.[11, 31, 140]

ADR signals from pharmacy order and laboratory test results in nursing homes are likely to differ from those used in the hospital setting. This is because the number and types of medications prescribed and the laboratory tests ordered for nursing home residents vary

considerably from those of hospitalized patients.[141] With the trend towards centralization of laboratory, pharmacy, and Minimum Data Set data, resident-specific information available in electronic format is becoming increasingly more available in nursing homes.[142] The purpose of this study was to develop a consensus list of laboratory, pharmacy, and Minimum Data Set signals that can be used by a computer system in the nursing home to detect potential ADRs.

3.3 METHODS

3.3.1 Literature Review and Identification of Initial Set of Signals

We conducted a comprehensive literature search to create a preliminary list of signals that can be used to detect potential ADRs in nursing homes. With the assistance of a medical librarian, we searched OVID MEDLINE, OVID CINHAL, and EMBASE for articles published in all languages between January 1, 1985, and July 1, 2006. In OVID, we searched for the following medical subject headings (MeSH) keywords, and text words: aged, adverse drug event, adverse drug reaction, adverse drug reaction reporting systems, clinical event monitor, clinical decisions support systems, clinical laboratory information systems, clinical pharmacy information system, computer generated signals, decision support system, drug monitoring, homes for the aged, medication errors, nursing homes, and physiologic monitoring. In EMBASE, we searched for the above terms, plus the following EMTREE keywords: computer assisted drug therapy and drug surveillance program. The first author (SMH) supplemented the computerized search by reviewing the reference lists from the identified articles, recent reviews, textbooks, and personal files.

A total of 29 publications were identified.[6-8,10-35] Two authors (SMH and JTH) reviewed these publications for relevance, compiled a preliminary list of signals, and placed each potential signal into one of four categories: 1) laboratory/medication combination signals (triggered by abnormal laboratory values when certain medications are present); 2) medication concentration signals (triggered by elevated, or supratherapeutic medication concentrations); 3) antidote signals (triggered by administration of medications given to counteract the effects of a medication with toxic effects); 4) Resident Assessment Protocol (RAP)[143] signals (triggered by responses to certain Minimum Data Set items, and taking of certain medications). The first author (SMH) used standard pharmacology textbooks[144-146] to provide specific examples of medications that may be associated with the firing of each of the signals (e.g., elevated creatinine caused by diuretics or hyperglycemia caused by prednisone) with the goal of clarifying the signals. Then other members of the clinical investigative team (JTH, DAN, DBF, and SAS) reviewed and further refined the list of signals.

The final list consisted of 35 laboratory/medication combination signals, 16 medication concentration signals, 20 antidote signals, and 9 RAP signals, for a total of 80 signals (Appendix A) to be included in the Delphi survey.

3.3.2 Selection of Study Methodology and Participants

Our study involved the use of an Internet-based, two-round, modified Delphi survey of experts in the field of nursing home care. The Delphi methodology is a structured group interaction process that is directed in "rounds" of opinion collection and feedback.[147] We selected the modified web-based Delphi consensus method because research suggests that accurate and reliable assessments can be achieved by consulting a panel of experts and subsequently accepting

the group consensus as the best estimate of the answer to a particular question.[148] The modified Delphi method is especially useful in studies that deal with medication safety in older adults.[149-152] The methodology used in this study differed from the Delphi process developed by the RAND Corporation that relies on face-to-face meetings to achieve consensus.[153] However, the modified method enables a group of experts to be contacted inexpensively and without geographic limitations. The rounds of the survey were completed confidentially, allowing each participant to present and react to ideas without being biased by knowing the identities of other participants.

We selected a multidisciplinary expert panel of members from three professions: physicians, pharmacists, and advanced practitioners (i.e., physician assistants or nurse practitioners). We chose these professions because they are all involved in the monitoring phase of the medication use process (i.e., assess resident response to medication and document outcomes).[154] After obtaining the names of potential participants from national geriatrics or nursing home organizations, we selected individuals based on their extensive clinical practice or large number of publications in the area of nursing home care. Our goal was to have a similar number of participants from each profession. Because we had encountered a low response rate from some groups in a previous study,[50] we invited a total of 57 health care professionals, including 23 physicians, 13 pharmacists, and 21 advanced practitioners to participate.

To improve the response rate and reduce the possibility of nonrespondent bias, we employed multiple methods, including university sponsorship, nominal monetary incentives ($75 upon completion of both rounds), and having respondents complete the rounds on the Internet.[155]

3.3.3   Administration and Analysis of the Survey

We contacted the experts through an e-mail invitation included with round 1. We asked them to complete each survey round within 2 weeks, and sent them a reminder e-mail if they did not do so. During each round, we provided participants with a list of signals, a list of medications that might be associated with the firing of each signal, and supporting references concerning the signals. We asked them to use a 5-point Likert scale to evaluate their agreement or disagreement with statements concerning the likelihood that each signal would be associated with a potential ADR in the nursing home setting. The scale ranged from 1, (indicating strong disagreement), to 5, (indicating strong agreement). For the purposes of the study, we operationally defined a nursing home as having custodial, skilled, and subacute levels of care. At the completion of round 1, we gave the participants the opportunity to modify existing signals or provide suggestions for additional signals to include in round 2. We determined in advance that we would include any new or modified signals that were suggested by 2 or more participants.

After round 1, we compiled the scores and computed a weighted mean score and 95% confidence interval (CI) for each signal. The weighting of individual ratings was designed to ensure that all three professions had equal influence, regardless of the number of participants in each profession. Based on work previously published by our group,[156-158] we examined the lower and upper limits of the 95% CIs, and then classified each signal into one of three categories: accepted signals, defined as those having a score with a lower-limit 95% CI of ≥4.0 (indicating consensus agreement); rejected signals, defined as those having a score with an upper-limit 95% CI of <3.0 (consensus disagreement); or equivocal, defined as those having a score with a lower-limit 95% CI between 3.0 and 3.9 (indicating the need for reevaluation).

In round 2, we did not include the signals that were already accepted or already rejected. We included only the equivocal signals from round 1. For each equivocal signal, we provided each participant with his or her round 1 individual score and with the round 1 weighted mean group score to aid in the consensus-building process.

After round 2, we repeated the processes of compiling scores and computing weighted scores and 95% CIs. Again, the weighting of individual ratings ensured that all three professions had equal influence. We again classified signals as accepted if they had a lower-limit 95% CI of ≥4.0 (indicating consensus agreement). We classified all other signals as rejected.

For all statistical analyses, we used SAS version 9 for Windows (SAS Institute, Inc., Cary, NC). The University of Pittsburgh Institutional Review Board approved the study as exempt; hence, informed consent was not needed for study participation. The external funding sources had no involvement in study design or collection, analysis, or interpretation of data, nor did they review or approve this manuscript.

3.4   RESULTS

3.4.1   Round 1

For round 1, the study included 13 physicians, 10 pharmacists, and 13 advanced practitioners, for an overall response rate of 63.2% (36/57). The response rate was 56.5% (13/23) for the invited physicians, 61.9% (13/21) for the invited advanced practitioners, and 76.9% (10/13) for the invited pharmacists. The majority of participants were female (66.7%), were affiliated with an

academic medical center (63.9%), and worked in the nursing home setting for a median of 5 years (100%).

At the end of round 1, of the 80 signals that were considered, 32 were accepted, 0 were rejected, and 48 were equivocal. The accepted signals were 13 laboratory/medication combination signals (Table 5), 6 medication concentration signals (Table 6), 10 antidote signals (Table 7), and 3 RAP signals (Table 8). There were no signals suggested by two or more panelists.

Table 5. Final Consensus List of Laboratory/Medication Combination Signals for Detecting Adverse Drug Reactions in the Nursing Home Setting.

Laboratory/Medication Combination Signals*	Mean Score	95% CI
Hypoglycemia (as indicated by a low or decreasing glucose concentration) is found in an individual taking a drug that may cause or worsen hypoglycemia	4.6	4.4–4.8
Supratherapeutic (above upper limit of normal range) international normalized ratio (INR) is found in an individual taking warfarin	4.6	4.4–4.8
Clostridium difficile toxin is found in an individual taking a drug that may cause pseudomembranous colitis	4.5	4.3–4.7
Hyperkalemia (as indicated by a high or increasing potassium concentration) is found in an individual taking a drug that may cause or worsen hyperkalemia	4.5	4.3–4.7
Hypokalemia (as indicated by a low or decreasing potassium concentration) is found in an individual taking a drug that may cause or worsen hypokalemia	4.5	4.3–4.7
Thrombocytopenia (as indicated by a low or decreasing platelet count) is found in an individual taking a drug that may cause or worsen thrombocytopenia	4.5	4.3–4.7
Supratherapeutic activated partial thromboplastin time (PTT) is found in an individual taking heparin	4.4	4.2–4.7
Subtherapeutic concentration (below lower limit of normal range) of	4.4	4.2–4.6

thyroid-stimulating hormone (TSH) or elevated concentration of thyroxine (T4) is found in an individual taking a drug that may cause hyperthyroidism

Hyponatremia (as indicated by a low or decreasing sodium concentration) is found in an individual taking a drug that may cause or worsen hyponatremia	4.4	4.2–4.5
Leukopenia (as indicated by a low or decreasing white blood cell count) is found in an individual taking a drug that may cause or worsen leukopenia	4.3	4.1–4.6
Elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) concentration is found in an individual taking a drug that may cause hepatocellular toxicity	4.3	4.1–4.5
Elevated creatinine or blood urea nitrogen (BUN) concentration is found in an individual taking a drug that may increase creatinine or BUN	4.3	4.1–4.5
Supratherapeutic concentration of TSH or decreased concentration of T4 is found in an individual taking a drug that may cause hypothyroidism†	4.3	4.1–4.4
Agranulocytosis or neutropenia (as indicated by a low or decreasing neutrophil count) is found in an individual taking a drug that may cause or worsen agranulocytosis or neutropenia†	4.2	4.1–4.3
Elevated creatine phosphokinase (CPK) concentration is found in an individual taking a drug that may increase CPK	4.2	4.0–4.4

*Panel members rated each item on a 5-point Likert scale, with 5 indicating strong agreement with the likelihood that the item signaled an adverse drug reaction. The mean likelihood score and 95% confidence interval (CI) were calculated for each item. Panel consensus was indicated by a lower-limit 95% CI of ≥4.0.

†Panel consensus was not reached until round 2 of the Delphi survey.

Table 6. Final Consensus List of Medication Concentration Signals for Detecting Adverse Drug Reactions in the Nursing Home Setting.

Medication Concentration Signals*	Mean Score	95% CI
Aminoglycoside peak or trough concentration is supratherapeutic in an individual taking an aminoglycoside antibiotic (e.g., amikacin, gentamicin, or tobramycin)	4.4	4.2–4.7
Phenytoin concentration is supratherapeutic in an individual taking phenytoin	4.4	4.1–4.7
Lithium concentration is supratherapeutic in an individual taking lithium†	4.3	4.1–4.5
Theophylline trough concentration is supratherapeutic in an individual taking theophylline	4.3	4.0–4.7
Digoxin concentration is supratherapeutic in an individual taking digoxin	4.3	4.0–4.6
Procainamide concentration or N-acetylprocainamide (NAPA)concentration is supratherapeutic in an individual taking procainamide	4.3	4.0–4.6
Primidone (Mysoline) concentration or phenobarbital concentration is supratherapeutic in an individual taking primidone	4.3	4.0–4.5
Quinidine concentration is supratherapeutic in an individual taking quinidine†	4.2	4.1–4.4
Valproic acid concentration is supratherapeutic in an individual taking	4.2	4.1–

valproic acid†		4.4
Phenobarbital concentration is supratherapeutic in an individual taking phenobarbital†	4.2	4.0–4.5
Carbamazepine concentration is supratherapeutic in an individual taking carbamazepine†	4.2	4.0–4.4
Disopyramide (Norpace) concentration is supratherapeutic in an individual taking disopyramide†	4.2	4.0–4.4

*Panel members rated each item on a 5-point Likert scale, with 5 indicating strong agreement with the likelihood that the item signaled an adverse drug reaction. The mean likelihood score and 95% confidence interval (CI) were calculated for each item. Panel consensus was indicated by a lower-limit 95% CI of ≥4.0.

