Medication Safety in Clinical Trials: Role of the Pharmacist in Optimizing Practice, Collaboration, and Education to Reduce Errors

Jamie N. Brown*, PharmD, BCPS, BCACP; Sara R. Britnell*, PharmD, BCPS; Andrew P. Stivers*, PharmD; Jennifer L. Cruz*, PharmD, BCPS

*Durham VA Health Care System, Durham, NC; †University of North Carolina Medical Center, Chapel Hill, NC

Standardized safety practices for investigational drugs in clinical research protocols are limited and the vast majority of research pharmacists have concerns regarding its safety. Identified areas for medication safety risks include protocol complexity, medication ordering, and the processes for packaging, storage, and dispensing investigational medications. Inclusion of a pharmacist creates multiple mechanisms to promote safety and improve the quality of clinical research. This is accomplished through collaborating in the development of a research protocol, reviewing as a member of an advisory committee, developing mechanisms that contribute to safety, and assuring compliance with local and national regulations and standards. Ultimately, the profession of pharmacy has foundational responsibility for assuring the safe and effective use of medications, including investigational drugs in clinical research. It is through multidisciplinary collaboration that a research study will attain the highest standards for safety and maximize the quality and effectiveness of the data obtained in the clinical trial.

BACKGROUND

Safe practices for ordering, handling, dispensing, and administering investigational drugs have not been universally standardized and several areas of the medication-use process may pose safety risks during clinical research. Some of these risks are unique to clinical investigations and are less likely to be encountered when commercially-available products are used outside of the research setting. For example, toxicity risks to study subjects might not yet have been fully elucidated or drug interactions may not yet be entirely defined. Additionally, a variety of factors, such as protocol complexity and the need to maintain blinding in controlled studies may contribute to risks associated with product appearance, packaging, storage, ordering, and the dispensing process [1-3].

Safety concerns among pharmacists dispensing investigational drugs are not new. In 1984, Young et al. de-
scribed the results of a survey which showed that multiple areas of a research protocol were in need of improvement, including investigational drug information, drug accountability, and storage [4]. To further characterize safety concerns and practices related to investigational drugs, a national survey was conducted among pharmacists in investigational drug services (IDS†) within the Veterans Affairs Health System [5]. This study found that 81 percent of responders indicated some level of concern for safety risks. Several common concerns were related to the packaging of investigational drugs, such as lack of product differentiation, choice of font size/color, and absence of expiration dates and barcodes. Frequently, procedures were put in place for storage/security, temperature monitoring, and prescription labeling; however, some potentially beneficial practices were not common, such as repackaging of bulk medications into smaller units, and independent double checks by pharmacy staff at the point of dispensing. This study called for a standardized approach to defining and implementing safe practices for mitigating the inherent risks with investigational drugs [5].

There are several recognized safety processes used to minimize dispensing errors for commercial medications; however, these mechanisms are not always appropriate for investigational drugs. For example, the need to blind study participants to treatment groups impacts product appearance and packaging. Commercial medications utilize strategies to reduce confirmation bias such as designing products with different shapes, sizes, and colors (e.g. different tablet colors for different strengths), and imprinted codes for identification. Packages may also vary in appearance and size, and may be available in unit-of-use packaging, with tall man lettering to differentiate look-alike medication names (e.g. DOPamine vs DOBU-Tamine). In contrast, investigational drugs often lack distinguishing features because controlled studies may seek to conceal allocation to treatment arms; therefore, it may not be desirable to differentiate investigational products from one another. Table 1 compares investigational drugs safety risks with risk minimization strategies utilized for commercial medications.

