

# Practice Administration and Development: Medication Safety

Henry Cohen, Pharm.D., M.S., FCCM, BCPP, CGP

Kingsbrook Jewish Medical Center

Department of Pharmacy Services

Arnold & Marie Schwartz College of Pharmacy and Health Sciences

Long Island University

Brooklyn, New York



# Practice Administration and Development: Medication Safety

Henry Cohen, Pharm.D., M.S., FCCM, BCPP, CGP

Kingsbrook Jewish Medical Center

Department of Pharmacy Services

Arnold & Marie Schwartz College of Pharmacy and Health Sciences

Long Island University

Brooklyn, New York

**Learning Objectives**

1. Develop and implement a drug formulary proposal.
2. List the elements of a drug monograph for a new addition to the drug formulary.
3. Describe how to monitor and evaluate compliance with and impact of the medication use processes, including policies and guidelines using medication use evaluations (MUEs) and quality assurance (QA).
4. List high-risk medications and medication-related processes that are suited for an MUE.
5. Describe how to perform an MUE.
6. Compare and contrast between QA, performance improvement, and a gap analysis.
7. Compare and contrast between a medication error, an adverse drug event (ADE), an adverse drug reaction, and a preventable ADE.
8. Design an ADE reporting program, including committee structure and committee reporting mechanisms and methods of detecting, reporting, and managing ADEs.
9. Describe the documentation processes for clinical pharmacy services (CPS) and types of pharmacotherapeutic interventions.
10. Describe how to justify and document the financial value of CPS.
11. Describe the safety measures for drug interaction detection and prevention.

**Abbreviations in This Chapter**

ADE	Adverse drug event
ADR	Adverse drug reaction
ASHP	American Society of Health-System Pharmacists
CPOE	Computerized prescriber order entry
CPS	Clinical pharmacy services
DUE	Drug use evaluation
ICU	Intensive care unit
MUE	Medication use evaluation
PI	Performance improvement
PMR	Patient medical record
P&T	Pharmacy and Therapeutics (committee)
QA	Quality assurance
QI	Quality Improvement
SUP	Stress ulcer prophylaxis
TJC	The Joint Commission

**Self-Assessment Questions**

*Answers and explanations to these questions may be found at the end of this chapter.*

1. The pharmacy and therapeutics (P&T) committee would like to evaluate the use of pharmacotherapy in stress ulcer prophylaxis (SUP) in the intensive care unit (ICU). Which is the best method for making this evaluation?
  - A. Perform a medication use evaluation (MUE).
  - B. Administer a performance improvement (PI) initiative.
  - C. Review adverse drug event (ADE) data from the ICU.
  - D. Review medication error data from the ICU.
2. A 60-year-old woman is admitted to the surgical ICU with a history of penicillin allergy. She is administered cefazolin before a surgical procedure and develops a life-threatening anaphylaxis reaction. Which best describes this patient's reaction to cefazolin?
  - A. An ADR.
  - B. A side effect.
  - C. An ADE.
  - D. A preventable ADE.
3. Which is most accurately considered an effective tracer medication to aid in the detection of ADEs?
  - A. Naloxone.
  - B. Clopidogrel.
  - C. Propofol.
  - D. Enoxaparin.
4. Which is most likely to be considered an effective tracer medication to aid in the detection of ADEs?
  - A. Sumatriptan.
  - B. Lorazepam.
  - C. Kayexalate.
  - D. Amitriptyline.

5. Which drug selection criterion is most important when making decisions for drug formulary approval?
  - A. Unlabeled indications.
  - B. Date of U.S. Food and Drug Administration (FDA) approval.
  - C. Effectiveness.
  - D. Storage.
  
6. Which medication use process is best suited for an MUE?
  - A. Pharmacist verification times for routine orders in the ICU.
  - B. Management of warfarin-induced hypoprothrombinemia.
  - C. Drug interaction warnings on the computerized prescriber order entry (CPOE) system.
  - D. Duplicate warnings on the CPOE system.
  
7. Which is most appropriate when performing a quality improvement assurance (QA) survey for the allergy cross-reactivity of morphine with other opioids in the CPOE system?
  - A. Setting the threshold of allergy detection with codeine at 75%.
  - B. Using a sample size of 25 patients.
  - C. Setting the threshold of allergy detection with hydromorphone at 85%.
  - D. Reviewing duplicate therapy with other opioids.

**I. FORMULARY PROPOSALS**

- A. The drug formulary should be comprehensive and include all the medications needed for patient care.
- B. TJC Medication Management Standard requires hospitals to develop and approve the criteria for selecting medications into the drug formulary.
- C. At a minimum, the drug selection criteria should include the following:
  1. Indications for use (FDA label approved and off label)
  2. Efficacy and effectiveness
  3. Drug interactions
  4. Adverse effects
  5. Sentinel event advisories
  6. Cost acquisition and total cost of care
- D. The P&T committee is responsible for maintaining the drug formulary and ensuring that new medications that can improve patient care are reviewed for formulary inclusion.
- E. Critical care pharmacists should be cognizant of new medications and new medication dosage forms that may be used to improve the management of critically ill patients. Critical care pharmacists should collaborate with intensivists to request the addition or deletion of a drug from formulary.
- F. Box 1 lists the elements of a drug evaluation monograph that should be reviewed before approving a drug to the hospital formulary.

**Box 1. Elements of a Drug Evaluation Monograph**

1. Brand name
2. Generic name
3. Manufacturer
4. Therapeutic classification
5. FDA status: Prescription, nonprescription, or controlled substance
6. Look-alike sound-alike names with any other FDA label-approved medications
7. Look-alike sound-alike names with any other FDA label-approved medications on formulary
8. Date of FDA label approval
9. FDA rank (priority or standard)
10. FDA label-approved indication
11. Unlabeled indications
12. Potential unlabeled uses
13. Similar agents not on formulary
14. Similar agents on formulary
15. How the drug can be used when applied to available national guidelines
16. How the drug can be used when applied to hospital guidelines, protocols, or pathways
17. Dosage form

**Box 1. Elements of a Drug Evaluation Monograph (continued)**

18. Dosage strength
19. Mechanism of action
20. Absorption
21. Distribution
22. Metabolism
23. Excretion
24. Common adverse drug reactions
25. Significant or life-threatening adverse drug reactions
26. Boxed warnings
27. Precautions
28. Contraindications
29. Drug-drug interactions
30. Drug-food interactions
31. Drug-laboratory tests interactions
32. IV incompatibilities
33. IV compatibilities
34. Pregnancy category
35. Use during breastfeeding
36. Dosage regimen recommendations
37. Dosage regimen recommendations for special populations such as pediatrics, geriatrics, renal and hepatic impairment, and dialysis
38. Any special administration techniques (prescriber certification)
39. Preparations available
40. Storage
41. Any availability concerns (specialty pharmacy restrictions)
42. Critical review of pertinent clinical trials with salient critique and conclusions
43. Critical review of comparison trials with similar or alternative agents
44. Cost analysis including annual projected costs
45. Pharmacoeconomics analysis
46. Reimbursement from third-party payers
47. Are there any severe medication errors or sentinel events with this agent?
48. Does this medication need to be stored under specific circumstances to avoid medication errors or mix-ups?
49. Does this medication require tall man lettering labeling or precautionary/high-risk labeling to avoid potential medication errors or mix-ups?
50. Is the manufacturer-provided labeling considered clear and safe for dispensation?
51. Is an abuse potential associated with the use of this medication?
52. Patient education requirements

**Box 1. Elements of a Drug Evaluation Monograph** (*continued*)

53. Will this agent replace an existing agent, and should a formulary deletion take place?
54. Reason why this medication should be included in the formulary
55. Recommendation for addition to formulary
56. References

IV = intravenous.

- G. Evidence-Based Decisions Should Be Made When Adding Drugs to the Formulary.
- H. A comprehensive literature review should be used to determine a drug's efficacy and toxicity profile, with stronger levels of evidence guiding decisions.
1. Prospective double-blind randomized controlled trials should have greater weight than retrospective trials and meta-analyses.
  2. Case reports should only be used when no other evidence is available.
- I. It is important that the pharmacist(s) developing the drug evaluation monograph be adept in drug literature evaluation and pharmacoeconomics analysis.
- J. The drug evaluation should contain references to evidence, and opinion statements should be so noted.
- K. Internal prescribing data may also be used when making formulary decisions, such as
1. Quantity of drug used over a specified amount of time
  2. MUE data
  3. Adverse events data
  4. Medication error data
- L. Most new drugs are studied in 1500–3000 patients, which may make it difficult to detect less common severe or life-threatening adverse effects. Some drugs may cause life-threatening toxicity such as hepatic failure at a rate of 1:20,000 patients, thus requiring more than 100,000 postmarketing patient exposures before generating a signal of toxicity. It may be prudent to allow all new drugs to be on the market for 1–2 years and observe their safety profiles before admitting into the formulary.
- M. Drugs may be added to the formulary without any use restrictions, or they may be added with restrictions.
- N. Drugs can be restricted for many reasons, such as the following:
1. Efficacy
  2. Safety
  3. Patient-specific populations (because of limited efficacy or safety evidence)
  4. Cost
- O. It is common to restrict drugs to a prescriber who is a specialist or a clinical pharmacist specialist, a specialty unit such as the ICU, or a population such as pediatric patients or postoperative surgical patients.
1. For example, propofol may be restricted to use in intensive care and surgical units and/or to use by intensivists or anesthesiologists.
  2. Parenteral fosphenytoin may be restricted to use in the intensive care and surgical units and the emergency department and/or units, where appropriate continuous cardiac monitoring will take place such as in telemetry.



3. Antimicrobials are often restricted to approval from infectious disease physicians or infectious disease pharmacist specialists.
  4. Fidaxomicin indicated for *Clostridium difficile*-associated diarrhea may be restricted to infectious disease physicians or pharmacist specialists, but to better curtail costs, there may also be select criteria for use that the specialists must document before use.
  5. Dexmedetomidine indicated for sedation in intubated and mechanically ventilated patients during treatment in an ICU setting may be restricted to use by intensivists; however, to curtail costs, there may be additional criteria that must be met by the intensivist before use.
- P. Once a drug is admitted for formulary approval, periodic assessments in the form of an MUE or reviews of use, cost, safety, and efficacy should be made, preferably within 3–6 months and again in 1 year.
- Q. An assessment of all drugs that are on formulary within a class should be made annually or more often when there is an important change in prescribing information, when a landmark trial or publication affects the drug's use, or when new FDA label-approved agents are available within the drug class. Medication assessments typically prompt updates and modifications to the drug's current use.

**Patient Case**

1. Which criterion for drug selection is most important when making decisions for drug formulary approval?
  - A. Adverse events.
  - B. FDA status.
  - C. FDA rank.
  - D. Absorption.

**II. MEDICATION USE EVALUATIONS**

- A. TJC requires drug use evaluations (DUEs) to be completed to monitor the safety of medications.
- B. *MUEs* and *DUEs* are terms often used synonymously. Both DUEs and MUEs are PI and QA methods that ensure optimal medication therapy management and improve patient safety and outcomes.
- C. A DUE is drug- or disease-specific, whereas an MUE is a broader term with a broader scope that focuses on a drug or class of drugs, the process or processes, and the outcome, with a specific emphasis on improving patient outcomes. MUEs will focus on several elements of the medication process/use such as prescribing, pharmacist medication order validating or verifying, dispensing, preparing, administering, monitoring, patient education, and outcomes.
- D. The sample size of the MUE depends on the type of medication data being analyzed—generally, a sample of 20–30 patients is sufficient; however, more patients may need to be surveyed to analyze patient outcomes—generally, a sample size of 100 or more.
- E. Data collection for specific criteria can use a yes/no format with a section for comments, or open-ended questions can be used. With the use of CPOE and electronic medical records, data retrieval, monitoring, and generating specialized reports have become easily accessible.

- F. The type and number of MUEs should be determined by the risk mitigated when using a medication. Medications selected for an MUE may be based on the following:
1. High risk
  2. High volume
  3. ADEs
  4. Preventable ADEs
  5. Near-miss and harmful medication errors
  6. Nonformulary requests
  7. Pharmacy intervention data
  8. Treatment failures
  9. Physician or nurse identification or request
  10. Patient concerns
  11. Off-label use
  12. High cost
- G. Examples of medications and medication use processes in critically ill patients that may be selected for an MUE can be found in Boxes 2 and 3.

**Box 2.** List of Medications That Are Used in Critically Ill Patients and That Are Suited for an MUE

1. Vecuronium and rocuronium	20. Midazolam
2. Warfarin	21. Hydromorphone
3. Clopidogrel	22. Naloxone
4. Argatroban	23. Fidaxomicin
5. Enoxaparin	24. Daptomycin
6. Heparin	25. Linezolid
7. Tranexamic acid	26. Polymyxin and colistin
8. Desmopressin	27. Acyclovir
9. Insulin	28. Phenytoin and fosphenytoin
10. Vasopressors	29. IV valproic acid
11. Tirofiban	30. Darbepoetin alfa
12. IV metoprolol	31. Cosyntropin
13. IV nicardipine	32. Neostigmine
14. IV verapamil	33. IV pantoprazole or esomeprazole
15. Alteplase and tenecteplase	34. Octreotide
16. Digibind	35. IV acetaminophen
17. Propofol	36. IV ibuprofen
18. Ketamine	37. IV ketorolac
19. Dexmedetomidine	38. Conivaptan

IV = intravenous.