†Panel consensus was not reached until round 2 of the Delphi survey.

Table 7. Final Consensus List of Antidote Signals for Detecting Adverse Drug Reactions in the Nursing Home Setting.

Antidote Signals*	Mean Score	95% CI
Naloxone (Narcan) is given to an individual taking an opioid analgesic	4.6	4.4–4.9
Phytonadione (vitamin K) in oral, subcutaneous, or intravenous form is given to an individual taking warfarin	4.6	4.4–4.9
Dextrose 50%, glucagon, or liquid glucose is given to an individual taking a drug that may cause hypoglycemia	4.6	4.4–4.8
Protamine sulfate is given to an individual taking heparin	4.5	4.3–4.8
Digoxin immune Fab (Digibind) is given to an individual with a supratherapeutic digoxin concentration	4.5	4.2–4.8
Epinephrine is given to an individual taking a drug that may cause an anaphylactic reaction	4.4	4.1–4.8
Metronidazole (oral) or vancomycin (oral) is given to an individual who has recently taken a drug that may cause pseudomembranous colitis	4.4	4.1–4.7
Benztropine (Cogentin), diphenhydramine, or trihexyphenidyl (Artane) is given to an individual taking a drug that may cause extrapyramidal symptoms	4.4	4.1–4.6
Lepirudin (Refludan) is given to an individual taking a drug that may cause heparin-induced thrombocytopenia	4.4	4.1–4.6
Sodium polystyrene (Kayexalate) is given to an individual taking a drug that may cause hyperkalemia	4.3	4.0–4.6

*Panel members rated each item on a 5-point Likert scale, with 5 indicating strong agreement with the likelihood that the item signaled an adverse drug reaction. The mean likelihood score and 95% confidence interval (CI) were calculated for each item. Panel consensus was indicated by a lower-limit 95% CI of≥4.0. For all items shown, panel consensus was reached during round 1 of the Delphi survey.

Table 8. Final Consensus List of Resident Assessment Protocol (RAP) Signals for Detecting Adverse Drug Reactions in the Nursing Home Setting.

RAP Signals*	Mean Score	95% CI
Falls RAP is triggered in an individual taking a drug that may cause or worsen falls (falls with or without injury)	4.6	4.4–4.8
Delirium RAP is triggered in an individual taking a drug that may cause or worsen delirium (periodic disordered thinking or awareness)	4.5	4.3–4.7
Dehydration/Fluid Maintenance RAP is triggered in an individual taking a drug that may cause or worsen dehydration (fluid loss exceeding the amount of fluid intake)	4.4	4.2–4.6

*Panel members rated each item on a 5-point Likert scale, with 5 indicating strong agreement with the likelihood that the item signaled an adverse drug reaction. The mean likelihood score and 95% confidence interval (CI) were calculated for each item. Panel consensus was indicated by a lower-limit 95% CI of≥4.0. For all items shown, panel consensus was reached during round 1 of the Delphi survey.

3.4.2 Round 2

For round 2, the study included 11 of the 13 physicians, all 10 of the pharmacists, and all 13 of the advanced practitioners. The overall response rate for round 2 was 94.4% (34/36). At the end of round 2, of the 48 signals that were reconsidered because of their earlier equivocal classification, 8 were accepted. The accepted signals were 2 laboratory/medication combination signals (Table 5) and 6 medication concentration signals (Table 6).

Overall, 15 of 35 (42.9%) of the laboratory/medication combination signals, 12 of 16 (75%) of the medication concentration signals, 10 of 20 (50%) of the antidote signals, and 3 of 9 (33.3%) of the RAP signals reached consensus and were accepted.

The highest consensus scores (4.6; 95% CI, 4.4–4.9 or 4.4–4.8) were for naloxone when taking opioid analgesics; phytonadione (Vitamin K) when taking warfarin; dextrose, glucagon, or liquid glucose when taking hypoglycemic agents; medication-induced hypoglycemia; supratherapeutic international normalized ratio when taking warfarin; and triggering the Falls RAP when taking certain medications.

3.5   DISCUSSION

A multidisciplinary expert panel of nursing home physicians, pharmacists, and advanced practitioners were able to reach consensus agreement on a list of 40 signals that can be used by a computer system to detect potential ADRs in the nursing home setting. Laboratory/medication combinations accounted for over one-third of all signals that reached consensus. Of the 15 laboratory/medication combination signals that the panelists agreed were appropriate for the nursing home setting, 8 were not reported in the 2005 study of Gurwitz et al.,[11] which to our knowledge is the only published study concerning a clinical event monitor to detect potential ADRs in nursing homes. These 8 additional signals were drug-induced episodes of the following: hypoglycemia, hyponatremia, leukopenia, agranulocytosis/neutropenia, a supratherapeutic activated partial thromboplastin time, a supratherapeutic thyroid stimulating hormone concentration, an elevated creatinine or blood urea nitrogen concentration, and an elevated creatine phosphokinase concentration.

The next most common signal category reaching consensus was medication concentrations. The goal of therapeutic medication monitoring is to guide dosing by means of drug concentration measurements. This is particularly useful in cases in which the range between the dose necessary to achieve beneficial effects and the dose causing ADRs is narrow, and when the medication concentration is not readily predictable from the dose prescribed. Moreover, serum medication concentrations are likely to be most useful when used to help confirm or refute a resident's signs or symptoms suggestive of toxicity or lack of efficacy. When the panelists were asked to consider 16 medication concentration signals, they achieved consensus on 12 (75%), and it is not surprising that these were for drugs with narrow therapeutic ranges.

A recent study by Raebel et al.,[25] suggests that monitoring narrow therapeutic range drugs is not being done routinely, with as many as 50% of older adults not receiving drug concentration monitoring during 1 year of use. To reduce the potential for ADRs in the nursing home setting, the Center for Medicare and Medicaid Services (CMS) recommends routine periodic medication monitoring for most narrow therapeutic range drugs listed in their F329 guidelines (the deficiency citation for unnecessary drugs).[159] This CMS recommendation extends to all residents, regardless of whether they are exhibiting signs or symptoms suggestive of toxicity or lack of efficacy. It is important to note however that if a medication concentration comes back elevated when ordered for diagnostic purposes, the likelihood of a potential ADR is significantly higher then if it was being ordered on a routine basis. The rationale for this is that the prior odds of a potential ADR are significantly increased because the underlying assumption is that the resident is already receiving the medication of interest, and the prescribing clinician is aware of the possibility of an ADR.[113] Of note, our panelists reached consensus on 3 narrow

therapeutic range drugs not mentioned in the F329 guidelines—namely, concentrations of Class Ia antiarrhythmics including: procainamide, disopyramide, and quinidine.

Antidote signals accounted for one-quarter of the final 40 signals. Four of the 10 antidote signals had not been reported in the study of Gurwitz et al.,[11] and these were the administration of epinephrine, digoxin immune Fab, lepirudin, or a medication with anticholinergic properties to treat extrapyramidal symptoms. Four of the 10 antidote signals that had been reported by Gurwitz et al.[11] did not reach consensus in our study, and these were the administration of an antihistamine, an oral or topical steroid, or topical nystatin and the administration of a hypoglycemic agent to an individual taking glucocorticoids. It is important to note, that in a recent systematic review of the signals used by hospital-based clinical event monitors to detect potential ADRs, the antidote signal category had the lowest overall positive predictive values.[60] The authors of this review concluded that the performance characteristics of this signal category was lowest because antidotes can be used to treat multiple medical conditions, only a fraction of which are related to the presence of an ADR.

Unique to this study was that consensus was reached on 3 RAP signals. Studies in the nursing home setting are currently evaluating the effectiveness of computerized decision support systems on 2 of the RAP signals on which our panelists reached consensus—namely, the Falls RAP and the Delirium RAP.[160] This reflects that the evidence for certain medications being associated with these specific geriatric syndromes is generally well accepted.[161-162] Participants also reached consensus that the Dehydration/Fluid Maintenance RAP be used as a signal to detect potential ADRs for individuals taking certain medications.

3.5.1 Strengths and Limitations

Our study had several strengths. First, we chose to include a multidisciplinary panel of physician, pharmacist, and advanced practitioner experts to determine which signals can be used to detect potential ADRs. Our methodology ensured that all clinicians involved in the monitoring phase of the medication use process in the nursing home setting were included, and that their responses were weighted to ensure that each profession had an equal influence on the results. Second, to improve the survey response rate and reduce the possibility of nonrespondent bias, we employed multiple methods, including university sponsorship, monetary incentives, providing the survey on the Internet, and the distributing reminders to participants.[155] The overall initial and second round response rates in our study exceeded the minimally acceptable mean response rate of 60% for mail surveys reported in the medical literature.[163]

Our study had several potential limitations. First, we used a convenience sample of physician, pharmacist, and advanced practitioner experts to participate in the Delphi survey. As a result, the majority of respondents were affiliated with an academic institution. Using a random sampling technique may have strengthened the study by increasing the generalizability to the universe of clinical practitioners. Second, we did not hold face-to-face meetings of the panelists, a practice that is sometimes done with Delphi surveys.[148, 153, 164] Bringing the panelists together allows individual respondents to incorporate the perspectives of others, and may have resulted in further refinement of the signals while facilitating the consensus process. However, in person meetings might have limited the broad geographic representation we were able to achieve with the use of the Internet. In addition, by offering two rounds in the survey, respondents did benefit from seeing the opinions of others. Third, we did not provide 95% confidence intervals for equivocal signals to panelists during the second round. Information on

51

the distribution of responses may have been useful to the panelists in order to achieve consensus. Fourth, the panelists reached consensus on 40 signals at this time. As new research contributes more information about medication safety, the list of signals will need to be modified and may expand.

3.5.2   Implications and Further Research

The Institute of Medicine recommends that all health care facilities continuously assess medication safety through the development and evaluation of various types of data-driven triggers for detecting ADRs. This assessment should occur during routine monitoring, and for diagnostic confirmation of signs or symptoms suggestive of toxicity or lack of efficacy.[23, 41] Clinical event monitors can address this recommendation by integrating various sources of information for the purpose of ADR detection. All nursing homes are currently capable of transmitting Minimum Data Set information electronically, and the use of computerized laboratory and medication records is likely to increase significantly over the coming years.[73] These monitors are feasible given knowledge of the data structure of the information resources and certain programming capacity. In nursing homes with appropriate health information technology infrastructure, the results of our study can be used to create or modify clinical event monitor systems to automate the detection of potential ADRs.

In nursing homes without appropriate infrastructure, the results can be used to prioritize the signals to be included in a paper-based trigger tool. The trigger tool methodology, developed in part by the Institute of Healthcare Improvement, greatly simplifies the chart review process by allowing rapid and systematic examination of charts to extract relevant data. Trigger tools have been successfully used to demonstrate the benefits of low-cost error detection strategies focused

on high-risk medications in a variety of clinical settings.[165-166] Regardless of whether computer or paper-based methods for detecting potential ADRs are used, a more detailed assessment of the resident would be required to determine if an actual ADR is present.