Packaging of investigational drugs may also be problematic, particularly package sizes for both oral and injectable investigational drugs (Figure 1). Oral dosage forms may be provided by study sponsors in bulk containers, holding upwards of 10,000 tablets or capsules per container. This not only creates a challenge for storage, but also poses the risk of contaminating an entire drug supply if one blinded treatment allocation is erroneously mixed with the opposite blinded treatment allocation. On the other hand, injectable drugs may be packaged into vials smaller than that which is required for a single dose. This is often due to the need for dose titrations or dose ranging studies and may also pose safety risks. For example, if 20 vials are required to produce a dose for one subject, and only one or two vials are needed for another subject’s dose, the pharmacist can be desensitized to using such a large number of vials in preparing a single dose and therefore, less inclined to identify a potential error in

| Category           | Investigational Drug Safety Concerns                                                                 | Safety Mechanisms of Commercial Medications                                       |
|--------------------|------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Drug name          | Alpha-numeric identifier based on sponsor discretion                                                 | Generic and brand names reviewed/approved by FDA to minimize similarity among medications |
|                    | Identifier may change without notice                                                                   | Dear Health Care Provider letter                                                   |
| Packaging          | Lack of differentiation                                                                                  | Distinctive background colors                                                     |
|                    | Small black and white font                                                                             | Use of color and tall man lettering                                               |
|                    | Inadequate level of detail or information overload for multicenter studies                           | Packaging information standardized                                                |
|                    | Size/volume may not correspond to unit of use                                                       | Regulatory consideration                                                          |
|                    | Variability in package sizes due to titration or dose-ranging studies                               | Standardized package sizes                                                        |
| Product Characteristics | Similarity of appearance due to blinding                                                        | Different product sizes, shapes, and colors                                       |
|                    | Lack of imprint markings due to blinding                                                            | Unique imprint codes on tablets/capsules                                           |
| Expiration date    | May be absent or inaccurate on label; often updated during course of investigation                   | Set expiration date present on label                                               |

FDA = United States Food and Drug Administration
prescription ordering or dispensing [2].

Investigational drugs are addressed in legislation, regulatory standards, and guidance statements to varying degrees. Investigational new drug (IND) applications are covered in the United States Food and Drug Administration (FDA) Code of Federal Regulations Chapter 21, Part 312. This imposes rules regarding labeling to include a warning about investigational use, storage/security requirements for controlled substances, as well as requirements for informed consent and Investigational Review Board (IRB) involvement [6]. In addition, for medical centers within the Veterans Health Administration, a handbook defines storage requirements related to security and proper temperature conditions for investigational drugs. The handbook also requires policies and procedures to be created regarding the medication-use processes of prescription ordering and dispensing; however, it lacks details regarding specific safety practices to employ [7].

For hospitals accredited by The Joint Commission, Medication Management standard MM.06.01.05 states that investigational drugs should be managed safely in the hospital setting. Written processes should be in place to address the review, approval, supervision, and monitoring of study drugs, and to accommodate for continuation of home therapy if a hospital is not a participating study site. In addition, it identifies the pharmacy as the responsible party for storage and distributive activities of investigational drugs [8].

Despite these legal, regulatory, and accreditation requirements, there is a paucity of guidance characterizing practices that can be implemented to increase safety. In 1998, the American Society of Health-System Pharmacists published guidelines for clinical drug research [9]. This organization advises that the medication-use process for investigational drugs should mirror that of non-investigational drugs in terms of patient profile review, order verification, labeling, dispensing, etc. In addition, drugs should be labeled properly to ensure safe use, including expiration dates and lot numbers, and study sponsors are encouraged to leave space on the package labeling to permit additional labeling by pharmacists dispensing the drug.

Recently, the Hematology/Oncology Pharmacy Association issued its own guidance for best practices for oncology investigational drug services [10]. This is by far the most comprehensive and detailed statement to date regarding safe practices. It recommends incorporating several strategies such as use of computer software, bar-coding, expiration date tracking, order templates, clinical decision support (including warnings related to dose limits and various types of interactions), and pharmacy...
independent double checks at the point of dispensing, in addition to many of the legal and accreditation requirements already mentioned. Furthermore, it specifically recommends storing drugs separated by protocol and strength to reduce the risk for incorrect product selection during the dispensing process [10].

Currently, there is a paucity of published literature evaluating specific processes to ensure safe and accurate use of investigational drugs and the role of the pharmacist in this setting. Therefore, the purpose of this paper is to identify opportunities for the pharmacist to support the medication-use process for investigational drugs and to offer suggestions for reducing the risk for errors and improving patient safety as part of the multidisciplinary research team.