**Box 3.** Examples of High-Risk Medication-Related Processes That Are Suited for an MUE in Critically Ill Patients

1. Insulin infusions
2. Hypoglycemic protocols
3. Sedation protocols
4. Management of hypoprothrombinemia
5. Management of DTI overdose
6. Use of pneumatic compression devices for DVT prophylaxis
7. Stress ulcer prophylaxis
8. Vancomycin dosing and ordering serum levels
9. Aminoglycoside dosing and ordering serum levels
10. Intermittent infusions of antimicrobials (e.g., carbapenems, piperacillin/tazobactam)
11. Use of $\beta$ -blockers in myocardial infarction
12. Antihypertensive IV-to-PO switch therapy
13. Antihypertensive use in acute stroke
14. Antimicrobial IV-to-PO switch therapy
15. Fluid resuscitation
16. Management of GI bleeding
17. Use of total parenteral nutrition
18. Use of albumin
19. Vaccine administration
20. Management of <i>C. difficile</i> diarrhea
21. Monitoring for dysrhythmias with QTc-prolonging drugs
22. Use of IV sodium bicarbonate
23. IV push medication guidelines (rate of administration and medication preparation—diluted or undiluted)
24. Hyperkalemia management guidelines
25. Hypomagnesemia management guidelines
26. Surgical prophylaxis guidelines
27. Alcohol withdrawal management
28. Management of status epilepticus
29. Management of hyponatremia

DTI = direct thrombin inhibitor; DVT = deep venous thrombosis; GI = gastrointestinal; IV = intravenous; PO = oral; QTc = corrected QT (interval).

- H. Use of an MUE should preferentially be proactive and should be used to determine whether there are any gaps in practice or patient safety.
1. An *interventional MUE* is completed concurrently or prospectively, and if criteria are not met, an intervention by the pharmacist can and should be made to improve the use of the medication and patient outcomes.

2. A *noninterventional MUE* is completed concurrently or retrospectively through a medical record review and data are collected, but when criteria are not met, an intervention is not made, or an intervention cannot be made because the review is retrospective, there is no pharmacist-to-prescriber interaction during the review process.
- I. MUEs should have specific criteria set – These criteria are best determined by a multidisciplinary team of medication or disease experts.
  - J. MUE criteria may be approved by the P&T committee. The P&T committee may create an MUE subcommittee. Other hospital committees such as the quality improvement committee may also request that an MUE be performed. Other names for the MUE committees may include formulary committee, drug safety committee, therapeutic assessment committee, medication safety committee, and drug utilization review committee.
  - K. The MUE subcommittee should be multidisciplinary and may be composed of the following:
    1. Clinical pharmacists
    2. Physicians
    3. Nurses
    4. Administrators
    5. PI/QA representatives
    6. Risk management representatives
  - L. By virtue of the pharmacist's expertise in medication management, pharmacists will often chair or co-chair the MUE subcommittee and perform the MUE.
  - M. The MUE subcommittee can recommend drugs and drug processes that require an MUE to the P&T committee; alternatively, the P&T committee can request MUEs from the MUE subcommittee.
  - N. The MUE process includes reviewing the findings and developing plans of improvement. The results and conclusions of the MUE should be reported to the P&T committee and department chairs.
  - O. After plans of correction are determined and actions taken, a follow-up MUE should be completed to document that improvement has occurred successfully.
  - P. Periodic MUEs in the same area should be performed every 3–6 months for 1 year to ensure that the corrections made remain effective and that they are sustained. If any new changes have occurred in the medication use process, the MUE criteria should be reassessed and the new criteria incorporated.
  - Q. To correct the findings from the MUE, policy development and educational initiatives should take place, such as:
    1. In-service lectures
    2. Newsletter publications
    3. Drug alerts
    4. Guideline development
    5. Protocols
    6. Policy and procedures
    7. CPOE pathways, prescribing guides, or information or pop-up warnings

**Patient Case**

2. Which medication use process is best suited for an MUE?
  - A. Review of pharmacist notes on the patient medical record (PMR).
  - B. Review of accuracy of expiration dates placed on intravenous admixture products.
  - C. Vancomycin dosing and ordering of vancomycin blood levels.
  - D. Frequency of drug interaction warnings on the CPOE system.

**III. QUALITY ASSURANCE**

- A. QA is defined as a process to monitor the effectiveness and safety of the medication use process that includes prescribing, dispensing, and administering medications. QA reviews, when followed by PI, decrease ADEs and medication errors.
- B. A QA may be completed to confirm that a practice is being adhered to or that there are variances and deficiencies in practice that need to be improved.
- C. An appropriate sample size that will allow for appropriate evaluation should be used when performing a QA review.
- D. The goal of a QA is to achieve 100% compliance; however, an acceptable variance may be determined.
  1. Preventing pregnant patients from receiving a category X drug would require 100% compliance; no variance would be acceptable.
  2. Preventing patients on a nasogastric tube (NGT) from receiving an oral drug through the NGT that is crushed and mixed with water rather than a readily available liquid dosage form; the threshold in this case may be set below 100% (e.g., 90%)
  3. Allowing for a 10% variance in vancomycin serum levels to be reported as random rather than peaks or troughs because pharmacists may be able to interpret random levels, or in some cases, a random level may have been purposely ordered for monitoring purposes—in this case, a variance may be allowed
- E. An appropriate threshold or standard should be determined for all criteria or process indicators that are evaluated during a QA review.
- F. The QA review can be administered by a pharmacist or other health care personnel or by members of the hospital's QA team.
- G. QA reviews and data collection may be completed intradepartmentally, such as within the pharmacy department, the ICU, or the emergency department; or they may be completed interdepartmentally or hospital-wide.
- H. QA data can be reported to the department, a hospital unit committee such as the ICU committee, or the hospital P&T committee.
- I. Pharmacy departments may have dedicated part- or full-time personnel to complete QA and PI projects.
- J. When the QA is complete and found to be below the acceptable threshold or standard determined, it can be used to develop a PI project.

K. Examples of QA Reviews

1. Timing of electronic verification of stat medication orders
2. Medication storage in refrigerators
  - a. Refrigerator temperature monitoring and action when the temperature is incorrect
  - b. Multidose vials appropriately labeled with expiration date after opening
3. Disposal of medications on the patient care units, central pharmacy, or satellite pharmacy
  - a. Unused tablets, capsules, and liquids
  - b. Patches (e.g., fentanyl)
  - c. Intravenous bags with remaining medication when the infusion is complete
  - d. Chemotherapy
4. Medication labeling – Are all parenteral medications labeled with required information?
5. Does the CPOE system detect duplicate medication orders when prescribed?
  - a. Isosorbide mononitrate and nitroglycerin products
  - b.  $\beta$ -Blockers
  - c.  $\beta$ -Agonists
  - d. Acetaminophen products
  - e. Laxatives such as stimulants or surfactants
  - f. Insulin products
  - g. Opioids such as morphine and hydrocodone
  - h. First- and second-generation antipsychotics such as haloperidol and olanzapine
  - i. Influenza vaccine (the order is placed but not administered and reordered)
6. Are nurses able to scan the barcodes of medications before administration?
  - a. Tablets and capsules
  - b. Liquids
  - c. Inhalers
  - d. Intravenous medications prepared by the pharmacy
  - e. Total parenteral nutrition
7. Does the CPOE system accurately detect drug allergy cross-reactivity and does it provide hard stops?
  - a. Penicillins and cephalosporins
  - b. Penicillins and carbapenems
  - c. Sulfonamides and combination products such as sulfamethoxazole/trimethoprim
  - d. Sulfones and combination products such as piperacillin/tazobactam
  - e. Morphine and codeine
8. Medication reconciliation
  - a. Are medications reconciled accurately on admission and by whom?
  - b. Are medications reconciled accurately when transferring the patient within the health system such as from the emergency department to the ICU or from the ICU to the internal medicine ward?
  - c. What percentage of medications are reconciled within 24 hours of admission?
  - d. What is the frequency of pharmacist-to-physician communication regarding medication discrepancies?
  - e. What percentage of medications are not reconciled?
9. Medication administration
  - a. Are oral medications crushed when administered through a feeding tube?
  - b. Are liquid medications prescribed, when available, for feeding tube administration?
  - c. Are intravenous push medications administered at the correct rate (slow vs. fast)?
  - d. Have intravenous push medications that require dilution been diluted appropriately or been administered undiluted?

- e. Are subcutaneous medications administered in the correct location (e.g. arm or abdomen) as recommended by the drug manufacturer
  - f. Are intermittent intravenous infusions administered over the correct amount of time and is the entire medication administered?
  - g. Are clinicians documenting in the PMR the response to medications on the first dose?
10. Therapeutic drug level monitoring
- a. Are vancomycin trough levels ordered when the drug is at steady state?
  - b. Are tobramycin peak and trough blood levels ordered?
  - c. Were tobramycin peak and trough levels drawn at the correct time?
  - d. Are patients taking phenytoin monitored with phenytoin trough levels?
  - e. Are patients taking valproic acid monitored with valproic acid trough levels?
11. Do pharmacists document appropriately?
- a. Do pharmacists enter patient allergy data, and do they enter them accurately?
  - b. Are pharmacist notes and pharmacotherapeutic recommendations to prescribers appropriate and accurate?
  - c. Do pharmacists document ADEs, and do they document them accurately?
  - d. Do pharmacists communicate between pharmacists effectively when using the pharmacy profile?
  - e. Are the hand-off procedures between pharmacists documented and are they effective?
12. Are policies and procedures updated annually?
13. Are CPOE pathways updated annually?
14. Are hospital-wide protocols and guidelines updated annually?
15. Are drug-drug interactions detected and managed?

**Patient Case**

3. Which statement is most appropriate when performing a QA survey for allergy cross-reactivity for ampicillin with other agents that may cross-react in the CPOE system?
- A. Setting the threshold of allergy detection with cefazolin at 80%.
  - B. Allowing for a variance of 10% for allergy detection with meropenem.
  - C. Setting the threshold of allergy detection with ceftriaxone at 100%.
  - D. Allowing for a variance of 15% for allergy detection with amoxicillin

**IV. PERFORMANCE IMPROVEMENT, QUALITY IMPROVEMENT, AND A GAP ANALYSIS**

- A. The terms *PI* and *QI* are often used synonymously and are interchangeable. By definition, quality improvement and PI improve on the effectiveness and safety of the medication use process and include prescribing, dispensing, and administering medications.
- B. PI is usually performed together with QA. When there are variances in the process indicators of a QA, a PI should be conducted. For example, when performing a QA and it is detected that medication orders are not being validated by pharmacists in a timely fashion, a PI project can be initiated to determine the barriers; then, a plan of correction is designed to improve the variance.
- C. PI may also be used as a result of data from an MUE.
- D. It is important to set a threshold or standard goal for the process indicators for all PI projects.

- E. PI projects may be inter- or intradepartmental and generally require the collaboration of several disciplines.
- F. Many hospitals have a QA/PI department and a QA/PI committee – Pharmacists should be members of the QA/PI committee and will focus on projects that affect the medication use process.
- G. QA/PI projects or reports can be one-time reviews, or they can be completed on a continuous basis. Some QA/PI projects or reports can be closed after successful improvement has been noted; others need to be reported permanently for regulatory reasons such as medication errors and ADEs.
- H. A sample QA/PI report for pharmacotherapeutic interventions is depicted in Appendix 1.
- I. A gap analysis is an assessment of a practice model that may be within your health system or pharmacy and that is compared with a best practice model. A gap analysis may focus on pharmacy services, pharmacy technology, or a specific medication or medication process.
- J. A gap analysis for medication safety should include strategies for prevention and mitigation, assessment and detection, therapeutic use, critical thinking and knowledge, and education. A gap analysis should also include policies, procedures, protocols, guidelines, competencies, staffing models, educational methods, and other key components to maximize efficacy and prevent medication errors and harm.
- K. A gap analysis should include the specific action, the gap analysis question, the assessment with a response of the level of compliance or implementation (e.g., fully, partly, in progress, no activity, or noncompliant), and an action plan that includes prioritization, the person responsible, and a timeline for completion.
- L. Examples of a Gap Analysis Include the Following:
  - 1. Hypoglycemic agent adverse event prevention (Appendix 2)
  - 2. Opioid ADE prevention
  - 3. Anticoagulation agent ADE prevention
  - 4. Aminoglycoside ADE prevention
  - 5. Intravenous-to-oral conversion of antihypertensives
  - 6. Medication labeling
  - 7. Medication barcoding and scanning
  - 8. Narcotic diversion prevention
  - 9. Sterile admixture services
  - 10. Extemporaneous compounding services
  - 11. Pharmacist activities during a code or rapid response
  - 12. Pharmacy staffing models
  - 13. PPMI (Pharmacist Practice Model Initiative) adherence such that all patients have a right to the care of a pharmacist

**Patient Case**

4. Which is best suited for a PI project?
- A. A review of appropriate dosing of gentamicin in patients with sepsis.
  - B. A review of the number of patients receiving heparin for a pulmonary embolism who achieve a therapeutic partial thromboplastin time (PTT) within 24 hours was 40%.
  - C. A medication pass review of nurses administering medications through the feeding tube.
  - D. Ensuring the appropriate disposal of chemotherapy in the ICU satellite pharmacy.



