FINAL REPORT

UIC CENTER FOR EDUCATION AND RESEARCH ON THERAPEUTICS

Tools for Optimizing Prescribing, Monitoring and Education (TOP-MED)

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Abstract

Purpose

Our long-term objective was to improve the safety, efficacy, and cost-effectiveness of drug therapy by increasing the appropriateness of prescribing and the quality of monitoring. The short-term objective was to develop, redesign, refine, integrate, test, deploy, and disseminate tools and training materials in five key areas: drug formularies, drug utilization review, lab-pharmacy linkages, N-of-1 trials, and pharmacoeconomics.

Scope

Efforts to maximize the benefits and minimize the risks associated with drugs continue to be impeded by suboptimal prescribing, inadequate monitoring of patients' outcomes, and inadequate prescriber education and support to overcome these limitations. As a result, the US healthcare system suffers from persistent problems of underuse, overuse, and misuse of drugs, with unacceptably high rates of preventable errors, adverse effects, and suboptimal patient health outcomes. Our Center sought to remedy these problems by conducting a series of studies in five core project areas at UIC and five collaborating organizations.

Methods

We used a variety of qualitative and quantitative methods across the various projects, including retrospective review of electronic medical records, content analysis of transcribed meetings, and analyses of large claims databases.

Results

We had varying levels of success and productivity across the project areas. We were most successful and productive in our work on formulary decision making, drug utilization review, and lab-pharmacy linkages; we were less so in pharmacoeconomics and N-of-1 clinical trials.

Key Words: prescribing, monitoring, education, formularies, statistics, N-of-1, drug utilization review, clinical laboratory, pharmacoeconomics

Purpose

The specific aims from the original application were as follows:

1. Revitalize the drug formulary as an evidence-based tool for directing drug therapy decisions.
2. Re-engineer drug usage review (DUR) systems and processes so that data analysis is easier, more tightly linked to formulary decisions and criteria, timelier, and more likely to yield valid generalizations.
3. Reduce prescribing errors and enhance recognition of adverse drug effects in high-hazard contexts by linking lab and pharmacy information systems and generating clinical alerts when problems are detected.
4. Develop, deploy, and evaluate an N-of-1 trial service, integrated into a formulary restriction program, in order to support the goal of individualized therapy without succumbing to the unsafe, unscientific experimentation that is often now the norm.
5. Implement and study the impact of pharmacoeconomic support to enhance formulary decision making and to evaluate the cost-effectiveness of our other interventions.

Our Center has five main project areas, as described above. We report progress in each of these areas below. Within each project area, we describe studies and results, significance, and future plans. The final section lists publications, presentations, and enduring products.

Project Area 1. Revitalizing Formularies as the Nerve Center of Evidence-Based, Rational Drug Therapy

1.A. Specific Aim

To reinvigorate and transform the power and ability of the drug formulary to positively impact drug prescribing, by studying and enhancing nine value-added roles of the formulary and P&T committee.

1.B. Formulary-Specific New Drug Claims Checklist Tool

1.B.1. Methods

This tool was created in an iterative creative process by a panel of experts.

1.B.2. Results

The FLIP formulary drug application evaluation tool poses a series of questions that provide a framework for formulary decision making. These questions are designed to assist formulary committee members in evaluating claims made about drugs being considered for addition to the formulary and, if added, to assist in deciding what restrictions or special monitoring precautions should be put in place. Emphasis centers on the quality of the available evidence and on comparisons to therapeutic alternatives. The ultimate objective of the tool is to help committee members critically evaluate the role for a given drug in significantly improving patient outcomes related to specific indication(s). The tool is organized around the following six broad questions: (A) Evidence of need: Is there compelling evidence of a need to add this drug to our formulary? (B) Efficacy: What is the strength and quality of evidence to support claims for this drug? (C) Safety: What safety issues need to be considered? (D) Misuse impact potential: If placed on the formulary, what is the potential for misuse or overuse? (E) Cost issues: Can we justify the cost of this drug? (F) Decision-making information, calculations, timing, and process: What is the quality and completeness of evidence, and what are the deliberations of committee?