Further research is needed in several areas. Formal research is needed to determine the incidence and the positive predictive values of individual signals in nursing homes with different levels of care (e.g., custodial, skilled, and subacute care). Future studies are also needed to improve the performance characteristics of antidote signals, which can possibly be enhanced by linking the use of these medications to changes in drug therapy or interventions that occurred prior to their use. These data will help nursing homes further prioritize the signals to be included in their computerized or paper-based trigger tools, and will thereby help them maximize the detection of potential ADRs, and minimize the number of false-positive alerts. Studies should also be conducted to determine if certain errors of omission, including the failure to monitor narrow therapeutic index medications or conduct laboratory studies while prescribing certain medications, may lead to an increase in potential ADRs in the nursing home setting. Research is also needed to determine if ADR detection rates can be improved by combining multiple data sources (e.g., laboratory, pharmacy, and health care records) to gain a better understanding of the context of the data as they relate to residents' underlying medical conditions.[130-131, 167]

3.6   CONCLUSION

A multidisciplinary expert panel was able to reach consensus agreement on a defined list of signals of potential ADRs in nursing home residents. This is a necessary initial step toward detecting and reducing the future occurrence and impact of ADRs in the nursing home setting.

The results of this study can be used to prioritize an initial list of signals to be included in paper or computer-based method for potential ADR detection.

4.0 ASSESSING THE PERFORMANCE CHARACTERISTICS OF SIGNALS USED BY A CLINICAL EVENT MONITOR TO DETECT ADVERSE DRUG REACTIONS IN THE NURSING HOME

4.1 ABSTRACT

4.1.1 Objective

Adverse drug reactions (ADRs) are a common cause of morbidity and mortality in the nursing home (NH) setting. Traditional non-automated mechanisms for ADR detection are time-consuming, costly, and fail to detect the majority of ADRs. The objective of this study was to determine the incidence and positive predictive values of signals specifically designed for use by a clinical event monitor to detect ADRs in the NH setting.

4.1.2 Design

Case-series.

4.1.3 Measurement/Methods

All patients, except those enrolled in hospice, were included in the 15-week study period (October 1, 2007 to January 13, 2008) and who had one of 37 signals present were evaluated. Alerts were assessed using the Naranjo causality algorithm. Positive predictive values (PPVs) were calculated as the proportion of alerts that occurred, divided by the number of times that alerts occurred and ADRs were confirmed.

4.1.4 Results

The overall PPV for all signals combined was 81% (54/67), with individual signal PPVs ranging from 0-100%. The PPVs were 53% (10/19) for the antidote signals category and 96% (44/46) for the laboratory/ medication combination signals category. The majority 75% (12/16) of the preventable ADRs were laboratory/medication combination signals.

4.1.5 Conclusion

The results suggest that ADRs can be detected in the NH setting with a high degree of accuracy using a clinical event monitor that employs a set of signals derived by expert consensus.

4.2   INTRODUCTION

The most frequent medication-related adverse events in nursing homes in the United States are adverse drug reactions (ADRs).[7]   ADRs are defined by the World Health Organization as

unintended or noxious responses to a drug given in a dosage intended for prophylaxis, diagnosis, or therapy.[5] In the nursing home (NH) setting, the incidence of ADRs ranges from 1.19 to 7.26 per 100 patient-months. Although comprehensive chart review is the primary ADR case-finding technique for research, and is considered by some to be the "gold standard," it is time-consuming, costly, and impractical for routine clinical use.[30] Therefore, a critical need exists for the development of alternative strategies to detect ADRs in NHs.

ADRs can be detected by computerized clinical event monitors through the processing of pharmacy order signals and laboratory test result signals. Hospital studies indicate that these automated clinical decision support systems, which provide feedback to healthcare professionals based on information available in electronic format, are less expensive and much faster to use than manual chart reviews, and can identify events not often detected by clinicians during the course of routine care.[30] However, there is increasing concern about the false-positive alerts (i.e., alert fatigue) generated by hospital-based clinical event monitors which have been in use for over two decades, and have been described in more detail in a recent systematic review.[60]

More recently, computerized ADR detection has been examined in the ambulatory and NH settings using largely the same pharmacy and laboratory signals used by hospital-based systems.[11, 31] The objective of this study was to determine the incidence and positive predictive values of signals specifically designed for use by a clinical event monitor to detect ADRs in the NH setting.

4.3 METHODS

4.3.1 Setting and Subjects

The project was conducted in a single, independently owned, non-profit NH affiliated with the University of Pittsburgh Medical Center. The facility is located in a suburban setting, with 178 licensed beds. Prescribers were primarily community physicians and advanced practitioners (i.e., nurse practitioners and physician assistants). All patients, except those enrolled in hospice, were included in the 15-week study period (October 1, 2007 to January 13, 2008). The study protocol was reviewed and determined to be a quality improvement project by the University of Pittsburgh Institutional Review Board (IRB). The University of Pittsburgh Medical Center Total Quality Council approved this study as a quality improvement project. No additional IRB approval was required prior to publication.

4.3.2 Source of Patient Data

The Medical Archival System (MARS) data repository has been collecting and archiving clinical and financial records from all University of Pittsburgh Medical Center hospitals since 1986.[168] In order to collect relevant nursing-home specific patient data in electronic format, we developed a new data repository, called MARS-LTC. MARS-LTC contains long-term care (e.g., NH) specific patient data that are stored as they are generated. Current real-time data feeds exist for laboratory data (Quest Diagnostics), pharmacy data (Rx Partners-LTC), and census and Minimum Data Set data (Achieve Healthcare Technologies).

4.3.3 Clinical Event Monitor Description

MARS-AiDE is a rule-based expert system that consists of a knowledgebase of signals that are applied by a rule engine to patient data contained within MARS-LTC. An overview of the MARS-AiDE clinical event monitor is shown in the Figure 3 below.
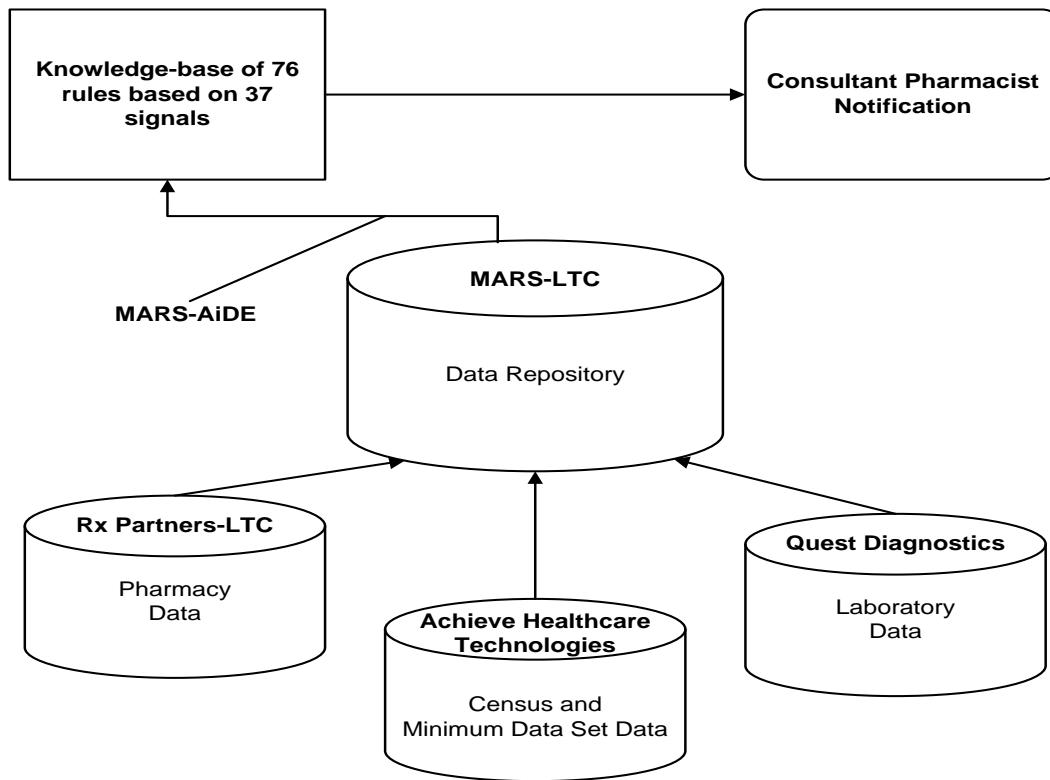
Figure 3. Overview of MARS-AiDE clinical event monitor for detecting adverse drug reactions.

We identified all active NH patients in the census database in MARS-LTC. Using the medical record number from the census, a list of active medications was generated. For certain rules, this information was then compared against current laboratory information. This process generated a list of alerts that fulfills the conditions of one or more of the signals, suggesting a potential ADR.

4.3.4 Signals Used by the Clinical Event Monitor

A detailed description of the development and selection of the knowledgebase of signals to detect potential ADRs in the NH is reported elsewhere.[78] Briefly, a multidisciplinary expert panel of NH physicians, pharmacists, and advanced practitioners reached consensus agreement on a list of 40 signals that a clinical event monitor can use to detect potential ADRs in the NH setting.

In this manuscript, we present the findings associated with 37 of the 40 signals categorized into one of the following three groups: 1) 15 laboratory/medication combination signals (triggered by abnormal laboratory values when certain medications are present); 2) 12 medication concentration signals (triggered by elevated, or supratherapeutic medication concentrations); and, 3) 10 antidote signals (triggered by administration of medications given to counteract the effects of a medication with toxic effects). The 3 Resident Assessment Protocol signals (triggered by responses to certain Minimum Data Set items, and taking of certain medications) will be presented in a subsequent publication.

For each of the 37 signals, we created additional rules to try and improve specificity. This resulted in a total of 24 laboratory/medication combination rules, 32 medication concentration rules, and 20 antidote rules. For example, the elevated creatinine or blood urea nitrogen concentration signal was operationalized into the following 3 rules: absolute increase ≥ 0.25 mg/dL in baseline serum creatinine, relative increase $> 25\%$ in baseline serum creatinine, and absolute increase ≥ 10 mg/dL in baseline blood urea nitrogen.

4.3.5 Knowledge Engineering/Development

For each of the 15 laboratory/medication combination signals, the first author (SMH) used standard pharmacy reference textbooks to create an initial list of medications that were reported to be associated with a particular laboratory abnormality. A drug information specialist (AHK) expanded the initial list of medications by using additional online references. The drug information specialist then conducted a comprehensive primary literature search using OVID, MEDLINE, and PUBMED for articles published in the English language between January 1, 1975, and July 1, 2007, using various MeSH terms and limiting the search to adults.

Based on the results of the primary literature search, additional medications were added if the evidence supporting the association between the medication and laboratory test of interest was derived from case reports or study designs with stronger empirical evidence (e.g., case series, cohort studies, case-control, cohort studies with controls, etc.). Similarly, medications were removed from the initial list if evidence was not sufficient to support the association between the medication and laboratory test of interest. Any discrepancies in the data regarding the association between the medication and laboratory test of interest were resolved by discussion between two study investigators (SMH and JTH).

4.3.6 Clinician Notification

Similar to other clinical event monitors, the rules within MARS-AiDE are used to define computer-detectable events that potentially indicate an ADR. The MARS-AiDE system is designed as a screening tool. Its signals and associated rules have been chosen to be sensitive, but not specific. When the conditions specified by a rule are met, the MARS-AiDE system

issues an alert to be acted upon by a consultant pharmacist (a pharmacist who is mandated by United States Federal law to review and manage the medication regimens of NH patients).