**V. ADVERSE DRUG EVENTS**

- A. In the United States, 770,000 injuries or deaths are caused by adverse drug reactions (ADRs) annually; the cost burden of ADEs is greater than \$5.6 million per hospital.
- B. A severe ADE increases the length of stay by 8–12 days at a cost of \$16,000–24,000.
- C. The cost burden of preventable ADEs in the United States is \$2 billion annually.
- D. Medical malpractice lawsuits are often related to or occur because of ADEs.
- E. The risk of ADEs increases when patients are critically ill and taking many high-risk medications—specifically intravenous medications—with several illnesses and multiorgan failure.
- F. TJC Medication Management Standard requires hospitals to respond to actual or potential ADEs, significant ADRs, and medication errors.
- G. At the very least, hospitals need to respond, document and report, and manage ADEs. The pharmacist is the drug expert and should play an integral in the ADE process.
- H. Definitions: Medication Errors, ADEs and ADRs
  1. A medication error is a mishap that occurs during prescribing, transcribing, dispensing, administering, adherence, or monitoring a drug. Medication errors that are intercepted and stopped before they occur are called “near misses.” Some medication errors cause harm, and some do not. Medication errors that cause significant harm may be reported through the health system’s patient incident reporting system.
  2. An ADE is an *injury* resulting from the use of a drug, which includes *harm* caused by the drug (ADRs and overdoses) and harm from the use of the drug, including dose reductions and discontinuations of drug therapy.
  3. An ADR defined by the World Health Organization (WHO) as “any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.”
  4. Karch and Lasagna define an ADR as “any response to a drug that is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose.”
  5. The primary difference between the WHO and the Karch and Lasagna ADR definitions is that, according to the WHO definition, therapeutic failures are an unintended effect and an ADR, whereas according to the definition by Karch and Lasagna, they are not. ADRs caused by therapeutic failures with easily retrievable, detailed data that document the drug and the therapeutic failure can have a significant impact on improving patient care.
  6. Overall, *ADE* is the broader term that is used to describe any *harmful* event associated with a medication, including inappropriate use such as an overdose, whereas *ADR* is used when an adverse response, including harm, occurs with normal use of the medication.
  7. Examples of therapeutic failures that may be documented as ADRs according to the WHO criteria include:
    - a. Clopidogrel failure to prevent an ischemic stroke
    - b. Enoxaparin failure to prevent DVT (deep venous thrombosis)
    - c. Famotidine failure to prevent intravenous ketorolac-induced gastropathy

- d. Pantoprazole failure to prevent gastrointestinal (GI) bleeding from a stress ulcer in a critically ill patient
  - e. Haloperidol failure for sedation in a delirious critically ill patient
8. Examples of ADRs
- a. Lorazepam when being used to treat anxiety may cause sedation – This is an adverse reaction; conversely, lorazepam for sedation in a critically ill patient is an intended effect, not an ADR.
  - b. Diphenhydramine causing sedation when it is being used to treat allergic rhinitis – This is an adverse reaction; conversely, diphenhydramine as a sedative hypnotic is an intended effect, not an ADR.

I. ADR or Side Effect

1. There is often controversy regarding whether all ADRs should be reported and documented and whether ADRs are the same as or different from side effects.
2. The American Society of Health-System Pharmacists (ASHP) defines a side effect as an expected well-known reaction resulting in little or no change in patient management, such as antihistamine-induced drowsiness.
  - a. The term *side effect* may minimize or downplay the risk of injury from medications.
  - b. It has been suggested that the term *side effect* be avoided in favor of the term *ADR*.
  - c. In general, *side effects* and *ADRs* are terms used synonymously.
3. Although the ASHP definition of a side effect differs from the WHO definition of an ADR, any reaction to a medication, including a side effect, must be documented in the PMR. It is also prudent and good practice to document side effects in the patient's ADE profile. Medication side effects are not without consequences and can lead to harmful effects. For example, an antihistamine-induced drowsiness may lead to a traumatic fall and hip fracture, resulting in hip replacement surgery. Documenting the ADR and managing the event with a lower dose of the antihistamine or switching to a less-sedating agent could prevent a side effect from spawning into a severe ADR.
4. ASHP further defines a side effect as an effect with a predictable frequency and an effect whose intensity and occurrence are related to the size of the dose. Predictable "side effects" should also be reported as ADRs, such as:
  - a. Insulin-induced hypoglycemia
  - b. Chemotherapy-induced nausea
  - c. Opioid-induced pruritus
5. Adverse effects whose intensity and occurrence are related to the size of the dose should also be reported as ADRs. The benefits of reporting and managing these side effects are primarily prevention. Examples of side effects caused by increasing the size of the dose are the following:
  - a. Increasing doses of insulin causing hypoglycemia
  - b. Increasing doses of morphine causing drowsiness
  - c. Increasing doses of valproic acid causing confusion
  - d. An increased dose of aspirin causing dyspepsia

J. Preventable ADEs

1. A preventable ADE occurs when a breach of standard professional behavior, practice, or technique was identified but or when necessary precautions were not taken, or when the event was preventable by modification of behavior, practice, technique, or care.
2. Results from any medication error that reaches the patient and causes harm
3. Events that are not clearly preventable may be classified as "possibly preventable."
4. About 30%–50% of all ADEs are preventable ADEs.
5. About 30% of the ADR-related hospitalizations are considered preventable.

6. Drug interactions account for 3%–5% of all preventable in-hospital ADRs.
7. Examples of non-preventable ADEs
  - a. Rash from an unknown allergen
  - b. Known ADRs without known mitigation strategies
  - c. Known ADRs that are accepted for the benefit of the drug (e.g., nausea with chemotherapy, dyspepsia with a nonsteroidal anti-inflammatory agent)
8. Examples of preventable ADEs
  - a. Heparin administration without the use of weight-based dosing causing an elevated PTT and an intracranial hemorrhage
  - b. Phenytoin mixed accidentally with dextrose rather than normal saline causing precipitation and lack of drug potency leading to a patient developing withdrawal seizures and status epilepticus
  - c. Levofloxacin intravenous and azithromycin intravenous prescribed to a patient receiving haloperidol with a known prolonged QTc (corrected QT) interval on the electrocardiogram and the patient develops torsades de pointes
  - d. Bactrim intravenous prescribed to a patient receiving warfarin causing inhibition of warfarin metabolism, displacement from warfarin's plasma protein-binding sites, and hypoprothrombinemia causing the patient to develop a GI bleed
  - e. Rivaroxaban prescribed to a patient for nonvalvular atrial fibrillation stroke prevention who is receiving rifampin; rifampin increases rivaroxaban hepatic metabolism through cytochrome P450 (CYP) 3A4 and induction of P-glycoprotein, which may cause subtherapeutic rivaroxaban serum levels and lead to decreased efficacy, in turn causing the patient to develop a stroke
  - f. Carbamazepine prescribed for an Asian patient with bipolar disorder without testing for the *HLA-B\*1502* allele; in turn, the patient develops carbamazepine-induced toxic epidermal necrolysis

#### K. FDA-Reportable ADEs

1. For reporting an ADE to the FDA, the FDA defines ADEs as serious adverse events related to drugs or devices in which “the patient outcome is death, life threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage. Reportable serious ADEs to the FDA may include:
  - a. Phenytoin-induced toxic epidermal necrolysis
  - b. Linezolid-induced thrombocytopenia with genitourinary hemorrhage
  - c. Clopidogrel-induced thrombotic thrombocytopenic purpura with seizures and hepatic failure and the use of plasmapheresis
  - d. Rivaroxaban-induced intracranial hemorrhage
  - e. Olanzapine-induced torsades de pointes
  - f. Gentamicin-induced irreversible auditory ototoxicity
  - g. Acetaminophen-induced hepatotoxicity
2. An example of a reportable adverse event caused by a device may be the mechanical failure of a pneumatic compression device leading to a pulmonary embolism and death.
3. The FDA is also interested in serious ADE reports for newly marketed drugs, or novel adverse events that have not been previously reported for new or old drugs.
4. The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse events and medication error reports that have been submitted to the FDA. The database is used as a postmarketing surveillance system for medications and therapeutic biological products.

5. The reporting of ADEs by health care professionals and consumers to the FDA is voluntary and may be done through the FDA's MedWatch program (initiated in 1993). All of the following may be reported with respect to an FDA-regulated medication, biologic, tobacco product, dietary supplement, cosmetic, or medical device:
    - a. Serious ADE
    - b. Serious ADR
    - c. Product quality problem
    - d. Product use error
    - e. Therapeutic in-equivalence
    - f. Therapeutic failure
  6. Clinicians may report an ADE directly to the drug's manufacturer. The pharmaceutical manufacturer has a legal responsibility to follow up with the reporter on all ADEs reported and to report the ADE to the FDA.
  7. ADE reports and medication error reports submitted directly by health care professionals or manufacturers are entered in the FAERS database.
  8. If the FDA detects a safety concern, it may take regulatory action to protect the public, such as updating the product labeling, restricting the drug, communicating the safety concerns to health care professionals and consumers, or removing the drug from the market.
- L. Designing an ADE Reporting Program
1. A comprehensive ADE program should have a policy and procedure, with guidelines for ADE detection, reporting, management, surveillance, and education.
  2. By virtue of the pharmacist's expertise in drug-induced diseases and the pharmacist's role in preventing and managing ADEs, pharmacists will often serve as chairman or co-chairman of the ADE committee.
  3. The ADE committee should be multidisciplinary and should be composed of the following:
    - a. Physicians
    - b. Pharmacists
    - c. Nurses
    - d. Risk management personnel
    - e. QA/PI personnel
    - f. Other health care providers
  4. In general, the ADE committee is a subcommittee of the P&T committee that will report to the P&T committee.
  5. The ADE committee should meet periodically and can meet monthly, bimonthly, or quarterly, depending on the number of reports and actionable items that need review.
  6. ADE data can be reported by specialty unit or service, such as:
    - a. Intensive care
    - b. Internal medicine
    - c. Telemetry
    - d. Rehabilitation
    - e. Psychiatry
    - f. Emergency medicine
    - g. Operating room
    - h. Oncology
    - i. Pediatric
    - j. Geriatric
  7. ADE data should be reported as mild, moderate, and severe ADEs – Definitions for each should be established (Box 4).

**Box 4.** Definitions for the Degree of ADE Severity (in ascending order of severity)<sup>a</sup>

1. Mild ADE: Results in heightened need of patient monitoring with or without a change in vital signs, but no ultimate patient harm, or any adverse event that results in the need for increased laboratory monitoring
2. Moderate ADE: Results in the need for aggressive intervention with antidotes and/or increased length of hospital stay (e.g., severe hypotension (e.g., BP < 90/50 mm Hg), bleeding necessitating transfusions)
3. Severe ADE: Results in harm to the patient, prolonged hospitalization, transfer to a higher level of care, permanent organ damage (e.g., irreversible hepatotoxicity or renal failure), or death with <i>probable</i> ADE causality nomogram score

<sup>a</sup>Other ADE severity scales are available.

BP = blood pressure.

8. The ADE subcommittee should designate which ADEs are preventable and should provide explanations regarding why they were preventable. Examples of preventable ADEs include
  - a. A patient receiving vancomycin who develops nephrotoxicity as a result of an incorrect high-dosing regimen and lack of serum level monitoring
  - b. A patient with epilepsy maintained on intravenous valproic acid who develops breakthrough seizures as a result of subtherapeutic valproate serum levels caused by a drug-drug interaction with the concomitant use of doripenem
9. The ADE committee will determine which ADEs will be reported to the FDA or and the manufacturer.
10. The committee should report the data regarding who is detecting ADEs and who reports, documents, and manages the ADEs.
11. The committee should provide trending data based on either drug or drug class.
12. The committee should benchmark the hospital's ADEs against itself in previous years and compare them with the data from other hospitals published in the biomedical literature. Total ADE data can be reported according to the following:
  - a. Total number of ADEs
  - b. ADEs per admission
  - c. ADEs per patient
  - d. ADEs per patient days
  - e. ADEs per doses dispensed
  - f. ADEs per doses administered
13. A popular method of reporting ADEs is by the total number of admissions, with an acceptable benchmark of 2.5%–10%. For example, a hospital with 10,000 admissions reporting 1000 ADEs would have a 10% ADE reporting rate.
14. ADE benchmarks are daunting to determine because of the many variables that affect the reporting methods, such as the ADE definition used by the facility or the definition used by the reporter, the number of clinical pharmacists or pharmacy residents available to report, the vigilance and emphasis of the reporting systems, and the use of technology or reports to increase reporting.