The tool has been published as an Appendix to the Academy of Managed Care Pharmacy's Format for Formulary Submissions, Version 3.0.

The AMCP format for formulary submissions version 3.0. *J Manag Care Pharm.* Jan 2010;16 (1 Suppl A):1-30.

A manuscript describing the tool and its intended use has been published in *PLOS Medicine*:
Schiff, G. D., Galanter, W. L., Duhig, J., Koronkowski, M., Lodolce, A., Pontikes, P., Busker, J., Touchette, D., Walton, S., **Lambert, B. L.** (2012). A prescription for improving drug formulary decision-making. *PLoS Med* 9(5), 1-7.

1.B.3. Significance

We think this represents a high-leverage opportunity for our tool to influence formulary decision making because of the widespread visibility and adoption of the AMCP format. Dossiers that are created based on our checklist tool should be more complete and should allow for more thorough and critical evaluation of new products.

1.B.4. Future Plans/Sustainability

Because the tool has been incorporated into the AMCP format for formulary submissions, its influence is likely to be long lasting.

1.C. Formulary Culture Survey

1.C.1. Methods

Design

We used a cross-sectional, observational design to obtain a preliminary assessment of a new measure of formulary culture.

Measure Development

Commonly accepted steps to develop a measure were followed, including: (1) have a measurement goal (measure formulary culture); (2) generate items; (3) select items; (4) format a questionnaire; (5) pilot test the items; (6) examine the properties of the measure; (7) revise and refine the measure; and (8) conduct large-scale validation of the measure. In this paper, we report our progress through the first six of these steps.

The measurement goal was to quantify the extent to which a positive formulary culture exists in a hospital. Items were generated based on input from the focus groups, review of the literature, and discussion with experts. We examined the literature and measures related to patient safety culture and its assessment on formularies and formulary myths, the broad literature on health outcomes and evidence-based medicine, and studies of conflicts of interest and bias introduced by pharmaceutical marketing efforts. In addition, we identified measures from other disciplines, such as educational psychometrics and health psychology, to aid in developing the format and structure of the questionnaire. We also organized focus groups with formulary committee members to identify specific themes for item development. The initial measure that was piloted included 49 items organized around five themes: (1) global trust, confidence, and credibility (five items); (2) structure and process of formulary committees (six items); (3) dimensions of formulary performance (24 items); (4) general attitudes (four items); and (5) familiarity with drug information resources (10 items). The response options were structured as five-point rating scales with a neutral or neither agree nor disagree middle option.

Participants

We recruited a convenience sample of residents and attending physicians from two large, urban, public teaching hospitals in a large Midwestern city. We contacted potential participants via email and through announcements at grand rounds and similar gatherings attended by clinicians. Entry into a lottery for an iPod was used to attract participation. The study was approved by the institution review boards of both institutions.

Data Collection

Investigators pilot tested the survey prior to survey rollout. We collected data using an online survey tool, Survey Monkey. We sent participants a link via email and, if interested, they followed the link and completed the survey.

Statistical Analysis

Exploratory factor analysis was conducted to determine the factor structure of the measure. Factor analysis revealed which items loaded or were grouped together based on the extent to which they were correlated. Items were extracted using principal component analysis. We used varimax rotation with Kaiser

normalization. Criteria applied to identifying factors included eigenvalues >1 and encompassing more than two items. We acknowledge that the total sample size is likely insufficient to undertake a rigorous factor analysis, which would be described as approaching "fair" (i.e., approximately 200 respondents). Informed largely by the factor analysis, items were regrouped into dimensions, and internal consistency reliability was evaluated using Cronbach's alpha. We analyzed the psychometric properties of the questionnaire to guide revisions that would help us construct summary scores for each of the hypothesized constructs. We examined internal consistency reliability using Cronbach's alpha. Using the results of these psychometric analyses, we identified issues with the items and made revisions to selected items and scales. The survey was revisited, and the response options structure was revised; some items were dropped or reworded. After reorganizing the items according to the psychometric analysis, we created summary scores. In the case of item nonresponse, a summary score was still calculated using simple mean imputation if 50% or more of the items in a scale were completed.