On a weekly basis during the study period, a consultant pharmacist received a list of patients by email that contained alerts detailing the possible ADRs during the previous 7 days. Each alert showed the patient's location, medical record number, attending physician, the rule that was triggered, and the date and time of the firing. Each alert also included extensive medication information, including the name, strength, frequency, route of administration, start and stop date, and if the medication was a standing or an as-needed (PRN) medication. If the alert was triggered by laboratory data, then each record also included the normal laboratory reference range, the most recent value, and the baseline value and corresponding dates (when available) (Figure 4).

100024 Firing date: 08/21/2007
Patient: Jane Smith ID: 0123456 Location: XYZ NH Physician: 1053349480 John Smith
Signal: (signal lab_med 15d) Elevated BUN (absolute increase of >= 10.0 mg/dl over
 baseline (within past 90 days) and on drugs that may increase BUN/creatinine
 * Baseline lab: (lab 751) UREANQ = 8.0 done on 06/05/2007
 * Current lab: (lab 752) UREANQ = 28.0 done on 08/21/2007
 * (pharm 1913) HYDROCHLOROTHIAZIDE TABS 25MG TAKE 1 TABLET BY MOUTH DAILY
 from 03/16/2007 to 08/22/2007

Figure 4. Sample MARS-AiDE alert.

4.3.7 Adverse Drug Reaction Assessments

For each potential ADR alert, the consultant pharmacist used a structured implicit review process according to the following criteria: whether an ADR was present, if the ADR was preventable, and the seriousness of the ADR.

We used the Naranjo causality algorithm[169] to determine the likelihood of whether an ADR was actually due to the drug identified by the clinical event monitor, rather than the result of other factors. The Naranjo algorithm is used to compute a weighted score based on answers to a short standardized questionnaire that correlates with causality probability (Appendix B). Similar to other clinical event monitor studies, computer alert signals with a score of ≥ 1 on the Naranjo scale, indicating a possible ADR, were classified as a true positives.[104]

ADRs were considered preventable if they were associated with a medication error. We used the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) definition of medication errors [170], defined as any event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Medication errors were further characterized by the step(s) in the medication use process where the error may have occurred, including: prescribing, order communication, dispensing, administering, and monitoring. ADRs were considered serious if they resulted in a transfer to a higher level of care (e.g., emergency department evaluation or hospitalization) or death.

After an extensive training period, between-pharmacist-investigator reliability for identifying and classifying ADRs was assessed through independent review of the same 10 medical records by the consultant pharmacist (SBS) and two study investigators (SMH and JTH). All three identified and classified the incidents the same way. To assure that the ADR assessments were applied consistently, a senior investigator (JTH) verified the accuracy for every tenth patient evaluated.

4.3.8 Calculation of Performance Characteristics

For counting purposes, multiple firings on the same day, for the same patient, for the same rule were counted as a single alert. Specifically, multiple firings triggered by a single drug administration (e.g., multiple administrations of sodium polystyrene for hyperkalemia) were treated as a single alert. Similarly, if multiple drugs generated multiple alerts (e.g., furosemide and lisinopril are being administered in the presence of increasing creatinine), they were treated as a single alert. When more than one drug was associated with a single potential ADR at a given time, the drug-event pair with the highest Naranjo was retained and used for all calculations.

To calculate a positive predictive value (PPV) for each signal, we divided the number of times that an alert was issued with respect to a particular rule and an ADR was confirmed (i.e., the number of true-positives), by the number of times the alert issued with or without an ADR being confirmed (i.e., the sum of true-positives and false-positives). Simple descriptive statistics were used to summarize ADR preventability and seriousness.

4.4   RESULTS

During the 15-week study period, there were a total of 274 unique patients that met inclusion criteria. The clinical event monitor processed 5,729 medication orders, generating 67 alerts, an average of 4.8 per week. The overall PPV for all signals combined was 81% (54/67). Individual signal PPVs ranged from 0-100% (Table 9). The PPVs were 53% (10/19) for the antidote signals category and 96% (44/46) for the laboratory/medication combination signals category.

Alerts were generated for 50% (5/10) of the antidote signals and 73% (11/15) of the laboratory/medication combination signals. There were no medication concentration signal firings.

Of the true positive firings, 30% (16/54) were considered preventable ADRs. The majority (75% or 12/16) of the preventable ADRs were laboratory/medication combination signals. Of the preventable ADRs, 88% (14/16) occurred at the monitoring and 69% (11/16) at the prescribing stage of the medication use process. Overall, 6% (3/54) of the confirmed ADRs were considered serious, requiring emergency department evaluation, or hospitalization. All ADRs that were rated as serious were also considered preventable.

Table 9. Positive Predictive Values (PPV) of Signals to Detect Potential Adverse Drug Reactions.

Antidote Signals	# of Alerts	# of ADRs	PPV (%)
Anticholinergic medication is given to a patient taking a drug that may cause extrapyramidal side effects	3	0	0
Dextrose 50%, glucagon, or liquid glucose is given to a patient taking a drug that may cause hypoglycemia	2	1	50
Metronidazole or vancomycin is given to a patient who has recently taken a drug that may cause pseudomembranous colitis	10	4	40
Sodium polystyrene is given to a patient taking a drug that may cause hyperkalemia	2	1	50
Vitamin K is given to a patient taking warfarin	4	4	100
Laboratory/Medication Signals			
Clostridium difficile toxin positive and taking a drug that may cause pseudomembranous colitis	2	2	100
Elevated alanine aminotransferase concentration and taking a drug that may cause or worsen hepatocellular toxicity	5	5	100
Elevated aspartate aminotransferase concentration and taking a drug that may cause or worsen hepatocellular toxicity	8	8	100
Elevated blood urea nitrogen ($\geq$ 10mg/dL of baseline)	4	4	100

and taking a drug that may increase blood urea nitrogen			
Elevated creatinine ($\geq$ 0.25mg/dL) and taking a drug that may increase creatinine	4	4	100
Elevated creatinine (> 25% of baseline) and taking a drug that may increase creatinine	4	4	100
Hyperkalemia and taking a drug that may cause or worsen hyperkalemia	2	2	100
Hypoglycemia and taking a drug that may cause or worsen hypoglycemia	2	2	100
Hypokalemia and taking a drug that may cause or worsen hypokalemia	1	1	100
Hyponatremia and taking a drug that may cause or worsen hyponatremia	6	5	83
Leukopenia and taking a drug that may cause or worsen leukopenia	2	2	100
Supratherapeutic international normalized ratio and taking warfarin	3	3	100
Thrombocytopenia and taking a drug that may cause or worsen thrombocytopenia	2	2	100
Supratherapeutic thyroid stimulating hormone and taking a drug that may cause or worsen hypothyroidism	1	0	0

4.5   DISCUSSION

Our results suggest that ADRs can be detected using a clinical event monitor in the NH setting with a high degree of accuracy. The overall PPV of 81% is substantially higher than PPVs previously reported in the literature, which range from 3-50%.[60] It is possible that our clinical event monitor performed better than previously described systems because: 1) we developed a list of consensus signals to detect potential ADRs by experts in geriatrics, rather than using existing hospital-based signals; 2) we simultaneously combined multiple data sources in order to enhance ADR detection; and, 3) we employed a standardized knowledge engineering process for the laboratory/medication combination signals category.

Similar to previous studies, signals associated with laboratory test results performed better than antidote signals.[60] The antidote signals category may not have performed as well because these medications can be used to treat multiple medical conditions, only a fraction of which are related to the presence of an ADR. Having a better understanding of the context of the data as they relate to patients' underlying medical conditions may help to improve this signal category's performance. It is also important to note that during the course of our study, no signals from the medication concentration category fired. This is not entirely surprising since previous research suggests that a substantial proportion of older adults do not receive appropriate laboratory monitoring while being prescribed chronic medications.[25]

Our results suggest that about one-third of the ADRs were preventable, and that of the preventable ADRs, 88% were associated with errors in the monitoring stage of the medication use process. This differs slightly from the only other study that used a clinical event monitor to

detect ADRs in the NH setting, where 42% were judged preventable and 80% occurred at the monitoring stage.[11]

4.5.1   Implications

Developing a clinical decision support system that has a relatively low false-positive rate is particularly important in order to reduce alert fatigue. Furthermore, having a system that produces an average of less than 5 alerts per week could allow for the routine inclusion of ADR assessments as part of the monthly medication regimen review process conducted by consultant pharmacists on all NH patients in the United States.

4.5.2   Future Direction

Further research needs to be conducted to do the following: 1) determine the incidence and PPVs of the 3 Resident Assessment Protocol signals selected by expert consensus; 2) validate the findings of this study for a longer period of time in NHs with differing resident or facility characteristics; and, 3) describe the epidemiology and patient characteristics associated with ADRs detected by our clinical event monitor. The results of this study are being used by our health-system to select appropriate signals to develop a clinical event monitor system that can maximize the detection and possible prevention of potential ADRs, while minimizing the number of false-positive alerts.

4.6   CONCLUSION

The results suggest that ADRs can be detected in the NH setting with a high degree of accuracy

using a clinical event monitor that employs a set of signals derived by expert consensus.

5.0   SUMMARY OF STUDY FINDINGS

In the first paper, we identified the importance of using PPVs in performing accurate assessments of individual signals used to automate the detection of ADEs in the hospital setting. Based on this experience, we were also able to hypothesize why the performance characteristics were generally poor, and think of simple solutions for potentially improving them. Finally, we recognized that the signals used in hospital-based active medication monitoring systems are likely to be different from those used in other clinical environments such as the NH setting. Consequently, a new set of setting-specific signals were needed.

In the second paper, we used the list of signals in the hospital setting as a starting point, but then conducted a comprehensive literature search to create a preliminary list of signals that can be used to detect potential ADRs in nursing homes. We then queried a panel of experts in geriatrics to complete an Internet-based, two-round, modified Delphi survey to develop a consensus list of laboratory, pharmacy, and Minimum Data Set signals that an active medication monitoring system can use to detect potential ADRs in the NH setting. Panelists reached consensus agreement on 40 signals, including several signals that have never been used in any previous system to detect ADRs.

In the third paper, we described the implementation and pharmacist evaluation of a clinical event monitor using signals previously developed by a panel of experts in geriatrics. The results suggest that ADRs can be detected in the NH setting with a high degree of accuracy using

a clinical event monitor that employs a set of signals derived by expert consensus. The overall positive predictive value for all signals combined was 81%, representing the highest overall value ever reported in the literature.

5.1   SIGNIFICANCE OF STUDY FINDINGS

ADEs among NH patients are common and costly problems that are likely to increase substantially due to the aging U.S. population, and the increasing need for NH services. A lack of easily identifiable patient-specific risk factors makes it difficult to routinely detect these events. Systems analyses of ADEs suggest that suboptimal medication monitoring is the most common factor underlying these events in the NH. Current strategies that rely on voluntary reporting, such as incident reports, direct observation of medication passes, and retrospective chart review are time-consuming, costly, and impractical for routine clinical use. Several prominent quality improvement organizations recommend active medication monitoring systems as a potential solution to improving medication safety. Active medication monitoring systems are particularly needed to detect ADEs in priority populations such as institutionalized elderly because of the long-standing concern about the quality of their pharmaceutical care. The compilation of the three projects presented in this dissertation are the initial steps and first reported accounts of the development and testing of an active medication monitoring system for use in the NH setting.

5.2   FUTURE RESEARCH DIRECTION AND IMPLICATIONS

Preliminary data collected by our group demonstrates that ADRs can be detected in the NH setting with a high degree of accuracy using an active medication monitoring system that employs a set of signals derived by expert consensus. However, research conducted using a more rigorous study design, over a longer duration of time, and in a larger number of NHs is necessary before recommendations can be made about how the results of our study may affect clinical practice or have policy implications. From a clinical perspective, if the active medication monitoring system is shown to be effective, it can help physicians detect and respond to ADEs more frequently and quickly when compared to usual care. More widespread implementation of the system has great potential to reduce impairment of functional and cognitive status, morbidity, mortality, and health services utilization for institutionalized elderly. From a policy perspective, if shown to result in cost-savings, our results can be used to inform CMS and other large healthcare systems (e.g., the VA) to institute pharmacy regulations in the U.S. that promote the more widespread use of such active medication monitoring systems.