**M. Documenting ADEs in the PMR**

1. Allergy data are always documented in the PMR and are a required element in the patient's profile, which also includes demographics, diagnosis, and pregnancy category. Preferably, the medication that caused the allergy, the type of reaction, and when the allergy occurred should be documented.
2. A drug-induced allergy is an ADE. It is tantamount to report and document ADE data in the PMR for the same purpose as is documenting allergy data—to prevent recurrence with the same drug or a drug from the same or similar drug class and to mitigate risk when the same drug may need to be used again or to mitigate risk when other medications that can cause the same adverse event are used.

3. ADE data should be recorded in the electronic medical record and should be a permanent record that is maintained in the record infinitely.
4. For severe ADEs: When the same drug is prescribed, the CPOE system could be programmed to cause a hard stop and prevent the drug from being prescribed or a hard stop requiring a text message with an explanation for use. For example, a case of isoniazid-induced hepatotoxicity may be classified as a severe ADE, and if prescribed to the same patient again, the prescriber would receive a hard stop and would need to provide an explanation for its use in order to have the order validated by the pharmacist.
5. For moderate ADEs: When the same drug is prescribed, the CPOE system could be programmed to highlight or warn the prescriber or require a text response with an explanation for its continued use.
6. For mild ADEs: When the same medication is prescribed, the CPOE system could be set to highlight the prescriber, or the data could be retrievable for review but without prompting the clinician. A case of enalapril-induced hypotension may be recorded as a mild ADE and be maintained for informational purposes but will not prevent the medication from being prescribed to the patient again, nor will it require the prescriber to provide an explanation.

#### N. Methods of ADE and Medication Error Surveillance

1. ADEs can be detected prospectively and retrospectively. Pharmacists may detect ADEs prospectively while on patient care daily rounds, or from communication with patients while administering medication histories or discharge counseling. Pharmacists may also detect ADEs retrospectively through chart reviews or during medication histories.
2. An excellent method of prospective ADE and medication error detection is through direct observation; this can be accomplished using the medication pass method in which the pharmacist observes nurses in the medication administration process and notes any errors or ADEs that occur. Other examples of direct observation may include nurses observing nurses or physicians observing physicians during medication administration.
3. ADEs can be detected by nurses during patient care activities such as medication administration or during monitoring activities such as vital signs or through patient concerns. Nurses are often the first caregiver to detect the following:
  - a. Injection-site reactions
    - i. Hematomas
    - ii. extravasation
  - b. Vital sign changes
    - i. Antimicrobial-induced drug fevers
    - ii. Digoxin-induced bradycardia
    - iii. Opioid-induced respiratory depression
  - c. Drug-induced nausea or dyspepsia
4. Physicians often detect adverse reactions from abnormal laboratory data, while administering a physical examination, during drug administration, or from patient concerns.
5. A source for detecting ADEs is by monitoring the CPOE system for trigger or tracer drugs – These terms are used synonymously. Trigger or tracer drugs are drugs that are routinely prescribed to treat ADEs such as antidotes or physiologic antagonists or agents for gastric decontamination.
6. Examples of tracer drugs are:
  - a. Dextrose for hypoglycemia
  - b. Naloxone for opioid-induced respiratory depression
  - c. Protamine for heparin toxicity
  - d. Activated charcoal for drug toxicity such as with phenytoin or acetaminophen
7. The trigger drug list can be monitored by clinical pharmacists, allowing the pharmacist to ensure that ADE documentation occurred and appropriate management is taking place.

8. The CPOE system can be programmed with a list of tracer drugs so that when a prescriber orders a tracer drug, he or she is asked whether the order is for an ADE and, if so, what type of ADE occurred. The potential ADE can then be reported and managed by the clinical pharmacist. One of the benefits of this system is that it captures ADEs that might not have been reported, especially when a clinical pharmacist may not be present on the unit or on daily patient care rounds, and it allows for an increased number of physician-reported ADEs. Figure 1 depicts a CPOE sample screen prompting prescribers to report an ADE. A list of trigger or tracer drugs is depicted in Box 5.

Enter Medication Orders      Adverse Drug Reactions      06/12/03 0942  
 TEST ,PHARM2      09/26/00 0757  
 Attn Dr: TRAINING DOCTOR2      K      NA      CL      CR  
 Allergies: PENICILLINS      SALICYLATES

Drug Name: BENADRYL      Dose: 50.      MG

An ADR is any noxious and unintended response to a drug which occur at doses normally used in man. Examples include: allergic reactions, rashes, itching, nausea, vomiting. See below for more examples.

1. Was this drug ordered due to a possible adverse drug reaction?       Y       N     

2. Type of reaction     

3. List possible causative drug (if known)     

3. What is your beeper number? (should follow-up be needed)     

JCAHO Standard PI.4.5.4 states that all significant adverse drug reactions are assessed.

F2 Main Menu       F4 ADR EXAMPLES  
 F3 Skip Order       Press Enter to Continue

PHMADR01      Ovr      Field Help

Figure 1. CPOE Sample Screen for Adverse Drug Reaction Reporting

**Box 5. Medications Used as Triggers or Tracers to Aid in Reporting ADEs**

1. Atropine sulfate 1-mg injection	12. Kaopectate suspension
2. Activated charcoal suspension	13. Kayexalate
3. Benztropine PO/IM/IV	14. Loperamide
4. Diphenhydramine PO/IM/IV	15. Diphenoxylate/atropine
5. D50 IV push	16. Metronidazole IV/PO
6. Digibind	17. Naloxone
7. Epinephrine 0.15-mg injection	18. Prednisone solution/tablet
8. Epinephrine 1-mg injection	19. Protamine
9. Fidaxomicin	20. Sodium phosphate injection or solution
10. Flumazenil	21. Vancomycin capsule
11. Hydrocortisone cream/ointment or injection	22. Vitamin K

D50 = dextrose 50%; IM = intramuscularly; IV = intravenously; PO = orally.

9. Therapeutic drug level and abnormal laboratory value monitoring can be another source for ADE detection.
10. The pharmacy may design daily reports that contain all the abnormal drug serum levels such as the phenytoin, digoxin, lithium, amiodarone, vancomycin, and aminoglycoside levels. The clinical pharmacist can then review all cases of supra-therapeutic concentrations for ADEs such as:
  - a. Phenytoin-induced confusion, ataxia, or nystagmus
  - b. Amiodarone-induced pulmonary or thyroid toxicity
11. A daily report can also provide abnormal electrolytes and abnormal serum creatinine and hepatic function (bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase ALT) to detect drug-induced adverse effects such as:
  - a. Rifampin-induced hepatotoxicity
  - b. Lisinopril-induced hyperkalemia
  - c. Ketorolac-induced nephrotoxicity
  - d. Esomeprazole-induced hypomagnesemia
12. Other methods of reporting ADEs include calling an ADE telephone hotline, preferably with an easy-to-remember telephone number (e.g., 333 or A = 2, D = 3, E = 3). ADE forms may be used and maintained on all nursing units or readily available in the hospital's intranet, and when completed, they can be forwarded to the clinical pharmacist and/or the ADE committee. A sample ADE form with the Naranjo Nomogram for Causality is depicted in Appendix 3.
13. ADEs can also be reported by notifying the clinical pharmacist, the central pharmacist, or any pharmacy personnel.
14. The self-reporting of fatal ADEs can be problematic and lead to underreporting for several reasons, such as:
  - a. Cases are not properly described in the PMR.
  - b. The actual cause of death, although drug induced, is usually reported in biological terms (e.g., cardiac or respiratory arrest) on the death certificate.
  - c. Clinicians are not comfortable incriminating themselves because they may have prescribed the medication that led to the fatality.
  - d. It may be difficult to directly discern the drug as the cause of the fatality.

**Patient Cases**

5. Which best classifies the degree of severity of an ADE in a patient who develops enalaprilat-induced asymptomatic hyperkalemia ( $K^+ = 5.7$  mEq/L) managed with one dose of Kayexalate?
  - A. Mild.
  - B. Moderate.
  - C. Severe.
  - D. Life threatening.
6. Which best classifies the degree of severity of an ADE in a patient who develops intravenous haloperidol-induced torsades de pointes that is successfully treated with intravenous magnesium?
  - A. Mild.
  - B. Moderate.
  - C. Severe.



**Patient Cases** (*continued*)

*Questions 7 and 8 pertain to the following case.*

M.S., a 77-year-old man residing in a nursing home, has been taking lisinopril 10 mg daily for the past 3 months. He is admitted to the ICU with lisinopril-induced angioedema presenting with severe tongue swelling, stridor, and shortness of breath that required a tracheotomy. He had no history of allergies and did not miss any doses of lisinopril.

7. Which best describes this patient's reaction to lisinopril?
  - A. An ADE.
  - B. A preventable ADE.
  - C. A medication error.
  - D. A preventable ADR.
  
8. Which best classifies the degree of severity of this patient's ADE to lisinopril?
  - A. Mild.
  - B. Moderate.
  - C. Severe.

**VI. DOCUMENTATION PROCESSES USED FOR CRITICAL CARE PHARMACY SERVICES**

- A. The evidence of economic benefit and improvement of patient safety for clinical pharmacy services (CPS) and critical care pharmacy services is well established.
- B. Clinical pharmacy interventions that affect patient care should be documented in the PMR.
- C. Documentation of CPS is also important to tabulate CPS and workload and to provide justification for maintaining and expanding services.
- D. There are generally three types of pharmacist interventions: formal consultations solicited by physicians, informal consultations solicited by physicians and health care providers, and unsolicited interventions.
- E. Collaborative Drug Therapy Management (CDTM) – When a prescriber and a pharmacist establish written guidelines or protocols authorizing the pharmacist to initiate, modify, or continue drug therapy for a specific patient. CDTM is a type of pharmacotherapeutic intervention that should be documented and reported.
- F. Documenting the Pharmacotherapeutic Intervention in the PMR Through the Electronic Medical Record or by Paper in the Medical Chart – Provides for transparency between all health care professionals—physicians, nurses, pharmacists, dietitians, respiratory therapists, and social workers.
- G. Pharmacists can also document interventions in the pharmacy profile; however, this method generally allows for review only by pharmacy personnel who have access to the pharmacy computer system such as pharmacists, pharmacy interns, pharmacy students, and pharmacy technicians.

- H. Both methods should be available for documenting pharmacotherapeutic interventions, and criteria should be established to determine which method is most appropriate.
- I. Pharmacists should have the authority to document pharmacotherapeutic interventions in the PMR.
- J. The Department of Pharmacy should have a policy and procedure for documenting clinical pharmacy interventions.
- K. Pharmacists should be trained and educated to document in the PMR. The ASHP Clinical Skills Program is a tool that can be used to train pharmacists to document in the PMR.
- L. Documentation methods may include the use of standard format documentation methods such as:
  - 1. SOAP (subjective, objective, assessment, plan)
  - 2. TITRS (title, introduction, text, recommendation, signature)
  - 3. FARM (findings, assessment, resolution, and monitoring)
- M. Unsolicited pharmacist interventions should be documented subtly, allowing the primary provider to decline the recommendation without incurring liability. Phrases that can be used include:
  - 1. “May consider”
  - 2. “Suggest”
  - 3. “May recommend”
  - 4. Alternatively, the wording for solicited consultations may be more direct.
- N. When feasible, written notes by pharmacists should be documented in the PMR after orally communicating with the clinician; this allows for any patient data discrepancies to be corrected and for agreement and confirmation between the prescriber and the pharmacist to execute the intervention.
- O. Pharmacists should follow up on their patient interventions daily and provide follow-up notes that include patient progress or new interventions, when needed.
  - 1. The pharmacist should provide his or her contact information.
  - 2. Co-signatures should be required for pharmacy residents, pharmacy interns, and pharmacy students.
- P. Continuous quality improvement should include quality indicators and periodic reviews of pharmacist-written documentation and consultations.
- Q. CPS should be evaluated for cost impact and cost outcomes savings.
- R. Many Web-based or hand-held electronic systems are available that can be used to document and report pharmacotherapeutic interventions and cost savings, such as:
  - 1. Quantifi by Senti7, Wolters Kluwer
  - 2. Clinical Measures by Gold Standard, Elsevier
- S. These reporting systems allow for collecting data, aggregating data, and benchmarking data against other hospitals and bed size, and they increase the credibility of data collection methods and results when evaluated by health care administrators.