We explored differences in the mean scores on each scale between attending physician and residents and between the two institutions. Attending physicians and residents were felt to potentially differ in their attitudes and knowledge due to level of training, time with an institution, and years of experience prescribing drugs and interacting with hospital administration and the drug and device industry. We suspected that structural differences between the two institutions (e.g., payer mix, case-mix, academic vs. nonacademic, etc.) might also lead to measurable differences in formulary culture. Evidence of differences between institutions would provide initial evidence of known-groups validity. Because our notions about institutions and levels of training were too speculative to yield directional hypotheses, we tested null hypotheses.

1.C.2. Results

We recruited 24 residents and 30 attending physicians from Institute A and 53 residents and 82 physicians from Institute B (Table 1). The initial version of the measure contained 49 items that were administered to the participants. Based on expert opinion, these items were organized into 14 themes that were proposed to belong to five domains.

Factor analysis revealed a six-factor solution after excluding the 10 items that listed drug information sources, which were deemed largely descriptive and dated. Upon revising the wording of some items, several redundant and/or poorly fitting items according to psychometric analysis were identified and dropped. The remaining 30 items were regrouped into six dimensions (Figure 1). The dimensions mostly demonstrated a generally acceptable level of internal consistency reliability (i.e., $\alpha > 0.70$): general attitudes toward formulary (five items: $\alpha = 0.82$); credibility of the formulary committee (six items: $\alpha = 0.78$); beliefs about formulary committee practices (six items: $\alpha = 0.60$); prescriber autonomy (five items: $\alpha = 0.64$); confidence in committee decisions ($\alpha = 0.50$); and physician attitudes toward industry influence ($\alpha = 0.72$).

Correlations between dimensions ranged from moderately strong (general attitudes toward formularies and credibility of the formulary committee, $r = 0.45$) to trivial (comfort with drug industry and credibility of the formulary committee, $r = 0.07$) (Table 2).

In comparing formulary culture between residents and attending physicians, attending physicians were more confident in committee decisions (58.6 vs. 44.7; $p < 0.001$) and less comfortable with drug industry influence (51.2 vs. 43.4; $p < 0.01$) compared with residents. Note that higher scores are associated with greater support for and belief in restrictive formularies and the ability of the committee to make evidence-based decisions in the absence of industry influence. In comparing institutions, respondents at the larger county hospital had more positive general attitudes toward formularies (56.7 vs. 51.2; $p < 0.01$).

1.C.3. Significance

Inspired by the success of various measures of patient safety culture, ours is the first effort to quantify formulary culture. We believe that valid and reliable measurement of formulary culture will motivate and enable organizations to improve their own formulary culture, and we believe that, just as with patient safety culture, these improvements should lead to improvements in patient outcomes related to drug therapy. We would welcome input from AHRQ staff who have been involved with the patient safety culture project.

1.C.4. Future Plans/Sustainability

A manuscript describing these results is in the final stages of preparation and will be submitted during the first quarter of 2013 (Lambert BL, Pickard AS, Duhig J, Galanter W, Solem C, Lodolce A, Koronkowski M, Schiff GD. [in preparation] Conceptualizing and developing a measure of formulary culture.) We then plan to

seek additional funding to further develop and test this measure and to understand the association between formulary culture and other measures of the quality, safety, and effectiveness of drug therapy.

1.D. Formulary Committee Structure and Processes Benchmarking and Ethnographic Study

1.D.1. Methods

Design. This is an longitudinal, observational study of formulary decision making and group dynamics.

Eligibility Criteria. All current members of the Pharmacy and Therapeutics (P&T, formulary) committees at sites 1, 2, and 3 were eligible.

Subject Selection. All current members of the Pharmacy and Therapeutics (P&T, formulary) committees at sites 1, 2, and 3 were included. The Site 1 committee consisted of 11 members. Site 2 had 25 official members. Site 3 committee had 33 official members. For each committee, not all members attend all meetings.

Recruitment. Investigators described the purpose of the research during a regularly scheduled P&T meeting and sought permission and consent of the members to participate.

Documentation of Informed Consent. We obtained full written, informed consent.