**COLLABORATIVE DEVELOPMENT OF A RESEARCH PROTOCOL**

Clinical research protocols continue to increase in complexity and often require the perspective of specialists in the development process [10]. This is particularly true for investigational drug studies which are governed by multiple regulatory bodies. Because medical researchers may lack training or experience in the management of investigational drugs, including anticipating challenges related to packaging, storage, dispensing, documentation, and medication safety, there is an opportunity for researchers to collaborate with a multi-disciplinary group of practitioners, including pharmacists, to optimize practices. Ultimately, the profession of pharmacy is based on the foundational responsibility for assuring the safe and effective use of medications. This includes the safe and effective use of investigational drugs in clinical research [11].

When developing a protocol, the pharmacist has an opportunity to contribute specifically to the portions of the protocol related to drug information and medication management. This may include reviewing or writing sections specific to the management of the investigational drug such as the drug information section of the research protocol, reviewing the informed consent form for appropriate language regarding benefits and risks, as well as developing supporting documents such as drug information supplements, patient diaries or other adherence processes [10]. An accurate and complete drug information section is critical to ensure that the investigational drug will be prepared, dispensed, and administered appropriately and in a way that complies with federal and state regulations, as well as institutional policies and practices. Thus, it is important that the drug information section is comprehensive and includes the source/supplier of the products, preparation, stability, compatibility, dispensing, administration, storage, accountability, and safety considerations such as contraindications, adverse drug reactions, and interactions [10]. If it is not possible for a pharmacist to be involved in the development of the research protocol, it is paramount that a pharmacist at each site prospectively reviews this information to determine if the institution can support and carry out the protocol [12].

**MEMBERSHIP ON RESEARCH COMMITTEES**

The Scientific Review Committee (SRC) is responsible for providing peer review for the scientific merit, priority, and feasibility of a research study. A pharmacist should be included on the SRC to provide expertise in the area of medication use. Specifically, a pharmacist is well positioned to evaluate a trial’s scientific merit and feasibility in the areas of drug supply management, applicability and requirements for an IND application, administration and dosing strategy, applicability of additional regulatory requirements (e.g. Risk Evaluation and Mitigation Strategy programs), medication safety strategies, and research support staff [10]. Review by a pharmacist is especially important for non-funded, smaller scale investigator-initiated trials that lack the clinical resources of better funded studies.

In addition to the SRC, the research protocol must be submitted to an IRB, which is tasked with reviewing and monitoring biomedical research involving human subjects with the purpose of safeguarding the patient’s welfare. Although similar to reviewing a protocol for the SRC, a pharmacist on the IRB will be able to review the appropriateness of drug information, accuracy and completeness of the informed consent describing the pharmacological effects and anticipated risks and benefits, and the process for reporting adverse reactions [2,3]. Pharmacist members of the IRB also have the opportunity to serve as a liaison between the committee and the IDS [10].

**CLINICAL DECISION SUPPORT SYSTEMS**

Pharmacists may contribute an expert perspective and lead efforts in integrating information technology into the medication-use process for investigational drugs. The prescribing phase of the medication use-process is consistently identified as the greatest contributor to medication errors [13-16]. Errors with prescribing medicines have been shown to occur in up to 39.1 percent of medication orders for hospitalized patients [17]. Furthermore, harm due to these prescribing errors has been reported to occur in approximately 1 percent of admitted patients [13]. For patients cared for in the ambulatory setting, medication errors have been reported to occur in 7.6 percent of prescriptions accounting for 11 percent of adverse
DEVELOPMENT OF ORDER SETS/TEMPLATES FOR PROVIDERS

The use of order sets to guide prescribing have been shown to result in improved adherence to pre-specified protocols [26]. The Institute for Safe Medication Practices, an organization focused on advancing patient safety through the reduction of medication errors, has been a leading advocate for standardized order sets [27-29]. Standardized order sets can minimize incorrect or incomplete prescribing, ensure compliance with protocol-specific dosing regimens, improve compliance with recommended processes of care, and ensure clarity when communicating orders [10,26]. The guiding principle of order sets is that they reduce the reliance on individual prescribers’ memory. As such, this tool is well-suited to aid in prescribing investigational drugs and is considered a best practice. Specifically, there are multiple components that should be included in an order set [10]. Table 2 presents order set best practices for an investigational drug protocol.