APPENDIX A

INITIAL LIST OF 80 POTENTIAL SIGNALS FOR ADVERSE DRUG REACTIONS IN THE NURSING HOME SETTING, BASED ON A COMPREHENSIVE LITERATURE SEARCH AND CLINICAL INVESTIGATIVE REVIEW

Medication/Laboratory Combinations

Agranulocytosis or neutropenia (as indicated by a low or decreasing neutrophil count) is found in an individual taking a drug that may cause or worsen agranulocytosis or neutropenia (e.g., ticlopidine)

Anemia (as indicated by a low or decreasing hemoglobin or hematocrit concentration) is found in an individual taking a drug that may cause or worsen anemia (e.g., nonsteroidal anti-inflammatory agents)

Clostridium difficile toxin is found in an individual taking a drug that may cause pseudomembranous colitis (e.g., fluoroquinolone antibiotics)

Elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) concentration is found in an individual taking a drug that may cause hepatocellular toxicity (e.g., thiazolidinediones)

Elevated creatine phosphokinase (CPK) concentration is found in an individual taking a drug

that may increase CPK (e.g., statins)

Elevated creatinine or blood urea nitrogen (BUN) concentration is found in an individual taking a drug that may increase the creatinine or BUN concentration (e.g., diuretics)

Eosinophilia (as indicated by a high or increasing eosinophil count) is found in an individual taking a drug that may cause or worsen eosinophilia (e.g., proton pump inhibitors)

Erythrocytosis (as indicated by a high or increasing hemoglobin or hematocrit concentration) is found in an individual taking a drug that may cause or worsen erythrocytosis (e.g., epoetin alpha)

Hyperammonemia (as indicated by a high or increasing ammonia concentration) is found in an individual taking a drug that may cause or worsen hyperammonemia (e.g., valproic acid)

Hyperamylasemia (as indicated by a high or increasing amylase concentration) is found in an individual taking a drug that may cause or worsen hyperamylasemia (e.g., nonsteroidal anti-inflammatory agents)

Hyperbilirubinemia (as indicated by a high or increasing bilirubin concentration), elevated alkaline phosphatase (ALP) concentration, or elevated gamma-glutamyltransferase (GGT) concentration is found in an individual taking a drug that may cause cholestatic hepatotoxicity (e.g., allopurinol)

Hypercalcemia (as indicated by a high or increasing calcium concentration) is found in an individual taking a drug that may cause or worsen hypercalcemia (e.g., calcium supplements)

Hyperchloremia (as indicated by a high or increasing chloride concentration) is found in an individual taking a drug that may cause or worsen hyperchloremia (e.g., laxatives)

Hyperglycemia (as indicated by a high or increasing glucose concentration) is found in an

individual taking a drug that may cause or worsen hyperglycemia (e.g., prednisone)

Hyperkalemia (as indicated by a high or increasing potassium concentration) is found in an individual taking a drug that may cause or worsen hyperkalemia (e.g., potassium sparing diuretics)

Hyperlipidemia (as indicated by high or increasing lipid concentrations) is found in an individual taking a drug that may cause or increase cholesterol (e.g., colchicine)

Hypermagnesemia (as indicated by a high or increasing magnesium concentration) is found in an individual taking a drug that may cause or increase magnesium (e.g., magnesium supplements)

Hypernatremia (as indicated by a high or increasing sodium concentration) is found in an individual taking a drug that may cause or worsen hypernatremia (e.g., prednisone)

Hypertriglyceridemia (as indicated by a high or increasing triglyceride concentration) is found in an individual taking a drug that may cause or increase triglyceride (e.g., cyclosporine)

Hyperuricemia (as indicated by a high or increasing uric acid concentration) is found in an individual taking a drug that may increase uric acid (e.g., nicotinic acid)

Hypoalbuminemia (as indicated by a low or decreasing albumin concentration) is found in an individual taking a drug that may decrease albumin by causing anorexia (e.g., acetylcholinesterase inhibitors)

Hypocalcemia (as indicated by a low or decreasing calcium concentration) is found in an individual taking a drug that may cause or worsen hypocalcemia (e.g., valproic acid)

Hypoglycemia (as indicated by a low or decreasing glucose concentration) is found in an individual taking a drug that may cause or worsen hypoglycemia (e.g., insulin)

Hypokalemia (as indicated by a low or decreasing potassium concentration) is found in an

76

individual taking a drug that may cause or worsen hypokalemia (e.g., diuretics)

Hypomagnesemia (as indicated by a low or decreasing magnesium concentration) is found in an individual taking a drug that may cause or worsen hypomagnesemia (e.g., thiazide diuretics)

Hyponatremia (as indicated by a low or decreasing sodium concentration) is found in an individual taking a drug that may cause or worsen hyponatremia (e.g., selective serotonin reuptake inhibitors)

Hypophosphatemia (as indicated by a low or decreasing phosphate concentration) is found in an individual taking a drug that may cause or worsen hypophosphatemia (e.g., sorbitol,)

Leukocytosis (as indicated by a high or increasing white blood cell count) is found in an individual taking a drug that may cause or worsen leukocytosis (e.g., etanercept)

Leukopenia (as indicated by a low or decreasing white blood cell count) is found in an individual taking a drug that may cause or worsen leukopenia (e.g., beta-lactam antibiotics)

Subtherapeutic concentration (below lower limit of normal range) of thyroid-stimulating hormone (TSH) elevated concentration of thyroxine (T4) is found in an individual taking a drug that may cause hyperthyroidism (e.g., amiodarone)

Supratherapeutic concentration (above upper limit of normal range) of TSH or decreased concentration of T4 is found in an individual taking a drug that may cause hypothyroidism (e.g., amiodarone)

Supratherapeutic activated partial thromboplastin time (PTT) is found in an individual taking heparin

Supratherapeutic international normalized ratio (INR) is found in an individual taking warfarin

Thrombocytopenia (as indicated by a low or decreasing platelet count) is found in an individual taking a drug that may cause or worsen thrombocytopenia (e.g., clopidogrel)

Thrombocytosis (as indicated by a high or increasing platelet count) is found in an individual taking a drug that may cause or worsen thrombocytosis (e.g., beta-lactam antibiotics)

Medication Concentrations

Acetaminophen concentration is supratherapeutic in an individual taking acetaminophen

Aminoglycoside peak or trough concentration is supratherapeutic in an individual taking an aminoglycoside antibiotic (e.g., amikacin, gentamicin, or tobramycin)

Carbamazepine concentration is supratherapeutic in an individual taking carbamazepine

Digoxin concentration is supratherapeutic in an individual taking digoxin

Disopyramide (Norpace) concentration is supratherapeutic in an individual taking disopyramide

Lithium concentration is supratherapeutic in an individual taking lithium

Phenobarbital concentration is supratherapeutic in an individual taking phenobarbital

Phenytoin concentration is supratherapeutic in an individual taking phenytoin

Primidone (Mysoline) concentration or phenobarbital concentration is supratherapeutic in an individual taking primidone

Procainamide concentration or N-acetylprocainamide (NAPA) concentration is supratherapeutic in an individual taking procainamide

Quinidine concentration is supratherapeutic in an individual taking quinidine

Salicylate (aspirin, salsalate, or choline magnesium trisalicylate) concentration is supratherapeutic in an individual taking salicylate

Theophylline trough concentration is supratherapeutic in an individual taking theophylline

Tricyclic antidepressant (e.g., amitriptyline, desipramine, or imipramine) concentration is supratherapeutic in an individual taking a tricyclic antidepressant

Valproic acid concentration is supratherapeutic in an individual taking valproic acid

Vancomycin peak or trough concentration is supratherapeutic in an individual taking vancomycin

Antidotes/Tracer Medications

Anticonvulsant (e.g., benzodiazepine or phenytoin) is given to an individual taking a drug that may cause seizures (e.g., tramadol)

Antidiarrheal (e.g., loperamide, diphenoxylate, or bismuth) is given to an individual taking a drug that may cause diarrhea (e.g., laxatives)

Antiemetic (e.g., ondansetron, promethazine, or prochlorperazine) is given to an individual taking a drug that may cause nausea (e.g., opioid analgesics)

Antifungal (e.g., clotrimazole, fluconazole, miconazole, or nystatin) is given to an individual taking a drug that may cause oral or vaginal candidiasis (e.g., antibiotics)

Antihistamine (e.g., diphenhydramine or hydroxyzine) is given to an individual taking a drug that may cause a drug-induced rash (e.g., beta-lactam antibiotics)

Atropine is given to an individual taking a drug that may cause bradycardia (e.g., beta-blockers)

Benztropine (Cogentin), diphenhydramine, or trihexyphenidyl (Artane) is given to an individual taking a drug that may cause extrapyramidal symptoms (e.g., metoclopramide)

Dextrose 50%, glucagon, or liquid glucose is given to an individual taking a drug that may cause hypoglycemia (e.g., insulin)

Digoxin immune Fab (Digibind) is given to an individual whose digoxin concentration is supratherapeutic

Epinephrine is given to an individual taking a drug that may cause an anaphylactic reaction

(e.g., aspirin)

Flumazenil (Romazicon) is given to an individual taking a benzodiazepine (e.g., lorazepam)

Lepirudin (Refludan) is given to an individual taking a drug that may cause heparin-induced thrombocytopenia

Lidocaine is given to an individual taking an antiarrhythmic agent (e.g., procainamide)

Metronidazole (oral) or vancomycin (oral) is given to an individual who has recently taken a drug that may cause pseudomembranous colitis (e.g., fluoroquinolone antibiotic)

Naloxone (Narcan) is given to an individual taking an opioid analgesic (e.g., morphine)

Phytonadione (Vitamin K) is given to an individual taking warfarin

Protamine sulfate is given to an individual taking heparin

Sodium polystyrene is given to an individual taking a drug that may cause hyperkalemia (e.g., potassium sparing diuretics)

Steroids (oral) are given to an individual taking a drug that may cause a drug-induced rash (e.g., beta-lactam antibiotics)

Steroids (topical) are given to an individual taking a drug that may cause a drug-induced rash (e.g., aspirin)

Resident Assessment Protocols (RAPs)

Activities of Daily Living Function RAP is triggered in an individual taking a drug (e.g., barbiturates) that may impair or worsen activities of daily living (bed mobility, transfers, eating, toilet use, or ambulation)

Behavioral Symptoms RAP is triggered in an individual taking a drug (e.g., anticholinergics agents) that may cause or worsen behavioral symptoms (wandering, being verbally abusive,

being physically abusive, being socially inappropriate, or resisting care)

Cognitive Loss RAP is triggered in an individual taking a drug (e.g., benzodiazepines) that may cause or worsen cognitive impairment (changes in level of consciousness, cognitive skills for daily decision-making, short-term or long-term memory, thinking, awareness, or recall)

Dehydration/Fluid Maintenance RAP is triggered in an individual taking a drug (e.g., diuretics) that may cause or worsen dehydration (fluid loss exceeding the amount of fluid intake)

Delirium RAP is triggered in an individual taking a drug (e.g., anticholinergic agents) that may cause or worsen delirium (periodic disordered thinking or awareness)

Falls RAP is triggered in an individual taking a drug (e.g., opioid analgesics) that may cause or worsen falls (falls with or without injury)

Mood State RAP is triggered in an individual taking a drug (e.g., beta-blockers) that may cause or worsen mood states (depression, anxiety, sad mood, or sleep cycle issues)

Nutritional Status RAP is triggered in an individual taking a drug (e.g., acetylcholinesterase inhibitors) that may cause or worsen weight loss (chewing, swallowing, oral pain, weight changes, or dysgeusia)

Urinary Incontinence RAP is triggered in an individual taking a drug (e.g., diuretics) that may cause or worsen urinary incontinence (control of urinary bladder function or bowel movements)

Naranjo's Causality Algorithm (refer to detailed instructions):

	Yes	No	DK
1. Are there previous conclusive reports of this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued OR was a specific antagonist (i.e., antidote) was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0
5. Are there alternative causes (other than the drug) that could, on their own, have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0

7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic (i.e., above normal reference range)?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when it was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence (i.e., laboratory data)?	+1	0	0
POINT TOTAL=			

Scoring: Doubtful ≤ 0; Possible 1-4; Probable 5-8; Definite ≥ 9

BIBLIOGRAPHY

1. Avorn J, Gurwitz JH. Drug use in the nursing home. *Ann Intern Med.* 1995;123(3):195-204.

2. Doshi JA, Shaffer T, Briesacher BA. National estimates of medication use in nursing homes: findings from the 1997 medicare current beneficiary survey and the 1996 medical expenditure survey. *J Am Geriatr Soc.* Mar 2005;53(3):438-443.