- T. To document raw drug cost savings from switching to less expensive medications, the following method may be applied: subtract the cost of the originally prescribed drug therapy (drug daily cost multiplied by the number of days prescribed) from the cost of the less expensive drug therapy (drug daily cost multiplied by the number of days prescribed). Using this method, the cost of intravenous diluents and admixture fluids and syringes used in the preparation process may be included.
- U. Documentation of interventions for reporting to other hospital committees such as the P&T committee should include the following elements:
1. Date, time
  2. Type of intervention
  3. Drug used
  4. Prescriber name, service, and type (attending or resident)
  5. Duration of time spent completing the intervention
  6. Whether the intervention was accepted, denied, or clarification achieved
- V. Pharmacotherapeutic intervention data should be presented and sensationalized at as many committee opportunities as possible—this increases the visibility and corroborates the importance of the pharmacy department and the critical care pharmacy services. Pharmacotherapeutic intervention data should be presented to the following:
1. ICU committee
  2. P&T committee
  3. QA committee
  4. Utilization review committee
  5. Medical executive committee
- W. Box 6 lists the types of pharmacotherapeutic interventions that can be reported.
- X. Pharmacotherapeutic intervention data may be presented quarterly (Figure 2) and should include the type of intervention (Figure 3) and both the raw drug cost savings derived from switching to less expensive drugs and the outcome cost savings such as preventing an adverse event and increasing the length of stay (Figure 4).

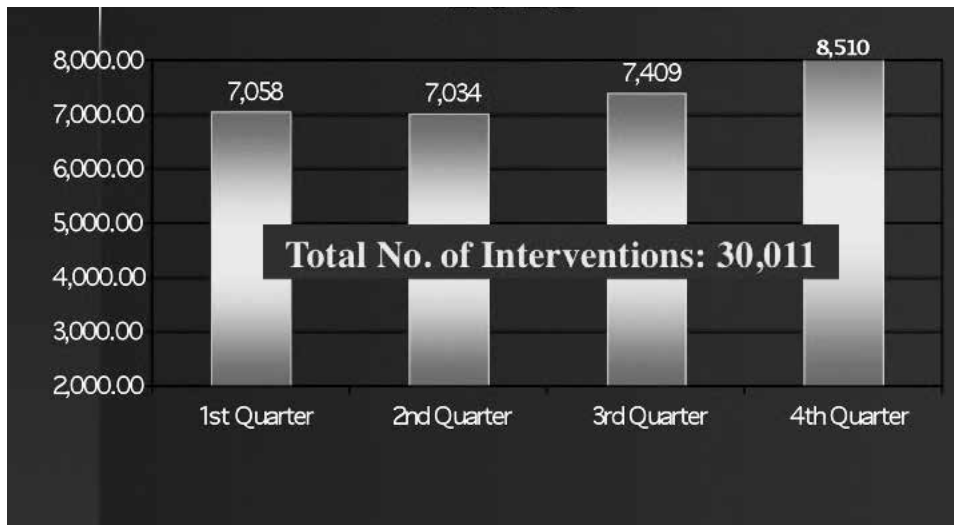
**Box 6. Types of Pharmacotherapeutic Interventions**

1. Discontinue drug	22. Medication reconciliation
2. Switch drug	23. Discharge counseling
3. Switch drug for less expensive but equally safe and effective drug	24. Written patient education provided
4. Drug dosing	25. Patient adherence to medications
5. Drug dosage form	26. Adverse drug reaction
6. Drug route	27. Overdosage
7. Pharmacokinetic consultation	28. Subtherapeutic dose
8. Pharmacotherapy consultation	29. Medication error
9. Intravenous to oral switch therapy	30. Monitoring for efficacy
10. Contraindication	31. Monitoring for toxicity

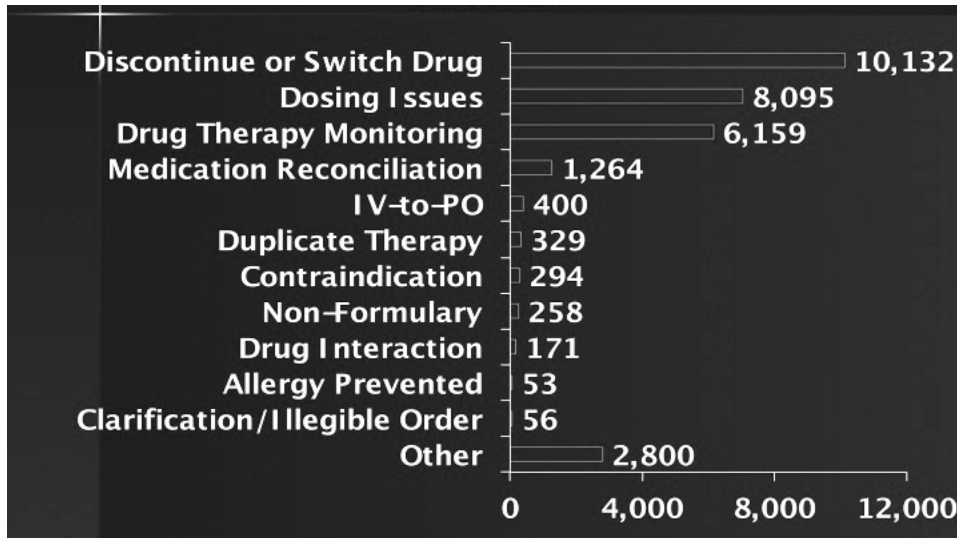
**Box 6.** Types of Pharmacotherapeutic Interventions (*continued*)

11. Duplicate therapy	32. Ordering laboratory tests for monitoring drug efficacy and toxicity
12. Nonformulary switch to formulary	33. Clarification of medication order
13. Nonformulary approval	34. Untreated indication
14. Drug unavailable	35. Failure to receive medication
15. IV drug incompatibility	36. Immunization recommendation
16. Drug-drug interaction	37. Immunization administered
17. Drug-food interaction	38. Health risk assessment
18. Drug-laboratory test interaction	39. Rapid response interventions
19. Pharmacogenomics interaction	40. Code interventions
20. Therapeutic interchange	41. CDTM interventions
21. Allergy prevention	

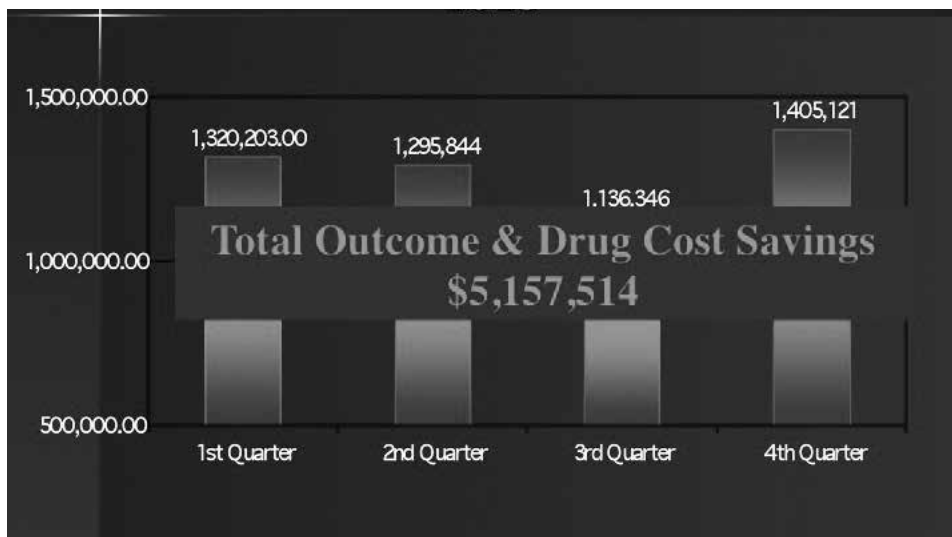
CDTM = collaborative drug therapy management; IV = intravenous.



**Figure 2.** Pharmacotherapy Interventions 2013



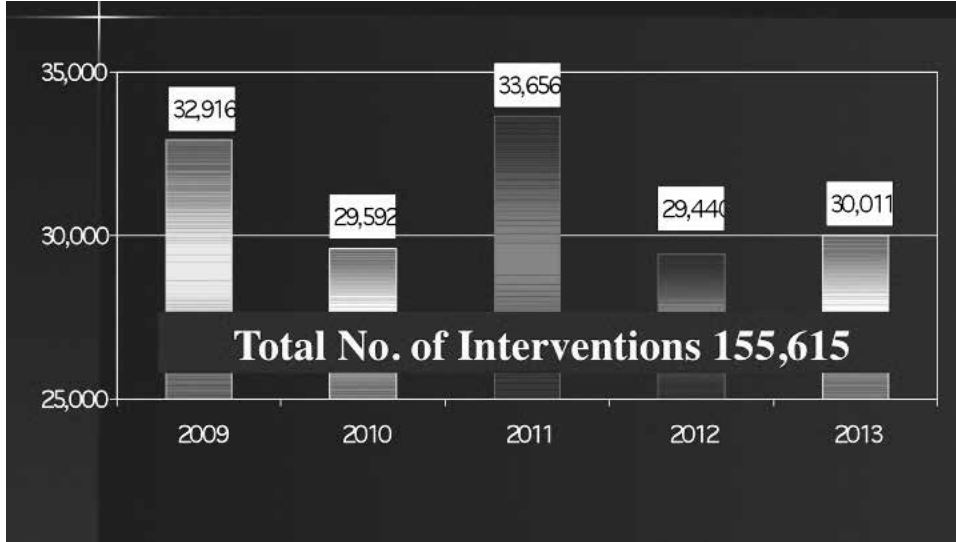
**Figure 3.** Pharmacotherapy Intervention Types 2013



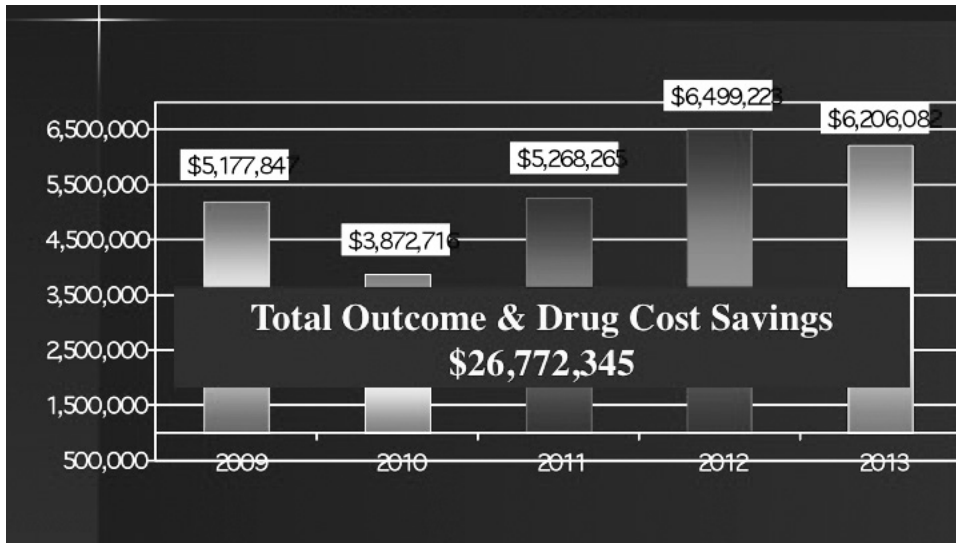
**Figure 4.** Raw and Outcome Drug Cost Savings 2013

- Y. It is also prudent to benchmark the total annual number of pharmacotherapeutic interventions with previous years (Figure 5) and the cost savings with previous years (Figure 6) and to provide rational explanations for any discrepancies noted.
- Z. Pharmacotherapeutic interventions that are reported may be prioritized according to their clinical impact on patient safety and cost savings. Examples of high-priority pharmacotherapeutic interventions that should be reported include the following:
1. Allergy prevented
  2. Contraindication prevented
  3. Drug dosing adjustments
  4. Duplicate therapy avoided

5. Drug interactions avoided
6. Medication reconciliation intervention
7. Ordering laboratory tests for monitoring of drug safety and efficacy
8. Switching drug for less expensive but equally safe and effective drug



**Figure 5.** Annual Pharmacotherapy Interventions 2009–2013



**Figure 6.** Annual Raw Drug and Outcome Cost Savings 2009–2013

## VII. DRUG INTERACTIONS

- A. Definition of Drug Interactions
  - 1. When the effects of one drug can be changed by the presence of another
  - 2. Can be benign and insignificant
  - 3. Can be harmful and life threatening
  - 4. Almost always completely preventable
    - a. Avoid the combination and switch to an alternative therapy.
    - b. Adjust doses to compensate for the interaction.
    - c. If the combination cannot be avoided, monitor for efficacy and toxicity of the *object* drug.
  
- B. A documented drug interaction with known outcomes can be considered an ADR, a medication error, or a preventable ADR.
  