A critical step in implementing evidence-based order sets is establishing procedures for an independent review prior to the activation of the order set, preferably completed by the principal investigator. This also holds true for updates as a result of protocol amendments. Additionally, it is equally important to have a process in place to retire order sets that are no longer utilized. As investigational studies close, deactivating associated order sets can eliminate inappropriate selection of incorrect study protocols by prescribers.

Pharmacists are uniquely positioned to provide valuable input on the development of order sets. With regards to prescribing, pharmacists are familiar with reviewing and verifying medication orders for completeness, accuracy, appropriateness, and compliance with legal, regulatory, and accreditation standards. This familiarity is ad-

| Benefits of Computerized Provider Order Entry | Best Practices for Order Set Components |
|---------------------------------------------|----------------------------------------|
| Improved legibility                         | Protocol name and investigator contact information |
| Reduced transcription errors                | Patient-specific identifiers |
| Use of standard names, catalogues, and dictionaries | Dosing options and calculations, including titrations and tapers |
| Automated calculations                      | Protocol-directed dose modifications |
| Creation of alerts and reminders            | Medication-specific supportive care |
| Ability to link patient-specific data and information | Laboratory ordering and monitoring |
| Ability to screen for at risk populations    | Medication safety information (e.g. drug interaction, expected adverse drug reactions, etc.) |
| Establishment of evidence-based order sets  | Patient monitoring recommendations |
| Monitor for adherence to best practice      | Date and time of order authorization |

Table 2. Integration of Information Technology for Investigational Drugs [10,25]
vantageous when developing order sets as these criteria can all be evaluated in advance of its use. As medication experts, pharmacists will often consider treatments that are necessary but are frequently overlooked as part of the primary order set indication (e.g., rescue agents, as needed adjunctive medications, etc.). Pharmacists are also familiar with medication preparation and dispensing operations and can best configure medication admixtures within order sets to facilitate efficient drug delivery. Furthermore, pharmacists may offer insight into required or essential monitoring that should accompany medication orders such as laboratory tests, imaging studies, or monitoring parameters [30].

**CREATION OF TARGETED ALERTS**

CPOE systems utilizing CDS are able to integrate rule-based decision support and targeted alerts and reminders for the benefit of providers during the prescribing phase. Rule-based decision support can assist in selecting the correct therapy for the indication and calculating the correct dose based on the medication’s prescribing information. Alerts can take many forms including interaction alerts (e.g., drug-drug, drug-allergy), dose limit alerts, drug-disease state consideration alerts (e.g., labs monitoring, pregnancy status); however, all intend to reduce the potential for medication-related harms. Alerts combined with order sets contribute to the greatest likelihood for reduction in prescribing-based medication errors [24]. Additionally, CDS for investigational drugs should also include alerts confirming patient registration into a study protocol. Thus, in the case of a mismatch, an alert notifies the prescriber that the patient is not enrolled in the study associated with the investigational drug he or she is attempting to prescribe.

**INVESTIGATIONAL DRUG SERVICE BEST PRACTICES**

There are several ways in which IDS pharmacists can standardize practice to promote safety. One of these is the development of well-defined standard operating procedures for the various tasks involved in the management of investigational drugs. The creation of standard operating procedures helps to ensure consistency of practice, and this is particularly important for investigational drug inventory control, dispensing procedures, shortages, unblinding procedures, and management of patients during hospital admissions. These should be regularly reviewed to ensure that processes are carried out as described and no further revisions are needed [10].

For any new protocols under consideration, pharmacists should conduct a proactive risk assessment to identify safety concerns that may result in medication errors. These concerns should be reviewed with the principal investigator to highlight error prone elements of the study protocol and develop countermeasures to reduce the likelihood of error. Once initiated, additional safety concerns or errors that occur within the study protocol should be reported. Reporting safety concerns and errors should encourage the sponsor to make methodological adjustments in the protocol development and design process to avoid similar safety risks on future studies.