Procedure. We made audio recordings of Pharmacy and Therapeutics (P&T) committee meetings at each site. We placed one omnidirectional microphone on the conference table to capture audio. We repeated the procedure at each meeting for approximately 12 months. Recordings were then transcribed, and subsequent analysis will be based on the transcripts.

Analysis Plan. Analysis will be qualitative, searching for themes.[13,14] Analysis will focus on the following themes: formulary assumptions and misconceptions, general critical review areas of discussion, specific issues raised for specific drugs, and comparisons and contrasts among different formularies. We used ethnographic software (e.g., Atlas ti) to assist in our coding and analysis of the data. Transcripts were analyzed by multiple coders. Each coder went through the data, labeling instances of the formulary myths and also identifying important themes and topics. Coders then compared their marked up transcripts and their newly identified categories. The category systems were revised after discussion, and the transcripts were analyzed again, marking them up with the revised category labels. Finally, exemplary quotations were selected to illustrate the main themes or categories, and these quotes formed the data in subsequent manuscripts.

In addition, we analyzed the agendas for all recorded meetings, developed a coding system for agenda items, and performed a descriptive analysis of the resulting codes.

1.D.2. Results. All data collection is complete for this project. Thirty-one meetings were recorded, 10 from Site 1, 10 from Site 2, and 11 from Site 3. All recordings have been transcribed, and we have begun to code and analyze the data. Table 1 summarizes the distribution of agenda items across the three different committees, illustrating the wide range of topics and activities that are routinely addressed.

Table 1. Percent of Agenda Items of Various Types at Three Different P&T Committees

Code	Site 1	Site 2	Site 3
1. Add	13%	7%	11%
2. Remove	15%	11%	1%
3. Restrict	0%	5%	1%
4. Other	14%	4%	0%
5. Guidelines	11%	1%	38%
6. Safety Alerts	10%	7%	1%
7. Budget/Utilization	0%	4%	8%
8. P&T Policy	3%	6%	1%

Code	Site 1	Site 2	Site 3
9. Stocking	0%	0%	0%
10. Shortages	6%	0%	0%
11. Review Minutes	9%	3%	7%
12. New Members	0%	0%	2%
13. Affiliated Sites	2%	13%	14%
14. Subcommittees	13%	32%	17%
15. Unknown	2%	4%	0%
16. Announcement	0%	4%	0%
Total	100%	100%	100%

1.D.3. Significance

Very little is known about the inner workings of these highly influential and ubiquitous formulary committees. The significance of this study lies in its ability to break down the boundaries between the separate committees and go beyond the highly personal dynamics of P&T meetings to better understand broader themes, shortcomings, effective approaches, and leadership issues.

1.D.4. Future Plans/Sustainability

Our plan is to complete a manuscript describing the themes that arose in discussions involving the addition of new drugs to the formulary.

Project Area 2. Multifaceted Approach to Quality Improvement Via Drug Utilization Review

2.1. Innovative Statistical Methods for Large-Scale Drug-AE Screening

2.1.A. Specific Aim

To develop innovative statistical methods for large-scale drug/adverse event screening. This aim has not been modified from the original application.

2.1.B. Studies and Results

In the past year, we have focused largely on the development of the DRUGStat program, which applies methods originally developed for environmental monitoring applications to drug-safety surveillance. The methodology is based on Poisson prediction limits, which permit longitudinal screening for changes in the rate of adverse events over time and identifying drug adverse event interactions for a particular drug out of a larger class of drugs. The statistical foundation of these methods are described in the second edition of the book *Statistical Methods for Groundwater Monitoring* by Gibbons, Bhaumik, and Aryal (Wiley, New York, 2009). The program, which is now completed and ready for release, is capable of simultaneously screening hundreds of drugs for hundreds of adverse events. The system is completely automatic and is based on large-scale medical claims data rather than using traditional approaches based on spontaneous reports. As an example of an intra-drug comparison, a background time-window can be established (e.g., the first 6 months of a drug on the market), a Poisson prediction limit can be computed, and the rate of the AE during future monitoring periods (e.g., quarters) can be compared with the background rate. The program also tests for increasing trend in the rate of AEs. This can be done automatically for large sets of drugs and AEs. Results are presented in graphical and tabular formats. The inter-drug module compares the rate of an AE for an individual drug with a background Poisson prediction limit established for a single or class of "background" drug(s) during the same period of time. As an example, we can compare each individual antidepressant for a given AE (e.g., suicide attempts) to a Poisson prediction limit established for all antidepressants as a group (or all other antidepressants excluding the antidepressant of interest). Again, results are presented in graphical and tabular formats, and large numbers of target drugs and AEs can be simultaneously evaluated. The program is designed for large-scale exploratory analytics and is useful for hypothesis generation and surveillance rather than for definitive hypothesis testing.