3. Centers for Medicare & Medicaid Services. MDS 2.0 Public Quality Indicator and Resident Reports: Use of 9 or More Different Medications. http://www.cms.hhs.gov/MDSPubQIandResRep/03_qireports.asp?isSubmitted=qi3&group=03&qtr=21. Accessed August 31, 2009.

4. Venulet J, Ten-Ham M. Methods for monitoring and documenting adverse drug reactions. *Int J Clin Pharmacol Ther.* Mar 1996;34(3):112-129.

5. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet.* Oct 7 2000;356(9237):1255-1259.

6. Naranjo CA, Shear NH, Lanctot KL. Advances in the diagnosis of adverse drug reactions. *J Clin Pharmacol.* 1992;32(10):897-904.

7. Handler SM, Wright RM, Ruby CM, Hanlon JT. Epidemiology of medication-related adverse events in nursing homes. *Am J Geriatr Pharmacother.* Sep 2006;4(3):264-272.

8.   Gurwitz JH, Field TS, Rochon P, Judge J, Harrold LR, Bell CM, et al. Effect of computerized provider order entry with clinical decision support on adverse drug events in the long-term care setting. *J Am Geriatr Soc.* 2008;56(12):2225-2233.

9.   Bootman JL, Harrison DL, Cox E. The health care cost of drug-related morbidity and mortality in nursing facilities. *Arch Intern Med.* 1997;157(18):2089-2096.

10.   Gurwitz JH, Field TS, Avorn J, McCormick D, Jain S, Eckler M, et al. Incidence and preventability of adverse drug events in nursing homes. *Am J Med.* 2000;109(2):87-94.

11.   Gurwitz JH, Field TS, Judge J, Rochon P, Harrold LR, Cadoret C, et al. The incidence of adverse drug events in two large academic long-term care facilities. *Am J Med.* Mar 2005;118(3):251-258.

12.   Bernabei R, Gambassi G, Lapane K, Sgadari A, Landi F, Gatsonis C, et al. Characteristics of the SAGE database: a new resource for research on outcomes in long-term care. SAGE (Systematic Assessment of Geriatric drug use via Epidemiology) Study Group. *J Gerontol A-Biol.* Jan 1999;54(1):M25-33.

13.   Harrington C, Chapman S, Miller E, Miller N, Newcomer R. Trends in the Supply of Long-Term-Care Facilities and Beds in the United States. *J Appl Gerontol.* 2005;24(4):265-282.

14.   Field TS, Gurwitz JH, Avorn J, McCormick D, Jain S, Eckler M, et al. Risk factors for adverse drug events among nursing home residents. *Arch Intern Med.* Jul 9 2001;161(13):1629-1634.

15.   Cooper JW. Probable adverse drug reactions in a rural geriatric nursing home population: a four-year study. *J Am Geriatr Soc.* 1996;44(2):194-197.

16. Alfred L, Golden A, Preston R, Silverman M, Bergman R. Implementation of a pharmacist directed program to monitor adverse drug reactions. *Consult Pharm.* 2000;15:1032-1037.

17. Nguyen JK, Fouts MM, Kotabe SE, Lo E. Polypharmacy as a risk factor for adverse drug reactions in geriatric nursing home residents. *Am J Geriatr Pharmacother.* Mar 2006;4(1):36-41.

18. Gerety MB, Cornell JE, Plichta DT, Eimer M. Adverse events related to drugs and drug withdrawal in nursing home residents. *J Am Geriatr Soc.* Dec 1993;41(12):1326-1332.

19. Bain KT. Adverse drug reactions and current state of drug regimen review in nursing facilities: need for a change? *Consult Pharm.* Jul 2007;22(7):586-592.

20. Huff ED. Systems analysis of adverse drug events. *JAMA.* 1996;275(1):33-34; discussion 34-35.

21. Leape LL, Bates DW, Cullen DJ, Cooper J, Demonaco HJ, Gallivan T, et al. Systems analysis of adverse drug events. ADE Prevention Study Group. *JAMA.* 1995;274(1):35-43.

22. Karsh BT. Beyond usability: designing effective technology implementation systems to promote patient safety. *Qual Saf Health Care.* Oct 2004;13(5):388-394.

23. Institute of Medicine. *Preventing Medication Errors*. Washington, DC: National Academy Press; 2006.

24. Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA.* Oct 18 2006;296(15):1858-1866.

25. Raebel MA, Carroll NM, Andrade SE, Chester EA, Lafata JE, Feldstein A, et al. Monitoring of drugs with a narrow therapeutic range in ambulatory care. *Am J Manag Care.* May 2006;12(5):268-274.

26. Raebel MA, Lyons EE, Andrade SE, Chan KA, Chester EA, Davis RL, et al. Laboratory monitoring of drugs at initiation of therapy in ambulatory care. *J Gen Intern Med.* Dec 2005;20(12):1120-1126.

27. Higashi T, Shekelle PG, Solomon DH, Knight EL, Roth C, Chang JT, et al. The Quality of Pharmacologic Care for Vulnerable Older Patients. *Ann Intern Med.* 2004;140(May 4):714-720.

28. Hanlon J, Handler S, Maher R, Schmader K. Geriatric Pharmacotherapy and Polypharmacy. In: Fillit H, Rockwood K, Woodhouse L, eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology.* Seventh ed ed. London, UK: Churchill Livingstone; (in press).

29. Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA.* 1995;274(1):29-34.

30. Bates DW, Evans RS, Murff H, Stetson PD, Pizziferri L, Hripcsak G. Detecting adverse events using information technology. *J Am Med Inform Assoc.* Mar-Apr 2003;10(2):115-128.

31. Honigman B, Lee J, Rothschild J, Light P, Pulling RM, Yu T, et al. Using computerized data to identify adverse drug events in outpatients. *J Am Med Inform Assoc.* May-Jun 2001;8(3):254-266.

32. Jha AK, Laguette J, Seger A, Bates DW. Can Surveillance Systems Identify and Avert Adverse Drug Events? A Prospective Evaluation of a Commercial Application. *J Am Med Inform Assoc.* Sep-Oct 2008;15(5):647-653.

33. Handler SM, Shirts BH, Perera S, Becich MJ, Castle NG, Hanlon JT. Frequency of laboratory monitoring of chronic medications administered to nursing facility residents: results of a national internet-based study. *Consult Pharm.* May 2008;23(5):387-395.

34. Conditions of participation: skilled nursing facilities. *CFR Sec 405.1127(a)*; 1975:228.

35. Martin CM, McSpadden CS. Changes in the state operations manual: implications for consultant pharmacy practice. *Consult Pharm.* Dec 2006;21(12):948-961.

36. Hennessy S, Bilker WB, Zhou L, Weber AL, Brensinger C, Wang Y, et al. Retrospective drug utilization review, prescribing errors, and clinical outcomes. *JAMA.* Sep 17 2003;290(11):1494-1499.

37. Holland R, Desborough J, Goodyer L, Hall S, Wright D, Loke YK. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. *Br J Clin Pharmacol.* Mar 2008;65(3):303-316.

38. Clark TR. Gap analysis: assessing the value perception of consultant pharmacist services and the performance of consultant pharmacists. *Consult Pharm.* Sep 2008;23 Suppl C:3-15.

39. Institute of Medicine. *Preventing Medication Errors*. Washington, DC: National Academies Press; 2007.

40. National Quality Forum. *Safe Practices for Better Healthcare: A Consensus Report* 2003.

41. Institute of Medicine. *Patient Safety: Achieving a New Standard for Care*. Washington, D.C.: The National Academies Press; 2004.

42.   Shojania KG, Duncan BW, McDonald KM, Watchter RM. *Making Health Care Safer: A Critical Analysis of Patient Safety Practices.* Rockville, MD: Agency for Healthcare Research and Quality; 2001. 43.

43.   U.S. Department of Health and Human Services and Centers for Medicare & Medicaid Services, Guidance to surveyors for long term care facilities. *State Operations Provider Certification* [http://www.cms.hhs.gov/transmittals/downloads/R22SOMA.pdf. Accessed September 10, 2008.

44.   Kilbridge PM, Classen DC. Automated surveillance for adverse events in hospitalized patients: back to the future. *Qual Saf Health Care.* Jun 2006;15(3):148-149.

45.   Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. *Arch Intern Med.* Jun 23 2003;163(12):1409-1416.

46.   Garg AX, Adhikari NK, McDonald H, Rosas-Arellano MP, Devereaux PJ, Beyene J, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. *JAMA.* Mar 9 2005;293(10):1223-1238.

47.   Durieux P, Trinquart L, Colombet I, Nies J, Walton R, Rajeswaran A, et al. Computerized advice on drug dosage to improve prescribing practice. *Cochrane Database of Systematic Reviews.* 2008(3):CD002894.

48.   Yourman L, Concato J, Agostini J. Use of computer decision support interventions to improve medication prescribing in older adults: a systematic review. *Am J Geriatr Pharmacother.* 2008;6(2):119-129.

49. Chaudhry B, Wang J, Wu S, Maglione M, Mojica W, Roth E, et al. Systematic review: impact of health information technology on quality, efficiency, and costs of medical care. *Ann Intern Med.* May 16 2006;144(10):742-752.

50. Handler S, Castle N, Studenski S, Perera S, Fridsma D, Nace D, et al. Patient safety culture assessment in the nursing home. *Qual Saf Health Care.* Dec 2006;15(6):400-404.

51. Institute of Medicine. *Retooling for an Aging America: Building the Health Care Workforce*. Washington, DC: The National Academies Press; 2008.

52. Levy C, Palat SI, Kramer AM, Levy C, Palat S-IT, Kramer AM. Physician practice patterns in nursing homes. *J Am Med Dir Assoc.* Nov 2007;8(9):558-567.

53. Bonner AF, Perera S, Castle NG, Handler SM. Patient Safety Culture: A Review of the Nursing Home Literature and Recommendations for Practice. *Ann Long Term Care.* 2008;16(3):18-22.

54. Institute of Medicine. *Improving the Quality of Care in Nursing Homes*. Washington, D.C.: National Academy Press; 1986.

55. Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. *JAMA.* 1991;266(20):2847-2851.

56. Jha AK, Kuperman GJ, Teich JM, Leape L, Shea B, Rittenberg E, et al. Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. *J Am Med Inform Assoc.* May-Jun 1998;5(3):305-314.