Of particular relevance to the IDS pharmacist is the management of study drug supply. This includes procurement, inventory, storage, and maintenance of blinding. The IDS is accountable for each dose of investigational drug it receives, dispenses, disposes, transfers, or returns [9,10]. This is usually accomplished through the use of drug accountability record forms. These forms must meet specific requirements as outlined by the FDA, and each drug in the study must have its own accountability form [6]. The IDS pharmacist also ensures that the study drug is stored appropriately. Due to safety and accountability concerns, investigational drugs should be stored in a secure area that is separated from non-investigational drug supply [9,10]. Access to this area should be restricted to only research personnel. Investigational drugs should also be separated by protocol, as several active studies may utilize the same drug [10]. Due to potential labeling concerns with sponsor-provided packaging, IDS pharmacists should find ways to highlight different strengths of drugs within the same protocol to reduce the risk of dispensing the wrong strength to study subjects [2,31]. This may include practices such as adding auxiliary labeling to bottles or differentiating using baskets or dividers. The IDS should also provide constant temperature monitoring of investigational drug storage conditions, with a specific action plan for handling temperature excursions [10]. If an excursion occurs, the protocol typically requires the pharmacist to quarantine the drug and alert the study sponsor. The sponsor can then provide guidance on whether further use of the investigational drug is appropriate.

The IDS pharmacist should also create dispensing instructions for each individual protocol [32]. These instructions can be used to assist involved personnel who may be unfamiliar with the protocol and will promote consistent practices throughout the study. When dispensing the investigational drug, site-specific labeling should be included such as information about the patient, the pharmacy, and the investigational drug. State and federal regulations can vary on what must be included on this label, and the IDS pharmacist can ensure that these requirements are met [10]. All investigational drugs must contain the statement: “Caution: New drug—Limited by federal or United States law to investigational use” [6]. After filling the prescription, a clear chain of custody should be established for the investigational drug until it
is delivered to the subject.

The IDS pharmacist also has the resources to support study audits and site visits. Different organizations may review a study, including the sponsor, the institution in which the study is being carried out (e.g. a Research Office or oversight department), The Joint Commission, and the FDA. Audits or site visits may occur at different stages of a protocol, such as before initiation, during the active phase, or after completion. The IDS pharmacist can provide auditors with policies, procedures, and study documentation and can support inspections of areas where investigational drugs are received, stored, and dispensed [10]. Maintaining a well-organized IDS pharmacy can make audits easier and more successful for the study group. IDS pharmacies have also demonstrated proficiency in serving as an investigational drug coordinating center for multi-center studies [33].

EDUCATION TO THE MEDICAL TEAM

Aside from their role in the dispensing process, pharmacists receive extensive training and are considered experts in different aspects of pharmacotherapy. As such, pharmacists are optimal resources for providing drug information. This is particularly important in the setting of investigational drugs, where traditional information resources may not be available. Investigational drugs are often not included in monograph resources (e.g. Lexi-comp, Micromedex), nor is FDA-approved prescribing information available during the initial phases of clinical trials. The IDS pharmacist plays a large role in ensuring that all parties involved in the dispensing, administration, and other ancillary roles in the investigational process are provided with education on the medication-use process of the investigational drug.

One way that IDS pharmacists provide this education is through the creation of a local drug information data sheet outlining the important aspects of the drug and its appropriate use. This document contains a wide variety of information that can be helpful in different practice settings within the research site. Having an IDS pharmacist compile this information into one central, concise document saves time and effort when the information is needed. A comprehensive document should begin with the drug’s name, any synonyms and abbreviations, and basic information on pharmacology [9]. This involves the mechanism of action and pharmacokinetic parameters. This information can be particularly useful when determining whether adverse effects experienced during the study could be related to the investigational drug. In addition, it should include dosing ranges, schedules, contraindications, monitoring parameters, and information on preparation and administration that can be utilized by providers and nursing staff [9]. Additional information on toxicity and management of drug interactions may also be included, if known.

DISCUSSION

The use of medications to improve quality of life and manage diseases is continuing to increase as more effective and safer options are identified and developed through clinical research studies. The integrity of this research, as well as the safety of human subjects, is a vital responsibility of all health professionals involved [9]. Additionally, clinical trials continue to increase in complexity and often require the specialized support of an IDS for services such as blinding and drug preparation. Thus, pharmacists have become an essential partner in supporting clinical research studies in a variety of practice settings, specializing in all aspects of the medication-use process for investigational drugs.