- C. Drug Interaction Databases Include the Following:
  
- D. Lexicomp, Micromedex, Epocrates, Clinical Pharmacology, Hansten and Horn's Drug Interactions Analysis and Management, Stockley's Drug Interactions, and PDR Drug Interactions
  - 1. Most compilation databases have drug interaction software in which the pharmacist can provide a list of drugs, and the database will provide the type of interaction and severity.
  - 2. Lexicomp scale for drug interactions
    - A = No known interaction
    - B = No action needed
    - C = Monitor therapy
    - D = Consider therapy modification
    - X = Avoid combination
  - 3. Micromedex scale for drug interactions
    - a. Severity scale: Unknown, minor, moderate, major, contraindicated
    - b. Documentation scale: Excellent, good, fair, unknown
  - 4. Hansten and Horn's Drug Interactions Analysis and Management
    - a. Provides summary, risk factors, mechanism, clinical evaluation, related drugs, and references
    - b. Class of interaction with brief explanation
      - 1 = Avoid combination. Risk always outweighs benefit.
      - 2 = In general, avoid combination. Use combination only under special circumstances.
      - 3 = Minimize risk. Take action as necessary to reduce risk.
      - 4 = No action needed. Risk of adverse outcomes appears small.
      - 5 = No interaction. Evidence suggests no interaction.
  - 5. Stockley's Drug Interactions: Provides outcome, clinical evidence, mechanism, importance, and management
  
- E. Safety Measures to Avoid Drug Interactions
  - 1. Pharmacist review and validation
    - a. Pharmacists are highly trained in pharmacology and drug interactions and are expected to be highly knowledgeable in drug interactions.
    - b. Pharmacists' scope of practice includes a comprehensive review of patients' medications for drug interactions.
    - c. Do not bypass the pharmacists' check, such as with nurses overriding medications before removing drugs from automated dispensing cabinets.

- d. All prescription records maintained in one profiling system
  - e. Fill all medications in the same pharmacy to maintain a comprehensive and accurate medication record.
2. Using CPOE system and software that detects drug interactions
    - a. Pop-up warnings
    - b. Soft stops with explanation required
    - c. Hard stops
    - d. In general, does not detect pharmacodynamic antagonistic interactions such as a  $\beta$ -blocker and a  $\beta$ -agonist or a cholinergic drug with an anticholinergic drug
    - e. CPOE system must have drug interaction software activated. May prompt prescriber with a high frequency of messages and desensitize the prescriber to the warning
  3. Using the pharmacy computer system to detect drug interactions
  4. Education as a method to prevent drug interactions
    - a. Lectures, grand rounds, daily patient care rounds
    - b. Pocket drug cards
    - c. Drug alerts
    - d. Electronic drug information databases
- F. Pharmacokinetic Drug Interactions: One drug affects the absorption, distribution, metabolism, or excretion of the substrate drug – Phenytoin and rifampin
- G. CYP Isoenzymes
1. Embedded primarily in the lipid bilayer of the endoplasmic reticulum of hepatocytes
  2. Known as phase I reactions – Oxidation, reduction, and hydrolysis
  3. Primary CYP hepatic enzymes
    - a. 3A4
    - b. 2D6
    - c. 1A2
    - d. 2C9
    - e. 2C19
  4. Extrahepatic metabolism
    - a. 3A4
    - b. MAO (monoamine oxidase)
  5. Nomenclature based on gene sequence
    - a. Prefix **CYP** designates human cytochrome P450 (pronounced “sip”).
    - b. **CYP3** designates the gene family.
    - c. **CYP3A** designates the subfamily.
    - d. **CYP3A4** designates the individual gene.
    - e. 97% identical in their amino acid sequence
  6. Interaction is dependent on the half-life of the inhibitor.
    - a. Cimetidine inhibition occurs within 24 hours.
    - b. Amiodarone inhibition occurs within months.
    - c. Maximum effect occurs when substrate and inhibitor achieve steady state.



H. Pharmacodynamic Interactions

1. Also known as pharmacologic interactions
2. When drugs with additive, synergistic, or antagonistic effects are combined
  - a. Indomethacin plus aspirin and increased risk of GI bleeding
  - b. Warfarin plus aspirin and increased risk of GI bleeding
  - c. Linezolid plus tramadol and increased risk of Serotonin syndrome
  - d. Propofol plus midazolam and increased risk of Central nervous system depression
3. Antagonistic interactions
  - a. Albuterol and propranolol
  - b. Propranolol and dobutamine

I. How to Evaluate Drug Interaction Cases

1. Assessment of causation of a drug interaction includes a temporal relationship, consideration of the pharmacologic properties of the object and precipitant drug, patient factors and disease states, the possible contribution of other drugs, and, when possible, a positive de-challenge.
2. ADE nomograms such as the Naranjo nomogram are designed to evaluate ADEs, not drug-drug interactions; therefore, they should not be used to evaluate drug-drug interaction cases.
3. The Drug Interaction Probability Scale (DIPS) may be used to determine drug-drug interaction causation, including the adverse outcomes in a specific patient (see Appendix 4).
4. The DIPS is patterned after the Naranjo ADR Probability Scale. A series of 10 questions related to the drug interaction are assessed with yes, no, unknown, or not available answers and then scored and tabulated. The total score determines the probability of the drug-drug interaction occurring in the patient and is scaled as follows:
  - a. Highly probable: More than 8
  - b. Probable: 5–8
  - c. Possible: 2–4
  - d. Doubtful: 2 or fewer
5. When using the DIPS, the evaluator must have comprehensive knowledge of the pharmacologic properties of both the object and the precipitator drug, especially their pharmacokinetic and pharmacodynamic properties and their mechanisms of drug action and mechanisms of drug interactions.

## REFERENCES

1. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on drug formularies. *Am J Hosp Pharm* 1991;48:791-3.
2. American Society of Hospital Pharmacists. ASHP guidelines on formulary system management. *Am J Hosp Pharm* 1992;49:648-52.
3. American Society of Hospital Pharmacists. ASHP guidelines on preventing medication errors in hospitals. *Am J Hosp Pharm* 1993;50:305-14.
4. American Society of Health-System Pharmacists. ASHP guidelines on adverse drug reaction monitoring and reporting. *Am J Health Syst Pharm* 1995;52:417-9.
5. American Society of Health-System Pharmacists. ASHP guidelines on medication-use evaluation. *Am J Health Syst Pharm* 1996;53:1953-5.
6. American Society of Health-System Pharmacists. ASHP guidelines on the pharmacy and therapeutics committee and the formulary system. *Am J Health Syst Pharm* 2008;65:1272-83.
7. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. *JAMA* 1995;274:29-34.
8. Cooper SL, Somani SK. Pharmacy-based adverse drug reaction monitoring program. *Consult Pharm* 1990;5:659-64.
9. Dasta JF, Boucher BA, Brophy GM, et al. Intravenous to oral conversion of antihypertensives: a toolkit for guideline development. *Ann Pharmacother* 2010;44:1430-47.
10. Flowers P, Dzierba S, Baker O. A continuous quality improvement team approach to adverse drug reaction reporting. *Top Hosp Pharm Manage* 1992;12:60-7.
11. Greengold N L, Shane R, Schneider P, et al. The impact of dedicated medication nurses on the medication administration rate. *Arch Intern Med* 2003;163:2359-67.
12. Hakkarainen KM, Hedna K, Petzold M, et al. Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions—a meta-analysis. *PLoS One* 2012;7:e33236.
13. Hallas J, Harvald B, Gram LF, et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. *J Intern Med* 1990;228:83-90.
14. Hassan E, Badawi O, Weber RJ, et al. Using technology to prevent adverse drug events in the intensive care unit. *Crit Care Med* 2010;38(suppl):S97-S105.
15. Horn JR, Hansten PD, Chan LN. Proposal for a new tool to evaluate drug interaction cases. *Ann Pharmacother* 2007;41:674-80.
16. Howard RL, Avery AJ, Slavenburg S, et al. Which drugs cause preventable admissions to hospital? A systematic review. *Br J Clin Pharmacol* 2007;63:136-47.
17. Hypoglycemic Agent Adverse Drug Event Gap Analysis—Component of the Medication Safety Road Map. 2012 Minnesota Hospital Association. Available at <https://www.mnhospitals.org/Portals/0/Documents/ptsafety/ade/Medication-Safety-Gap-Analysis-Hypoglycemic.pdf>. Accessed January 26, 2015.
18. Karch FE, Lasagna L. Adverse drug reactions—a critical review. *JAMA* 1975;234:1236-41.
19. Kelly WN. Can the frequency and risks of fatal adverse drug events be determined? *Pharmacotherapy* 2001;21:521-7.
20. Kimelblatt BJ, Young SH, Heywood PM, et al. Improved reporting of adverse drug reactions. *Am J Hosp Pharm* 1988;45:1086-9.
21. Koppel R, Metlay JP, Cohen A. Role of computerized physician order entry systems in facilitating medication errors. *JAMA* 2005;293:1197-203.
22. Leape L, Cullen DJ, Clapp MD, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. *JAMA* 1999;282:267-70.
23. Leape LL, Bates DW, Cullen DJ, et al. Systems analysis of adverse drug events. ADE Prevention Study Group. *JAMA* 1995;274:35-43.
24. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-45.
25. Poon EG, Cina JL, Churchill WW, et al. Medication dispensing errors and potential adverse drug events before and after implementing barcode technology in the pharmacy. *Ann Intern Med* 2006;145:426-34.

26. Principles of a sound drug formulary system. In: Hawkins B, ed. *Best Practices for Hospital and Health System Pharmacy: Positions and Guidance Documents of ASHP*. Bethesda, MD: ASHP, 2006:110-3.
27. Prosser TR, Kamysz PL. Multidisciplinary adverse drug reaction surveillance program. *Am J Hosp Pharm* 1990;47:1334-9.
28. Raschetti R, Morgutti M, Menniti-Ippolito F, et al. Suspected adverse drug events requiring emergency department visits or hospital admissions. *Eur J Clin Pharmacol* 1999;54:959-63.
29. Rudis MI, Cohen H, Cooper B, et al. Position paper on critical care pharmacy services. *Pharmacotherapy* 2000;20:1400-6.
30. Schumock GT, Seeger JD, Kong SX. Control charts to monitor rates of adverse drug reactions. *Hosp Pharm* 1995;30:1088-96.
31. Vira T, Colquhoun M, Etchells E. Reconcilable differences: correcting medication errors at hospital admission and discharge. *Qual Saf Health Care* 2006;15:122-6.

**ANSWERS AND EXPLANATIONS TO PATIENT CASES****1. Answer: A**

Answer A is correct; TJC requires that the minimum drug selection criteria for adding a drug to the formulary include indications for use, effectiveness, drug interactions, adverse effects, sentinel event advisories, and cost. Answers B–D are incorrect; although it is important to include the FDA status and rank of a drug and the drug's absorption when reviewing a drug for formulary or when preparing a drug monograph, these are not required elements, nor will they be more important than ADEs when making formulary decisions.

**2. Answer: C**

An MUE is drug- or disease-specific and is best suited for reviewing vancomycin dosing and the ordering of vancomycin blood levels (Answer C is correct). Quality assurance surveys are best suited for monitoring the medication use process that may not be specific to a drug or disease, such as the review of a pharmacist's notes on the PMR, a review of accuracy of expiration dates placed on intravenous admixture products, and the frequency of drug interaction warnings on the CPOE system (Answer A, B, and D are incorrect).

**3. Answer: C**

When performing a QA survey for allergy cross-reactivity, the risk of even one failure can be life threatening; hence, the threshold should be set at 100%—no variance should be allowed. The only appropriate choice is setting the threshold of allergy detection with ceftriaxone at 100%, making Answer C correct and Answers A, B, and D incorrect.

**4. Answer: B**

Increasing the number of patients with pulmonary embolism receiving heparin who achieve a therapeutic PTT within 24 hours from only 40% to 100% is an excellent PI project and will improve the efficacy of heparin in the management of pulmonary embolism (Answer B is correct). A review of gentamicin dosing in patients with sepsis is best suited for an MUE, and if the results are poor, it will then be suited for a PI project (Answer A is incorrect). Similarly, a medication pass of medication administration through the feeding tube is best suited for a QA survey and, if not done correctly, will then be suited for a PI project (Answer C

is incorrect). Finally, ensuring the appropriate disposal of chemotherapy in the ICU satellite pharmacy is best suited for a QA project, and if variances are detected, a PI project can be performed (Answer D is incorrect)..

**5. Answer: A**

A mild ADE is defined as an ADE that resulted in a heightened need for patient monitoring with or without a change in vital signs, but no ultimate patient harm, or as any adverse event that resulted in the need for increased laboratory monitoring. Enalapril-induced hyperkalemia (K = 5.7 mEq/L) managed by one dose of Kayexalate did not require aggressive interventions nor lead to any patient harm but did require increased laboratory monitoring, making Answer A correct and Answers B–D incorrect.

**6. Answer: B**

A moderate ADE is defined as an ADE that resulted in the need for aggressive intervention with antidotes and/or an increased length of hospital stay. Haloperidol-induced torsades de pointes is a life-threatening dysrhythmia that requires aggressive and successful management with intravenous magnesium (Answer B is correct). A Severe ADE results in patient harm, prolonged hospitalization, transfer to a higher level of care, permanent organ damage, or death, which did not occur in this case, making Answer C incorrect. A mild ADE is defined as an ADE that resulted in a heightened need for patient monitoring with or without a change in vital signs, but no ultimate patient harm, or as any adverse event that resulted in the need for increased laboratory monitoring which did not occur in this case making Answer A incorrect.

**7. Answer: A**

Because this patient developed lisinopril-induced angioedema, had no history of allergy to angiotensin-converting enzyme inhibitors, and did not miss any doses of lisinopril, this ADE was not a preventable error and was not caused by a medication error, making Answer A correct and Answers B–D incorrect.