57. Levy M, Azaz-Livshits T, Sadan B, Shalit M, Geisslinger G, Brune K. Computerized surveillance of adverse drug reactions in hospital: implementation. *Eur J Clin Pharmacol.* 1999;54(11):887-892.

58. Murff HJ, Patel VL, Hripcsak G, Bates DW. Detecting adverse events for patient safety research: a review of current methodologies. *J Biomed Inform.* Feb-Apr 2003;36(1-2):131-143.

59. Morimoto T, Gandhi TK, Seger AC, Hsieh TC, Bates DW. Adverse drug events and medication errors: detection and classification methods. *Qual Saf Health Care.* Aug 2004;13(4):306-314.

60. Handler SM, Altman RL, Perera S, Hanlon JT, Studenski SA, Bost JE, et al. A systematic review of the performance characteristics of clinical event monitor signals used to detect adverse drug events in the hospital setting. *J Am Med Inform Assoc.* Jul-Aug 2007;14(4):451-458.

61. Tegeder I, Levy M, Muth-Selbach U, Oelkers R, Neumann F, Dormann H, et al. Retrospective analysis of the frequency and recognition of adverse drug reactions by means of automatically recorded laboratory signals. *Br J Clin Pharmacol.* May 1999;47(5):557-564.

62. Evans RS, Pestotnik SL, Classen DC, Bass SB, Burke JP. Prevention of adverse drug events through computerized surveillance. *Proc Annu Symp Comput Appl Med Care.* 1992:437-441.

63. Evans RS, Pestotnik SL, Classen DC, Horn SD, Bass SB, Burke JP. Preventing adverse drug events in hospitalized patients. *Ann Pharmacother.* Apr 1994;28(4):523-527.

64. Raschke RA, Gollihare B, Wunderlich TA, Guidry JR, Leibowitz AI, Peirce JC, et al. A computer alert system to prevent injury from adverse drug events: development and evaluation in a community teaching hospital. *JAMA.* 1998;280(15):1317-1320.

65. *Reducing and Preventing Adverse Drug Events To Decrease Hospital Costs.* Rockville, MD: Agency for Healthcare Research and Quality; 2001. AHRQ Publication Number 01-0020.

66. Silverman JB, Stapinski CD, Huber C, Ghandi TK, Churchill WW. Computer-based system for preventing adverse drug events. *Am J Health Syst Pharm.* Aug 1 2004;61(15):1599-1603.

67. Peterson JF, Williams DH, Seger A, Gandhi TK, Bates DW. Drug-lab triggers have the potential to prevent adverse drug events in outpatients. *J Am Med Inform Assoc.* Nov-Dec 2002;9(6):S39-40.

68. Hartis CE, Gum MO, Lederer JW, Jr. Use of specific indicators to detect warfarin-related adverse events. *Am J Health Syst Pharm.* Aug 15 2005;62(16):1683-1688.

69. Longo DR, Hewett JE, Ge B, Schubert S, Longo DR, Hewett JE, et al. The long road to patient safety: a status report on patient safety systems. *JAMA.* Dec 14 2005;294(22):2858-2865.

70. Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century.* Washington, DC: National Academy Press; 2001.

71. Osheroff JA, Teich JM, Middleton B, Steen EB, Wright A, Detmer DE. A roadmap for national action on clinical decision support. *J Am Med Inform Assoc.* Mar-Apr 2007;14(2):141-145.

72. Poon EG, Jha AK, Christino M, Honour MM, Fernandopulle R, Middleton B, et al. Assessing the level of healthcare information technology adoption in the United States: a snapshot. *BMC Med Inf Decis Mak.* 2006;6:1.

73.   Kaushal R, Bates DW, Poon EG, Jha AK, Blumenthal D, Harvard Interfaculty Program for Health Systems Improvement NHIN Working Group. Functional gaps in attaining a national health information network. What will it take to get there in five years? *Health Aff (Millwood).* Sep-Oct 2005;24(5):1281-1289.

74.   Hudak S, Sharkey S. *Health Information Technology: Are Long Term Care Providers Ready?*: California Healthcare Foundation; 2007.

75.   Subramanian S, Hoover S, Gilman B, Field TS, Mutter R, Gurwitz JH. Computerized Physician Order Entry with Clinical Decision Support in Long-Term Care Facilities: Costs and Benefits to Stakeholders *J Am Geriatr Soc.* 2007:1451-1457.

76.   Judge J, Field TS, DeFlorio M, Laprino J, Auger J, Rochon P, et al. Prescribers' responses to alerts during medication ordering in the long term care setting. *J Am Med Inform Assoc.* Jul-Aug 2006;13(4):385-390.

77.   Rochon PA, Field TS, Bates DW, Lee M, Gavendo L, Erramuspe-Mainard J, et al. Computerized Physician Order Entry with Clinical Decision Support in the Long-Term Care Setting: Insights from the Baycrest Centre for Geriatric Care. *J Am Geriatr Soc.* 2005;53(10):1780-1789.

78.   Handler SM, Hanlon JT, Perera S, Roumani YF, Nace DA, Fridsma DB, et al. Consensus list of signals to detect potential adverse drug reactions in nursing homes. *J Am Geriatr Soc.* May 2008;56(5):808-815.

79.   Handler SM, Hanlon JT, Perera S, Saul MI, Fridsma DB, Visweswaran S, et al. Assessing the Performance Characteristics of Signals Used by a Clinical Event Monitor to Detect Adverse Drug Reactions in the Nursing Home. *Proceedings / AMIA.* 2008:278-282.

80. Hripcsak G, Clayton PD, Jenders RA, Cimino JJ, Johnson SB. Design of a clinical event monitor. *Comput Biomed Res.* Jun 1996;29(3):194-221.

81. Rind DM, Safran C, Phillips RS, Wang Q, Calkins DR, Delbanco TL, et al. Effect of computer-based alerts on the treatment and outcomes of hospitalized patients. *Arch Intern Med.* 1994;154(13):1511-1517.

82. Haug PJ, Gardner RM, Tate KE, Evans RS, East TD, Kuperman G, et al. Decision support in medicine: examples from the HELP system. *Comput Biomed Res.* Oct 1994;27(5):396-418.

83. Haug PJ, Rocha BH, Evans RS. Decision support in medicine: lessons from the HELP system. *Int J Med Inf.* Mar 2003;69(2-3):273-284.

84. Institute of Medicine. *To Err Is Human: Building a Safer Health System.* Washington, DC: National Academy Press; 2000.

85. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. *JAMA.* 1997;277(4):301-306.

86. Senst BL, Achusim LE, Genest RP, Cosentino LA, Ford CC, Little JA, et al. Practical approach to determining costs and frequency of adverse drug events in a health care network. *Am J Health Syst Pharm.* Jun 15 2001;58(12):1126-1132.

87. Nebeker JR, Hoffman JM, Weir CR, Bennett CL, Hurdle JF. High rates of adverse drug events in a highly computerized hospital. *Arch Intern Med.* May 23 2005;165(10):1111-1116.

88. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA.* 1998;279(15):1200-1205.

89.   Bates DM, Spell N, Cullen DJ, Burdick E, Laird N, Petersen LA, et al. The Costs of Adverse Drug Events in Hospitalized Patients. *JAMA*. 1997;277(4):307-311.

90.   Cullen DJ, Bates DW, Small SD, Cooper JB, Nemeskal AR, Leape LL. The incident reporting system does not detect adverse drug events: a problem for quality improvement. *Jt Comm J Qual Improv.* 1995;21(10):541-548.

91.   Gandhi TK, Seger DL, Bates DW. Identifying drug safety issues: from research to practice. *Int J Qual Health Care.* Feb 2000;12(1):69-76.

92.   Classen DC, Pestotnik SL, Evans RS, Burke JP. Description of a computerized adverse drug event monitor using a hospital information system. *Hosp Pharm.* 1992;27(9):774, 776-779, 783.

93.   Payne TH, Savarino J. Development of a clinical event monitor for use with the Veterans Affairs Computerized Patient Record System and other data sources. *Proceedings / AMIA.* 1998:145-149.

94.   Kaushal R, Jha AK, Franz C, Glaser J, Shetty KD, Jaggi T, et al. Return on Investment for a Computerized Physician Order Entry System. *J Am Med Inform Assoc.* 2006;13(3):261-266.

95.   Kuperman GJ, Bobb A, Payne TH, Avery AJ, Gandhi TK, Burns G, et al. Medication-related clinical decision support in computerized provider order entry systems: a review. *J Am Med Inform Assoc.* Jan-Feb 2007;14(1):29-40.

96.   Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA*. Sep 15 1999;282(11):1054-1060.

97.   Huwiler-Muntener K, Juni P, Junker C, Egger M. Quality of reporting of randomized trials as a measure of methodologic quality. *JAMA*. Jun 5 2002;287(21):2801-2804.

98.   Fleiss JL. The statistical basis of meta-analysis. *Stat Methods Med Res.* 1993;2(2):121-145.

99.   Liang K, Zeger S. Longitudinal data analysis using generalized linear models. *Biometrika.* 1986;73:13-22.

100.   Lipsitz SR, Fitzmaurice GM, Orav EJ, Laird NM. Performance of generalized estimating equations in practical situations. *Biometrics.* Mar 1994;50(1):270-278.

101.   Diggle P, Heagerty P, Liang K, Zeger S. *Analysis of longitudinal data.* 2nd ed. New York, NY: Oxford University Press; 2002.

102.   Sutton A, Abrams K, Jones D, Sheldon T, Song F. *Methods for Meta-Analaysis in Medical Research.* Sussex, England: John Wiley and Sons; 2000.

103.   Song F, Khan KS, Dinnes J, Sutton AJ. Asymmetric funnel plots and publication bias in meta-analyses of diagnostic accuracy. *Int J Epidemiol.* Feb 2002;31(1):88-95.

104.   Evans RS, Pestotnik SL, Classen DC, Bass SB, Menlove RL, Gardner RM, et al. Development of a computerized adverse drug event monitor. *Proc Annu Symp Comput Appl Med Care.* 1991:23-27.

105.   Azaz-Livshits T, Levy M, Sadan B, Shalit M, Geisslinger G, Brune K. Computerized survelliance of adverse drug reactions in hospital: pilot study. *Br J Clin Pharmacol.* Mar 1998;45(3):309-314.

106.   Henz S. Improved ADR Detection without Using a Computer-Assisted Alert System. In: James B, ed. Salt Lake City, Utah: Institute of Healthcare Delivery Research.; 2000.

107.   Dormann H, Muth-Selbach U, Krebs S, Criegee-Rieck M, Tegeder I, Schneider HT, et al. Incidence and costs of adverse drug reactions during hospitalisation: computerised monitoring versus stimulated spontaneous reporting. *Drug Saf.* Feb 2000;22(2):161-168.

108. Jha AK, Kuperman GJ, Rittenberg E, Teich JM, Bates DW. Identifying hospital admissions due to adverse drug events using a computer-based monitor. *Pharmacoepidemiol Drug Saf.* Mar-Apr 2001;10(2):113-119.

109. Thuermann PA, Windecker R, Steffen J, Schaefer M, Tenter U, Reese E, et al. Detection of adverse drug reactions in a neurological department: comparison between intensified surveillance and a computer-assisted approach. *Drug Saf.* 2002;25(10):713-724.

110. Dormann H, Criegee-Rieck M, Neubert A, Egger T, Levy M, Hahn EG, et al. Implementation of a computer-assisted monitoring system for the detection of adverse drug reactions in gastroenterology. *Aliment Pharmacol Ther.* Feb 1 2004;19(3):303-309.

111. Brown S, Black K, Mrochek S, Wood A, Bess T, Cobb J, et al. RADARx: Recognizing, Assessing, and Documenting Adverse Rx events. *Proceedings / AMIA.* 2000:101-105.