The IDS pharmacist can perform a number of specific roles to assist in the successful implementation of an investigational drug study. These may include logistical duties such as procurement and provision of investigational drugs to subjects or investigators. Pharmacists may also have direct involvement in the development of a research protocol, review as a member of the SRC or IRB, or more informally as a consultant to provide recommendations on the ability of the institution to implement the requirements of the study protocol. The pharmacist also has a responsibility to facilitate regulatory compliance with all local, state, and federal requirements and to ensure the ethical conduct of clinical research studies [12]. This includes compliance with the FDA’s Code of Federal Regulations, The Joint Commission’s Medication Management standards for investigational drugs, and the American Society of Health-System Pharmacists’ Guidelines on Clinical Drug Research [6,8,9]. The IDS pharmacist is also responsible for providing operational and clinical guidance and oversight for investigational drugs.

Beyond the benefit of pharmacist involvement with consultative and logistical support of the study, the pharmacist can also have a dramatic impact on the risk management of research studies, which can result in improved medication safety for study subjects and decreased liability for the investigators. As a trained clinician with experience and expertise in the medication-use process, the pharmacist is able to identify areas of potential safety risks such as inappropriate labeling, storage, or dispensation requirements and can proactively create mechanisms to mitigate risks. The pharmacist is also able to critically evaluate the protocol to determine if there are opportunities for more efficient or effective processes for preparing and dispensing investigational drugs, as well as contribute to developing safeguards for prescribing investigational drugs through development of order sets/templates.
The inclusion of a pharmacist into the development and implementation of a clinical research study involving investigational drugs is essential for maintaining the highest standards for medication safety practices and ultimately, the quality, efficacy, and safety of the results of the study. The pharmacist has the potential to serve as a consultant during protocol development or review, support the implementation of the protocol at an institution, and provide continuous compliance or audit support. Ultimately, the pharmacist's background and training in the safe and effective use of medications naturally translates into the clinical research environment and allows investigators to more confidently and competently conduct clinical studies.

**REFERENCES**

1. Institute for Safe Medication Practices. ISMP medication safety alert! Safety problems posed by investigational drug name abbreviations and acronyms [Internet]. cited 2016. August 8. Available from: http://www.ismp.org/newsletters/acuteacare/articles/19971203.asp.

2. Institute for Safe Medication Practices. ISMP medication safety alert! Product-related issues make error potential enormous with investigational drugs [Internet]. cited 2016. August 8. Available from: https://www.ismp.org/newsletters/acuteacare/articles/20071101.asp.

3. Grissinger M. Reducing the potential for mistakes with investigational drugs. P&T. 2011;36:120–121,138.

4. Young L, Haakenson C, Weber J, Tosch T. National survey of pharmacy-coordinated investigational drug services. Am J Hosp Pharm. 1984;41:1792–6.

5. Cruz JL, Brown JN. Safety risks with investigational drugs: pharmacy practices and perceptions in the veterans affairs health system. Ther Adv Drug Saf. 2015;6:103–9.

6. Food and Drug Administration. Investigational new drug application. Code of Federal Regulations, Title 21, Chapter 312 [Internet]. cited 2016. August 8. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312.

7. Department of Veterans Affairs. VHA Handbook 1108.04. Investigational drugs and supplies [Internet], Washington, DC. 2012. cited 2016. August 8. Available from: http://www.va.gov/vhapublications/ViewPublication.asp?pub_ID=2497.

8. The Joint Commission E-dition. Accreditation requirements for hospital: medication management [Internet]. cited 2016. August 8. Available from: https://e-dition.jcrinc.com/ASEarch.aspx.

9. American Society of Health-System Pharmacists. ASHP guidelines on clinical drug research. Am J Health Syst Pharm. 1998;55:369–76.

10. Amin SR, Lee JS, Avila JG, Boron MJ, Conley S, Enos R, et al. HOPA investigational drug service best practice standards [Internet]. Hematology/Oncology Pharmacists Association. cited 2016. August 8. Available from: http://www.hopar.org/uploads/files/2016/HOPA16_IDS_Guidelines.pdf.