**8. Answer: C**

A severe ADE is defined as an ADE that results in harm to the patient, prolonged hospitalization, transfer to higher level of care, permanent organ damage, or death with the probable ADE causality nomogram score. Because this patient developed life-threatening lisinopril-induced angioedema and required a tracheotomy resulting in patient harm, hospitalization, and transfer to a higher level of care, this case meets the criteria for a “severe” ADE making Answer C correct and Answers A and B incorrect.

**ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS****1. Answer: A**

Evaluating the use of pharmacotherapy in SUP in the ICU is best suited for an MUE (Answer A is correct). The goal of an MUE is to ensure optimal medication therapy management and improve patient safety and outcomes for drug-related processes—in this case, pharmacotherapy in SUP. Although one component of an MUE is PI, a review of the quality should occur before determining whether a PI project is necessary (Answer B is incorrect). An interventional MUE incorporates a review of quality in the form of making a pharmacotherapeutic intervention—PI. Although reviewing ADE data and medication error data from the ICU is helpful in detecting and determining problems with the use of pharmacotherapy in SUP, they are isolated events and are reporter-dependent, and a lack of reports does not ensure that the use of pharmacotherapy in SUP is appropriate (Answers C and D are incorrect). Only an MUE is a robust and comprehensive method of evaluating the use of pharmacotherapy in SUP.

**2. Answer: D**

In this case, the patient had a documented history of penicillin allergy but still received cefazolin and developed a life-threatening anaphylaxis reaction—this is a medication error. Allergy cross-reactivity between penicillin and cefazolin is well documented; hence, this is a preventable ADE. A preventable ADE, by definition, is a medication error that occurs and reaches the patient to cause harm because of a breach of standard professional behavior or practice, hence, a preventable ADE best describes this case (Answer D is correct). Although this case of cefazolin-induced life-threatening anaphylaxis is an ADE, a preventable ADE best describes this case (Answer C is incorrect). In general, *ADRs* and *side effects* are synonymous terms, and a cefazolin-induced allergy is an ADR; however, a preventable ADE best describes this case (Answers A and B are incorrect).

**3. Answer: A**

Naloxone is an opioid antagonist and is an antidote indicated for opioid overdose, for the complete or partial reversal of opioid depression, including respiratory depression induced by natural or synthetic opioids. Because of naloxone's indication, it is an excellent tracer drug to detect opioid ADEs (Answer A is correct). Clopidogrel,

propofol, and enoxaparin are not antidotes and are not indicated nor routinely employed to treat or manage drug-induced disorders (Answers B, C, and D are incorrect).

**4. Answer: C**

Kayexalate is sodium polystyrene sulfonate and is an antidote for the treatment of hyperkalemia. Kayexalate is an excellent tracer drug to detect drug-induced causes of hyperkalemia such as angiotensin-converting enzyme inhibitors, potassium-sparing diuretics, spironolactone,  $\beta$ -blockers, heparin, and sulfamethoxazole/trimethoprim (Answer C is correct). Sumatriptan, lorazepam, and amitriptyline are not antidotes, and these agents are not indicated or routinely used to treat or manage drug-induced disorders (Answers A, B, and D are incorrect).

**5. Answer: C**

The Joint Commission (TJC) requires that the minimum drug selection criteria for selection of a drug to the formulary include indications for use, effectiveness, drug interactions, adverse effects, sentinel event advisories, and cost (Answer C is correct). Although it is important to include unlabeled indications, date of FDA approval, and storage when reviewing a drug for formulary or when preparing a drug monograph, these are not required elements, nor will they be more important than the drug's effectiveness when making formulary decisions (Answers A, B, and D are incorrect).

**6. Answer: B**

Evaluating the management of warfarin-induced hypoprothrombinemia is best suited for an MUE. The goal of an MUE is to ensure optimal medication therapy management and improve patient safety and outcomes for drug-related processes; an MUE is drug-, drug class-, or disease-specific—in this case, management of warfarin-induced hypoprothrombinemia (Answer B is correct). Quality assurance is defined as a process for monitoring the effectiveness and safety of the medication use process that includes prescribing, dispensing, and administering medications. Evaluating pharmacist verification times for routine orders in the ICU, drug interaction warnings on the CPOE system, and duplicate warnings on the CPOE system are not necessarily drug- or disease state-specific and are best suited for a QA review (Answers A, C, and D are incorrect).

**7. Answer: B**

When performing a QA, 20–30 patients will generally yield an effective sample size to ensure quality and safety in the medication use process. A sample size of 25 patients for a QA survey for the allergy cross-reactivity of morphine with other opioids in the CPOE system should be enough to detect a discrepancy in the system (Answer B is correct). An appropriate threshold for allergy detection should be 100% because even one missed event can be life threatening (Answers A and C are incorrect). Reviewing duplicate therapy with other opioids is not effective in determining the cross-reactivity of morphine with other opioids (Answer D is incorrect).

## Appendix 1

### Pharmacy Department

January 24, 2014

#### INDICATORS 2014 Data

MEASURE	BENCHMARK	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter
Pharmacotherapeutic interventions	None	7309	5748	7995	8540
Outcomes cost and raw drug cost savings from pharmacotherapeutic interventions	None	\$1,559,842	\$1,249,195	\$1,645,730	\$1,751,315

**Finding/Conclusion:** For 2010, the total number of pharmacotherapeutic interventions increased from the previous year to 21,023, realizing \$5,177,874 in outcomes and raw drug cost savings. For 2011, the total number of pharmacotherapeutic interventions remained 20,629, realizing \$5,268,265.54 in outcomes and medication use savings. For 2012, the total number of pharmacotherapeutic interventions increased to 32,916, realizing \$6,499,223 in outcomes and raw drug cost savings. For 2013, the total number of pharmacotherapeutic interventions was 29,592, realizing \$6,206,082 in outcomes and raw drug cost savings. These findings are consistent with previous years.

Pharmacotherapeutic interventions performed by clinical pharmacists consist of making downward and upward dosing adjustments of medications, providing pharmacokinetic consultations, avoiding drug-drug and drug-food interactions, avoiding toxic medications, avoiding drug-disease contraindications, avoiding drug-allergy interactions, approving and dosing of restricted antibiotics, switching patients from intravenous medications to oral medications, initiating more effective or safer drug therapies, initiating equally efficacious but less expensive medications, discontinuing unnecessary and duplicate medications, changing dosage forms according to patient tolerance, switching nonformulary to formulary medications, and making recommendations to monitor for efficacy and toxicity.

Clinical pharmacists review and respond to abnormal drug blood level assays and laboratory values such as serum chemistry and coagulation profiles as they pertain to medication management. Notes documenting the interventions are placed in the pharmacy profile. Depending on the quantity of pharmacotherapeutic interventions and the resulting cost savings, the Pharmacy Department's efforts to document clinical interventions, ensure medication safety, and contain medication-related costs have been very effective.

**Action Indicated:** No additional actions are required. The Pharmacy Department will continue to perform and document clinical interventions and evaluate the resulting cost savings.



Appendix 2. Hypoglycemic Agent Adverse Drug Event Gap Analysis

# Hypoglycemic Agent Adverse Drug Event Gap Analysis

## Component of the Medication Safety Road Map



Specific Action(s)	Gap Analysis Questions	Yes	No	If answered question "No" – identify the Specific Action plan(s) including persons responsible and timeline to complete.
<b>Prevention &amp; Mitigation Strategies</b>				
1) Systems and processes for blood glucose monitoring practices	<p><b>The facility has established blood glucose targets for:</b></p> <p>1a) Critically ill patients</p> <p>1b) Non-critically ill patients</p> <p>1c) Pregnant patients with GDM or pre-existing diabetes</p> <p>1d) Neonate/pediatric patients</p> <p><b>The facility has established blood glucose monitoring guidelines, (including point of care (POC) testing for more rapid test results), for:</b></p> <p>1e) Patients with diabetes</p> <p>1f) Patients with hospital-acquired hyperglycemia (without diabetes)</p> <p>1g) Pregnant women who are eating and have gestational diabetes mellitus or pre-existing diabetes</p> <p>1h) Neonate/pediatric patients</p>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>  <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>  <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
2) Management of insulin: procurement, storage, preparation, and dispensing practices	<p><b>The facility has processes in place to eliminate errors in prescribing, dispensing, and administration which includes:</b></p> <p>2a) Pharmacy prepares individual patient-scheduled doses of intermediate or long-acting insulins unless provided as individual patient insulin devices (e.g., pens)</p> <p>2b) Floor stocks of insulins is minimized or eliminated.</p> <p>2c) Insulin is not available from automated dispensing cabinet (ADC) without review of insulin orders by a pharmacist.</p> <p>2d) If override is allowed for emergent situation, an independent double check by two professionals occurs upon removal from ADC.</p> <p>2e) All insulin infusions, concentrated insulin (U-500) and diluted insulins individual patient specific doses are prepared in the pharmacy.</p> <p>2f) The number of standard concentrations used for insulin infusions is limited to one.</p> <p>2g) An independent double check is instituted prior to dispensing non-standard concentrations of sub-cutaneous insulin (eg. U500 and U10 insulin and preparations of IV infusions.</p>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
3) Management of insulin: ordering practices	<p>3a) The facility has a process in place to streamline formulary to single "brand" source for each insulin type with approved substitutions.</p>	<input type="checkbox"/>	<input type="checkbox"/>	
4) Management of insulin: administration and monitoring	<p><b>The facility has processes in place to ensure:</b></p> <p>4a) All insulin infusions are administered using an IV pump with free-flow protection and smart pump technology with appropriately defined max/min infusion rates, alerts and override criteria.</p> <p>4b) An independent double-check is required before administering all IV insulin.</p> <p>4c) An independent double-check is required before administering non-standard insulin concentrations (e.g. U-500).</p> <p>4d) Tuberculin syringes are removed from floor stock so they cannot erroneously be used for insulin.</p>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	

**Appendix 2. Hypoglycemic Agent Adverse Drug Event Gap Analysis (continued)**

Specific Action(s)	Gap Analysis Questions	Yes	No	If answered question "No" – identify the Specific Action plan(s) including persons responsible and timeline to complete.
	<p><b>Standard practices are established for subcutaneous insulin dosing for the following situations:</b></p> <p>4e) Non-standard insulin concentrations (e.g., U-500 insulin)                      4f) Correction scale(s)                      4g) Basal prandial dosing (carbohydrate/non-carbohydrate)                      4h) Pre-operative or pre-procedural protocol                      4i) Converting from oral agents to insulin</p> <p><b>Standard insulin infusion protocols exist and are in use for:</b></p> <p>4j) ICU                      4k) non-ICU                      4l) Diabetic ketoacidosis (DKA)                      4m) Hyperosmolar hyperglycemic state (HHS)                      4n) Pregnancy</p> <p><b>The facility has a policy in place for patients with self-managed subcutaneous insulin pumps which specifies:</b></p> <p>4o) Policy specifies and practice ensures that patient must be cognitively competent and safe to self-administer.</p> <p><b>Standard practices are established for oral and injectable non-insulin anti-hyperglycemic agents, which include:</b></p> <p>4p) Use of oral and injectable noninsulin anti-hyperglycemic agents (GLP1 analogs and pramlintide) is restricted in acute care settings. (Insulin is the preferred agent.)                      4q) Sulfonylurea agents are avoided with NPO patients and patients with inconsistent nutritional intake.                      4r) Thiazolidinedione use is avoided in patients with CHF.                      4s) Metformin use is avoided in patients who are critically ill, have a creatinine greater than 1.4 mg/dL females or 1.5 mg/dL males, have received IV contrast or have abnormal creatinine clearance.</p> <p>4t) There is a process in place to ensure that protocols/policies order sets are implemented and being used consistently.</p>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>  <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>  <input type="checkbox"/>  <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>  <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>  <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>  <input type="checkbox"/>  <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>  <input type="checkbox"/>	
<p>5) Implement appropriate mitigation strategies</p>	<p><b>The facility has a process in place for follow up after initial hypoglycemic reaction occurs which includes:</b></p> <p>5a) The adjustment of insulin dose.                      5b) The implementation of standard BG monitoring after treatment of hypoglycemia with glucagon or D50 (e.g., 0200 glucose check, glucose q 1 hr X 3).                      5c) A plan for ongoing monitoring and dose adjusting to prevent hypoglycemia recurrence.</p>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	
<b>Assessment &amp; Detection Strategies</b>				
<p>6) Systems and processes to aid in assessment and detection</p>	<p>6a) The facility's insulin administration record, glucose monitoring results, and carbohydrate intake are effectively displayed to allow caregivers to accurately and efficiently assess data.</p> <p><b>The facility implements real-time rules/alerts to flag low blood glucose triggers and changes in patient condition predisposing patient to hypoglycemia, which include:</b></p> <p>6b) Change in nutrition and/or fluid status – admission, acute illness, NPO for surgery, start/stop PN/EN, inconsistent nutrition in hospital.                      6c) Addition or discontinuation of medication(s) that affect blood glucose.                      6d) Disease state – acute renal failure (ARF), acute hepatic failure, severe sepsis/shock.                      6e) Transitions in care/handoffs.</p>	<input type="checkbox"/>  <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/>  <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	