112. Thurmann PA. Methods and systems to detect adverse drug reactions in hospitals. *Drug Saf.* 2001;24(13):961-968.

113. Goroll AH, Mulley AG, eds. *Primary Care Medicine: Office Evaluation and Management of the Adult Patient.* 5th ed ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.

114. Owens DK, Nease RF, Jr. A normative analytic framework for development of practice guidelines for specific clinical populations. *Med Decis Making.* Oct-Dec 1997;17(4):409-426.

115. Burkle T, Ammenwerth E, Prokosch HU, Dudeck J. Evaluation of clinical information systems. What can be evaluated and what cannot? *J Eval Clin Pract.* Nov 2001;7(4):373-385.

116. Poissant L, Pereira J, Tamblyn R, Kawasumi Y. The impact of electronic health records on time efficiency of physicians and nurses: a systematic review. *J Am Med Inform Assoc.* Sep-Oct 2005;12(5):505-516.

117. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* Feb 1996;17(1):1-12.

118. Cook DJ, Sackett DL, Spitzer WO. Methodologic guidelines for systematic reviews of randomized control trials in health care from the Potsdam Consultation on Meta-Analysis. *J Clin Epidemiol.* Jan 1995;48(1):167-171.

119. Irwig L, Tosteson AN, Gatsonis C, Lau J, Colditz G, Chalmers TC, et al. Guidelines for meta-analyses evaluating diagnostic tests. *Ann Intern Med.* Apr 15 1994;120(8):667-676.

120. Irwig L, Macaskill P, Glasziou P, Fahey M. Meta-analytic methods for diagnostic test accuracy. *J Clin Epidemiol.* Jan 1995;48(1):119-130; discussion 131-112.

121. Ash JS, Gorman PN, Seshadri V, Hersh WR. Computerized physician order entry in U.S. hospitals: results of a 2002 survey. *J Am Med Inform Assoc.* Mar-Apr 2004;11(2):95-99.

122. van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. *J Am Med Inform Assoc.* Mar-Apr 2006;13(2):138-147.

123. Kilbridge PM, Alexander L, Ahmad A. Implementation of a system for computerized adverse drug event surveillance and intervention at an academic medical center. *J Clin Out Manag.* 2006;13(2):94-100.

124. Kilbridge PM, Campbell UC, Cozart HB, Mojarrad MG. Automated surveillance for adverse drug events at a community hospital and an academic medical center. *J Am Med Inform Assoc.* Jul-Aug 2006;13(4):372-377.

125. Southon FC, Sauer C, Grant CN. Information technology in complex health services: organizational impediments to successful technology transfer and diffusion. *J Am Med Inform Assoc.* Mar-Apr 1997;4(2):112-124.

126. Bates DW, Evans RS, Murff H, Stetson PD, Pizziferri L, Hripcsak G. Policy and the future of adverse event detection using information technology. *J Am Med Inform Assoc.* Mar-Apr 2003;10(2):226-228.

127. Aschengrau A, Seage GR. *Essentials of epidemiology in public health.* Sudbury, MA: Jones and Baetlett Publishers0-7637-2537-4; 2003.

128. Kuperman G, Teich J, Tanasijevic M, Ma'Luf N, Rittenberg E, Jha A, et al. Improving response to critical laboratory results with automation: results of a randomized controlled trial. *J Am Med Inform Assoc.* 1999;6(6):512-522.

129. Pignone M, Rich M, Teutsch SM, Berg AO, Lohr KN. Screening for colorectal cancer in adults at average risk: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med.* Jul 16 2002;137(2):132-141.

130. Schiff GD, Klass D, Peterson J, Shah G, Bates DW. Linking laboratory and pharmacy: opportunities for reducing errors and improving care. *Arch Intern Med.* Apr 28 2003;163(8):893-900.

131. Wick JY, Zanni GR. Integrating pharmacy and laboratory systems: quality improvement implications. *Consult Pharm.* 2000;15(Oct):1009-1023.

132. Becich MJ, Gilbertson JR, Gupta D, Patel A, Grzybicki DM, Raab SS. Pathology and patient safety: the critical role of pathology informatics in error reduction and quality initiatives. *Clin Lab Med.* 2004 Dec 2004;24(4):913-943.

133. Bates DW, Cohen M, Leape LL, Overhage JM, Shabot MM, Sheridan T. Reducing the frequency of errors in medicine using information technology. *J Am Med Inform Assoc.* 2001;8(4):299-308.

134. Gurwitz JH, Field TS, Harrold LR, Rothschild J, Debellis K, Seger AC, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA.* 2003;289(9):1107-1116.

135. Honigman B, Light P, Pulling RM, Bates DW. A computerized method for identifying incidents associated with adverse drug events in outpatients. *Int J Med Inf.* Apr 2001;61(1):21-32.

136. Guay DR, Artz MB, Hanlon JT, Schmader KE. The pharmacology of aging. In: Tallis RC, Fillit HM, eds. *Brocklehurst's textbook of geriatric medicine and gerontology.* New York, New York: Churchill Livingstone; 2003:155-161.

137. Bakken S, Campbell KE, Cimino JJ, Huff SM, Hammond WE. Toward vocabulary domain specifications for health level 7-coded data elements. *J Am Med Inform Assoc.* Jul-Aug 2000;7(4):333-342.

138. Kawamoto K, Lobach DF. Proposal for fulfilling strategic objectives of the U.S. Roadmap for national action on clinical decision support through a service-oriented architecture leveraging HL7 services. *J Am Med Inform Assoc.* Mar-Apr 2007;14(2):146-155.

139. Hanlon JT, Schmader KE, Ruby CM, Weinberger M. Suboptimal prescribing in older inpatients and outpatients. *J Am Geriatr Soc.* 2001;49(2):200-209.

140. Field TS, Gurwitz JH, Harrold LR, Rothschild JM, Debellis K, Seger AC, et al. Strategies for detecting adverse drug events among older persons in the ambulatory setting. *J Am Med Inform Assoc.* Nov-Dec 2004;11(6):492-498.

141. Hanlon JT, Lindblad CI, Maher RL, Schmader KE. Geriatric pharmacotherapy. In: Tallis RC, Fillit HM, eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology*. New York, New York: Churchill Livingstone; 2003:1289-1296.

142. Kaushal R, Blumenthal D, Poon EG, Jha AK, Franz C, Middleton B, et al. The costs of a national health information network. *Ann Intern Med.* Aug 2 2005;143(3):165-173.

143. Hawes C, Morris JN, Phillips CD, Fries BE, Murphy K, Mor V. Development of the nursing home Resident Assessment Instrument in the USA. *Age Ageing.* Sep 1997;26 Suppl 2:19-25.

144. Aronson JK, ed. *Meyler's side effects of drugs: the international encyclopedia of adverse drug reactions and interactions.* 15th ed: Elsevier; 2006.

145. Tisdale JE, Miller DA, eds. *Drug-induced diseases: prevention, detection, and management*. Bethesda, MD: American Society of Health-System Pharmacists; 2005.

146. United States Pharmacopeial Convention. *Drug information for the health care professional.* Vol One. 26th ed. Greenwood Village, CO: MICROMEDEX; 2006.

147. Delbecq AL, Van de Ven AH, Gustafson DH. *Group techniques for program planning: a guide to nominal group and delphi processses*. Glenview, Ill.: Scott Foresman; 1975.

148. Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ.* 1995;311(7001):376-380.

149. Beers MH, Ouslander JG, Rollingher I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. *Arch Intern Med.* 1991;151(9):1825-1832.

150. Campbell SM, Cantrill JA. Consensus methods in prescribing research. *J Clin Pharm Ther.* Feb 2001;26(1):5-14.

151. Morris CJ, Cantrill JA. Preventing drug-related morbidity--the development of quality indicators. *J Clin Pharm Ther.* Aug 2003;28(4):295-305.

152. Morris CJ, Cantrill JA, Hepler CD, Noyce PR. Preventing drug-related morbidity--determining valid indicators. *Int J Qual Health Care.* Jun 2002;14(3):183-198.

153. McGlynn EA, Asch SM. Developing a clinical performance measure. *Am J Prev Med.* Apr 1998;14(3 Suppl):14-21.

154. Handler SM, Nace DA, Studenski SA, Fridsma DB. Medication error reporting in long-term care. *Am J Geriatr Pharmacother.* Sep 2004;2(3):190-196.

155. Edwards P, Roberts I, Clarke M, DiGuiseppi C, Pratap S, Wentz R, et al. Increasing response rates to postal questionnaires: systematic review. *BMJ.* May 18 2002;324(7347):1183.

156. Fouts M, Hanlon J, Pieper C, Perfetto E, Feinberg J. Identification of elderly nursing facility residents at high risk for drug-related problems. *Consult Pharm.* 1997;12(10):1103-1111.

157. Hajjar ER, Hanlon JT, Artz MB, Lindblad CI, Pieper CF, Sloane RJ, et al. Adverse drug reaction risk factors in older outpatients. *Am J Geriatr Pharmacother.* 2003;1(2):82-89.

158. Lindblad CI, Hanlon JT, Gross CR, Sloane RJ, Pieper CF, Hajjar ER, et al. Clinically important drug-disease interactions and their prevalence in older adults. *Clin Ther.* Aug 2006;28(8):1133-1143.

159. Department of Health & Human Services (DHHS) and Centers for Medicare & Medicaid Services (CMS). CMS Manual System, Pub. 100-07 State Operations Provider Certification, Transmittal 22. *CMS Manual System* [December 15, 2006; http://www.cms.hhs.gov/transmittals/downloads/R22SOMA.pdf. Accessed July 18, 2007.

160. Feinberg JL, Cameron KA, Lapane KL, Allsworth JE. The use of Gram Software to improve patient safety in nursing facilities. *Consult Pharm.* 2004;19(5):398-413.

161. Fink HA, Wyman JF, Hanlon JT. Falls. In: Tallis RC, Fillit HM, eds. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology*. New York, New York: Churchill Livingstone; 2003:1337--1346.

162. Kotylar M, Gray SL, Lindblad CI, Hanlon JT. Psychiatric manifestations of medications in the elderly. In: Malletta GJ, Agronin ME, eds. *Principles and Practices of Geriatric Psychiatry.* Philadelphia: Lippincott Williams & Wilkins; 2005:800.

163. Asch DA, Jedrziewski MK, Christakis NA. Response rates to mail surveys published in medical journals. *J Clin Epidemiol.* Oct 1997;50(10):1129-1136.

164. Saliba D, Schnelle JF. Indicators of the quality of nursing home residential care. *J Am Geriatr Soc.* Aug 2002;50(8):1421-1430.

165. Resar RK, Rozich JD, Classen D. Methodology and rationale for the measurement of harm with trigger tools. *Qual Saf Health Care.* Dec 2003;12(Suppl 2):ii39-45.

166. Rozich JD, Haraden CR, Resar RK. Adverse drug event trigger tool: a practical methodology for measuring medication related harm. *Qual Saf Health Care.* Jun 2003;12(3):194-200.

167. Raebel MA, Charles J, Dugan J, Carroll NM, Korner EJ, Brand DW, et al. Randomized trial to improve prescribing safety in ambulatory elderly patients. *J Am Geriatr Soc.* Jul 2007;55(7):977-985.

168. Yount R, Vries JK, Council C. The Medical Archival System: Information retrieval system based on distributed parallel processing. *Inf Proc Manag.* 1991;27(4).

169. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* Aug 1981;30(2):239-245.

170. Forrey RA, Pedersen CA, Schneider PJ. Interrater agreement with a standard scheme for classifying medication errors. *Am J Health Syst Pharm.* 2007;64(2):175-181.