11. Phillips MS. Clinical research: ASHP guidelines and future directions for pharmacists. Am J Health Syst Pharm. 1999;56(4):344–6.

12. Shehab N, Tamer H. Dispensing investigational drugs: regulatory issues and the role of the investigational drug service. Am J Health Syst Pharm. 2004;61(18):1882–4.

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

14. Bates DW, Leape LL, Petrycki S. Incidence and preventability of adverse drug events in hospitalized adults. J Gen Intern Med. 1993;8(6):289–94.

15. Kaushal R, Bates DW, Landrigan C, McKenna KJ, Clapp MD, Federico F, et al. Medication errors and adverse drug events in pediatric inpatients. JAMA. 2001;285(16):2114–20.

16. Bobb A, Gleason K, Husch M, Feinglass J, Yarnold PR, Noskin GA. The epidemiology of prescribing errors: the potential impact of computerized prescriber order entry. Arch Intern Med. 2004;164(7):785–92.

17. Franklin BD, Vincent C, Schachter M, Barber N. The incidence of prescribing errors in hospital inpatients. An overview of the research methods. Drug Safety. 2005;28(10):891–900.

18. Gandhi TK, Weingart SN, Seger AC, Borus J, Burdick E, Poon EG, et al. Outpatient prescribing errors and the impact of computerized prescribing. J Gen Intern Med. 2005;20(9):837–41.

19. Gandhi TK, Weingart SN, Borus J, Segar AC, Peterson J, Burdick E, et al. Adverse drug events in ambulatory care. N Engl J Med. 2003;348:1556–64.

20. Institute of Medicine. Preventing Medication Errors. Aspden P, Wolcott JA, Bootman JL, CronenTT, editors. Committee on Identifying and Preventing Medication Errors. Washington, DC National Academies Press; 2007.

21. Perrault LE, Metzger JB. A pragmatic framework for understanding clinical decision support. J Healthc Inf Manag. 1999;13:2–21.

22. Sim I, Gorman P, Greens RA, Haynes RB, Kaplan B, Lehmann H, et al. Clinical decision support systems for the practice of evidence-based medicine. J Am Med Inform Assoc. 2001;8(6):527–34.

23. Kaushal R, Shojania KG, Bates DW. Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. Arch Intern Med. 2003;163:1409–16.

24. Lehmann CU, Kim GR. Computerized provider order entry and patient safety. Pediatr Clin North Am. 2006;53(6):1169–84.

25. Mekhjian HS, Kumar RR, Kuehn L, Bentley TD, Teater P, Thomas A, et al. Immediate benefits realized following implementation of physician order entry at an academic medical center. J Am Med Inform Assoc. 2002;9(5):529–39.
26. Grissinger M. Guidelines for standard order sets. P T. 2014;39(1):10–50.
27. Institute for Safe Medication Practices. Design of preprinted cancer chemotherapy order forms is critical for patient safety. ISMP Medication Safety Alert! 1996;1(3):2.
28. Institute for Safe Medication Practices (ISMP). Designing preprinted order forms that prevent medication errors. ISMP Medication Safety Alert! 1997;2(8):1–2.
29. Institute for Safe Medication Practices (ISMP). It’s time for standards to improve safety with electronic communication of medication orders. ISMP Medication Safety Alert! 2003;8(4):1,3–4.
30. Cohen, T, Sanborn M. Director’s forum-pharmacist involvement in order set and protocol development. Hosp Pharm. 2008;43(5):424–7.
31. Dollinger C, Schwiertz V, Sarfati L, Gourc-Berthod C, Gue- dat MG, Aloux C, et al. SIMulation of medication error induced by clinical trial drug labeling: the SIMME-CT study. Int J Qual Health Care. 2016;28(3):311–5.
32. Siden R, Tamer HR, Skyles AJ, Weadox S, Redic K. Pharmacist-prepared dispensing guidelines for drugs used in clinical research. Am J Health Syst Pharm. 2012;69(12):1021–6.
33. Jeon JE, Mighty J, Lane K, McBee N, Majkowski R, Mayo S, et al. Participation of a coordinating center pharmacy in a multicenter international study. Am J Health Syst Pharm. 2016;73(22):1859–68.