**Appendix 2. Hypoglycemic Agent Adverse Drug Event Gap Analysis (continued)**

Specific Action(s)	Gap Analysis Questions	Yes	No	If answered question "No" – identify the Specific Action plan(s) including persons responsible and timeline to complete.
7) Management of insulin: assessment of nutrition and fluid status	<p>7a) The facility has a process in place to coordinate blood glucose checks, meals and insulin administration times.</p> <p><b>The facility has a process in place to monitor for mismatch between nutritional intake in patients with fixed prandial dosing:</b></p> <p>7b) Upon admission.</p> <p>7c) For patients with inconsistent nutritional intake or failure to eat after prandial insulin dose has been given.</p> <p>7d) At transitions in care.</p> <p><b>The facility has a process in place that requires new insulin orders and BG monitoring for patients on insulin with:</b></p> <p>7d. Change in nutrition status (e.g., new NPO status, transition from parenteral nutrition (PN) to enteral nutrition (EN), transition from continuous to cyclic PN or EN).</p> <p>7e. Discontinuation of TPN/dextrose containing IV fluid or EN.</p>	<input type="checkbox"/>	<input type="checkbox"/>	
8) Management of insulin: with other medications affecting blood glucose control	<p><b>The facility has a process in place for management of insulin used with other medications that may affect blood glucose control, which includes:</b></p> <p>8a) Assessing appropriateness of continuation of injectable non-insulin, anti hyperglycemic agents and oral agents upon admission.</p> <p>8b) Ensuring that appropriate warnings appear in information systems (e.g., CPOE, MAR, pharmacy) when medications that significantly alter BG levels or insulin regimen requirements are started or stopped or the dose is increased, e.g., Corticosteroid taper, Quinolones Octreotide, antipsychotic agents, continuous renal replacement therapy (CRRT), vasopressors, immunosuppressants.)</p>	<input type="checkbox"/>	<input type="checkbox"/>	
9) Management of insulin: with disease states affecting blood glucose control	<p><b>The facility has processes in place for management of insulin use in the following disease states:</b></p> <p>9a) Renal dysfunction: use of an algorithm to determine need for reduction of weight-based insulin dosing.</p> <p>9b) Liver dysfunction: use of an algorithm to determine need for reduction of weight-based insulin dosing.</p> <p>9c) Malnutrition/low body weight: use of an algorithm to determine need for reduction of weight-based insulin dosing.</p> <p>9d) Type 1 Diabetes: should have dextrose added to IV fluids if no caloric intake.</p> <p>9e) Hyperkalemia: Insulin should be used to treat hyperkalemia only via the use of a protocol that includes specific blood sugar monitoring.</p>	<input type="checkbox"/>	<input type="checkbox"/>	
10) Management of insulin: handoffs and transitions	<p><b>A standard hand-off/transition communication process is in place for all patients receiving insulin which includes the following information, at minimum:</b></p> <p>10a) Communication of last blood glucose check.</p> <p>10b) Date and time of last insulin dose given.</p>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Therapeutic Strategies</b>				
11) Systems and processes for insulin therapeutic strategy practices	<p>11a) The facility has a process in place to encourage co-management of insulin with patients who are capable and willing, (e.g., encourage patients to question doses and timing of insulin administration.)</p> <p><b>The facility has insulin management practices in place, which include:</b></p> <p>11a) Matching insulin prandial dosing to the amount of carbohydrate consumed.</p> <p>11b) Checking blood glucose within 30 minutes before meal</p>	<input type="checkbox"/>	<input type="checkbox"/>	

Appendix 2. Hypoglycemic Agent Adverse Drug Event Gap Analysis (*continued*)

Specific Action(s)	Gap Analysis Questions	Yes	No	If answered question "No" – identify the Specific Action plan(s) including persons responsible and timeline to complete.
	11c) Administering rapid-acting prandial insulin within 30 minutes post first bite. 11d) Avoiding dose stacking (e.g., Corrective insulin should not be given more frequently than every 4 hours for rapid-acting insulin or every 6 hours for regular insulin).	<input type="checkbox"/>	<input type="checkbox"/>	
12) Management of insulin:	<b>The facility has a process in place for management of hyperglycemic patients using basal/bolus insulin, which includes:</b> 12a) Intermittent sliding scale insulin regimens are consistently used with a basal insulin. 12b) Rapid acting insulin is the standard choice of therapy for prandial insulin. 12c) Prandial and correction scale insulin should be the same type of insulin and given in one injection when possible.  <b>The facility has a process in place for management of hyperglycemic patients using mixed insulin which includes:</b> 12d) Dosing occurs only before breakfast and before dinner; not at bedtime. 12e) Patients are monitored for nocturnal hypoglycemia. 12f) Change to basal/prandial if patient becomes NPO or exhibits inconsistent nutritional intake (e.g. poor appetite).	<input type="checkbox"/>	<input type="checkbox"/>	
13) Management of insulin:	<b>The facility has an established standard order set or protocol, approved by medical staff committee, in place for management of hypoglycemic patients which includes:</b> 13a) A standard method for management of hypoglycemia, including triggers to administer glucose, (e.g., blood glucose value below threshold, signs and symptoms of hypoglycemia) is readily available to caregivers. 13b) Allows nurses to administer hypoglycemia "rescue" agents without prior physician order. 13c) Hypoglycemia "rescue" agents (dextrose, glucagon) are readily accessible throughout the facility where care is provided.	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Critical Thinking &amp; Knowledge Strategies</b>				
14) Implement appropriate critical thinking and knowledge strategies	<b>The facility has a process in place which evaluates staff competencies related to hypoglycemic agent use including:</b> 14a) Hypoglycemia is always considered when a patient receiving insulin has an altered level of consciousness for no apparent reason. 14b) Hypoglycemia should not be ruled out as a cause of confusion or altered behavior based on a capillary BG result; a venous lab result should also be obtained.  <b>The facility provides interdisciplinary education on hypoglycemic agent therapy, which includes:</b> 14c) Initial training for new hires and existing staff, including protocols and guidelines. 14d) Post test incorporating a case-study approach to demonstrate proficiency; covers topics such as: frequency of glucose checks; non-standard insulin concentrations (e.g., U-500 insulin); correction insulin scale(s); basal insulin dosing; prandial insulin dosing (carbohydrate/non-carbohydrate); pre-operative or pre-procedural protocols; converting from oral agents to insulin. 14e) Plan for targeting gaps in knowledge. 14f) Hypoglycemic agent education is provided to direct care staff when new relevant information is available.	<input type="checkbox"/>	<input type="checkbox"/>	

**Appendix 2.** Hypoglycemic Agent Adverse Drug Event Gap Analysis (*continued*)

Specific Action(s)	Gap Analysis Questions	Yes	No	If answered question "No" – identify the Specific Action plan(s) including persons responsible and timeline to complete.
<b>Patient Education</b>				
15) Provide patient and family education	<p><b>The facility has a process in place to educate patients and families using teach-back method on diabetes "survival skills" to ensure safe therapy including:</b></p> <p>15a) Nutritional management                      15b) Self-blood glucose monitoring                      15c) Medication management                      15d) Hyperglycemia and hypoglycemia recognition                      15e) Treatment and prevention                      15f) Exercise                      15g) Sick day guidelines                      15h) Resources                      15i) Post-discharge follow-up appointment</p>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	



Minnesota Hospital Association



**Appendix 3. Adverse Drug Event Reporting Form**

<b>ADVERSE EVENT INFORMATION</b>						ADE#: <input style="width: 100px;" type="text"/>								
1. NAME	2. PATIENT ID #	3. LOCATION	4. AGE	5. SEX	6. REACTION ONSET DATE									
					7. DATE OF REPORT									
8. DESCRIBE REACTION AND ITS MANAGEMENT. (Continue on the back if necessary. Use Arial Narrow Font Size 10)					9. Check all appropriate									
					<input type="checkbox"/> Patient Expired									
					<input type="checkbox"/> Reaction Treated with Drug									
					<input type="checkbox"/> Resulted in, or prolonged inpatient hospitalization									
					<input type="checkbox"/> None of the Above									
					10. Did event abate after stopping the drug?									
					<input type="checkbox"/> YES									
					<input type="checkbox"/> NO									
					<input type="checkbox"/> MAYBE									
					11. Was patient's electronic allergy/ADE profile updated									
					<input type="checkbox"/> YES									
					<input type="checkbox"/> NO									
(If no, please explain on second page)														
12. RELEVANT TESTS/LABORATORY DATA														
<b>SUSPECTED DRUG(S) INFORMATION</b>														
13. SUSPECTED DRUG(S) Give manufacturer & lot number for vaccine/ biologics/ biotechnological					17. DATES OF ADMINISTRATION									
14. DOSE AND FREQUENCY			15. ROUTE OF ADMINISTRATION		18. DURATION OF ADMINISTRATION									
16. INDICATION(S) FOR USE														
<b>CONCOMITANT DRUG HISTORY</b>														
19. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (Exclude those used to treat the reaction)														
20. OTHER RELEVANT HISTORY (e.g., diagnoses, past medical history, allergies, pregnancy, etc.)														
INITIAL REPORTER (In confidence)														
<p>JCAHO Standard PI. 2.20 states that all serious adverse drug reactions are intensely analyzed. Standard MM. 6.20 maintains that the responsible individual complies with internal and external reporting requirements for adverse drug reactions. (2006 Comprehensive Accreditation Manual for Hospitals)</p> <p>Please take the time to complete this form for each suspected adverse drug reaction, and forward it to the Department of Pharmacy for reporting at the next Adverse Drug Reaction Subcommittee meeting.</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 15%;">Date</td> <td style="width: 15%;">Time</td> <td style="width: 25%;">MD notified about possible ADR</td> <td style="width: 45%;">Pharmacist's Signature</td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </table> <p>Submission of a report does not necessarily constitute an admission that the drug caused the reaction</p>					Date	Time	MD notified about possible ADR	Pharmacist's Signature					NAME AND ADDRESS OF REPORTER (Including zip code)	
					Date	Time	MD notified about possible ADR	Pharmacist's Signature						
TELEPHONE NO. (Include area code)														
HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?					<input type="checkbox"/> YES									
					<input type="checkbox"/> NO									

**Appendix 3.** Adverse Drug Event Reporting Form (*continued*)

**KJMC ADVERSE DRUG EVENT REPORTING FORM**  
**The Naranjo Nomogram for Causality**

ASSESSMENT	YES	NO	DON'T KNOW	SCORING SYSTEM
1. Are there previous reports of this reaction? (If no, please provide documentation of search strategy)	+1	0	0	Based on the total score, circle the term that best defines this ADR:  $\geq 9$ Definite  5 – 8 Probable  1 – 4 Possible  $\leq 0$ Doubtful
2. Did the ADR appear after the suspected drug was administered? (If no, please explain).	+2	-1	0	
3. Did the ADR improve when the drug was discontinued or a specific antagonist was administered? (If no, please explain).	+1	0	0	
4. Did the ADR reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could, on their own, have caused the ADR? (If yes, please explain).	-1	+2	0	
6. Did the ADR 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?	+1	0	0	
8. Was the ADR more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patients have a similar reaction to the same or similar drugs in any other previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
<b>TOTAL SCORE</b>				

(Source: Clin Pharmacol Ther 1981;30(2):239-45.)

**Appendix 4. Drug Interaction Probability Scale**

The Drug Interaction Probability Scale (DIPS) is designed to assess the probability of a causal relationship between a potential drug interaction and an event. It is patterned after the Naranjo ADR Probability Scale (Clin Pharmacol Ther 1981;30:239-45).

**Directions:**

- o Circle the appropriate answer for each question, and add up the total score.
- o Object drug = Drug affected by the interaction.
- o Precipitant drug = Drug that causes the interaction.
- o Use the Unknown (Unk) or Not Applicable (NA) category if (a) you do not have the information or (b) the question is not applicable (eg, no Dechallenge; dose not changed, etc.).

Questions	Yes	No	NA/Unk
1. Are there previous credible reports of this interaction in humans?	+1	-1	0
2. Is the observed interaction consistent with the known interactive properties of precipitant drug?	+1	-1	0
3. Is the observed interaction consistent with the known interactive properties of object drug?	+1	-1	0
4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	+1	-1	0
5. Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug? (if no dechallenge, use Unknown or NA and skip Question 6)	+1	-2	0
6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	+2	-1	0
7. Are there reasonable alternative causes for the event? <sup>a</sup>	-1	+1	0
8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	+1	0	0
9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?	+1	0	0
10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	+1	-1	0

<sup>a</sup>Consider clinical conditions, other interacting drugs, lack of adherence, risk factors (eg, age, inappropriate doses of object drug). A NO answer presumes that enough information was presented so that one would expect any alternative causes to be mentioned. When in doubt, use Unknown or NA designation.

**Total Score** \_\_\_\_\_ Highly Probable: >8  
 Probable: 5-8  
 Possible: 2-4  
 Doubtful: <2