We also have written a User's Guide. The program runs under Windows and is currently being beta tested at the Hines VA. Once completed, it will be freely distributed via the Center for Health Statistics website, www.healthstats.org.

In addition, Drs. Gibbons, Hur, and Bhaumik and colleagues produced a large number of CERT and CERT-affiliated publications describing and illustrating the use of these methods, typically to document the association between psychoactive drugs and certain adverse effects, especially suicide.

2.1.C. Significance

We have developed a series of novel, statistically sound approaches to analyzing spontaneous adverse event reports and medical claims data. These new methods can help meet the growing societal need for valid approaches to passive and active surveillance for adverse drug effects.

2.1.D. Future Plans/Sustainability

We will release a version of the software to the public in 2013, and we will submit for publication a manuscript illustrating the application of the methods to anticonvulsant and antidepressant safety data from the VA.

2.2. Design, Implementation, Evaluation, and Dissemination of Medication Prescribing Guidelines in a National Consortium of Health-Systems: Translation of Evidence into Practice

2.2.A. Specific Aims

To develop, implement, evaluate, and disseminate clinical prescribing guidelines in a national consortium of health systems. This aim has not been modified from the original application.

2.2.B. Studies and Results

2.2.B.1. Methicillin-resistant Staphylococcus Aureus (MRSA)

Purpose. The use of policies and practices regarding surveillance, decolonization, and treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections and the formulary status of various antimicrobial agents used to treat MRSA were characterized.

Methods. A 61-item questionnaire was sent to the director of pharmacy at each of 263 acute care hospitals that were members of a national group purchasing organization.

Results. Responses were received from 102 hospitals (38.8%). Active surveillance culture protocols were in place at 44 hospitals (44%). Nearly 75% engaged in key antimicrobial stewardship activities, whereas only 18% reported having a formal antimicrobial stewardship team. MRSA decolonization policies existed in approximately 25% of the respondent hospitals. Vancomycin was on the formulary in all hospitals with few restriction policies, whereas the newer anti-MRSA agents (linezolid, daptomycin, and tigecycline) were on the formulary in most hospitals but with restrictions. Vancomycin was the most commonly used antimicrobial for the treatment of various MRSA infections, followed by linezolid. Nearly 70% of the respondent hospitals reported having a vancomycin-specific dosing or monitoring guideline in place. Most specified the use of actual body weight for dosing and trough serum concentrations at steady state for therapeutic monitoring (84% and 91%, respectively). Most guidelines did not address the use of a loading dose to attain a high target trough or methods for choosing alternative agents.

Conclusion. Acute care hospitals in the United States varied in their policies and practices of surveillance, decolonization, and treatment of MRSA infections, but most were consistent with national guideline recommendations.

Significance. Given the large variability in the MRSA prevalence data nationally and globally, it is important to understand the factors that contribute to such variability. Our study, albeit cross-sectional in nature, attempts to address this question by using existing data to explore relationships that may exist between recommended policies and practices and MRSA prevalence. Our results complement the existing evidence in current literature and generate new hypotheses that may stimulate further research.

Future Plans/Sustainability. No future plans, and the results have been published:

Yang, Y., McBride, M. V., Rodvold, K. A., Tverdek, F., Trese, A. M., Hennenfent, J., Schiff, G. D., Lambert, B. L., & Schumock, G. T. (2010). Hospital policies and practices on prevention and

treatment of methicillin-resistant *Staphylococcus aureus*. *American Journal of Health-System Pharmacy,* 67(12):1017-24.

2.2.B.1. Anticoagulation Use

Purpose. The use of anticoagulant therapy for the prevention and treatment of venous thromboembolism (VTE) and acute coronary syndrome (ACS) among hospital inpatients was evaluated.

Methods. Medication-use data were retrospectively collected on 1,716 patients who received anticoagulants for VTE or ACS at 42 community hospitals during the period of April-June 2009; all hospitals in the sample were members of the same large health care organization. Descriptive analyses were performed to characterize anticoagulant use, patient safety, compliance with national prescribing guidelines, and performance on relevant Joint Commission quality measures.

Results. The most common indications for anticoagulant use were VTE prophylaxis (67.5% of cases), ACS (13.5% of cases), and VTE treatment (11.9% of cases). The agents most commonly used for VTE prophylaxis were subcutaneous enoxaparin (70% of cases) and subcutaneous unfractionated heparin (UFH). Overall, the anticoagulant regimen used was consistent with national prescribing guidelines in 67.5% of cases; however, rates of appropriate prescribing were lower in subgroups of patients with renal impairment, obesity, or both (63.6%, 42.5%, and 63.6%, respectively). Reported anticoagulant-related adverse events during the study period mainly involved minor or major bleeding, which occurred in 36% and 32% of cases, respectively. Compliance with The Joint Commission core measures ranged from 49.1% for core measure VTE-3 (warfarin overlap therapy) to 72.3% for VTE-4 (monitoring of UFH dosages and platelet counts by protocol).

Conclusion. Among hospitals in a large national healthcare system, the most common use of anticoagulants in hospitalized patients was for VTE prevention, followed by ACS and VTE treatment. Enoxaparin and UFH were the most commonly used agents for each indication, and the selection and use of anticoagulants were in compliance with national guidelines in the majority of patients for whom those drugs were prescribed.

Significance. Inpatient use of anticoagulation therapy is the subject of intense quality improvement and risk management scrutiny at the local and national level because it is an expensive, risky, and---at the same time---potentially extremely effective form of treatment for several common, serious diseases in hospitalized patients. Specialty societies have recently introduced new guidelines for the use of anticoagulants in inpatients, but little is known about adherence to these guidelines in routine practice. Our survey identified specific areas of guideline nonadherence that lend themselves naturally to quality improvement. If successful, such quality improvement programs should improve the safety and effectiveness of anticoagulation therapy for inpatients in this health system, and the successes and failures of the program should produce generalizable lessons about how to conduct similar surveys and interventions in the future.

Future Plans/Sustainability. No future plans. The project is complete, and the results have been published:

Tiryaki, F., Nutescu E.A., Hennenfent, J., Karageanes, A., Koesterer, L., Lambert B. L., Schumock, G. (2011). Anticoagulation therapy for hospitalized patients: Patterns of use, compliance with national guidelines and performance on quality measures. *American Journal of Health-System Pharmacy.* 68(13), 1239-1244.

Project Area 3. Linking Lab and Pharmacy

3.A. Specific Aims

We proposed to conduct and support electronic lab-pharmacy surveillance activities and to measure and compare their impact in a number of academic and community practicing settings. This aim has not been modified from the original application.

3.B. Studies and Results

3.B.1. Inpatient Lab-Med Linkage

The main lab-med project was composed of an active, multicenter, inpatient intervention and an analysis of prior alerts at the University of Illinois Hospital (UIH). During this timeframe for the multicenter,

inpatient intervention, a second set of inpatient once-a-day alerts was implemented at UIH. These alerts were related to the anticoagulants heparin, low-molecular-weight heparin, aspirin, clopidogrel, prasugrel, and warfarin. At UIH, a 450-bed hospital, there were roughly 5-10 alerts/day. Also during this time, both the phase I alerts and phase II alerts were implemented at John J. Stroger, Jr. (Stroger) Hospital. In addition, the phase II alerts were implemented at Northwestern Memorial Hospital (NMH) using a third-party vendor and were being run intermittently rather than daily. Both the phase I and II alerts and daily program processes were presented to members of the eight community hospital Advocate Health Care group's decision support committee for consideration of implementation.

Prior analysis of alerts implemented at UIH to try to prevent and correct hyperkalemia based on a variety of lab-med pairs was completed. The alerts were multimodal, generated both at the time of med ordering and at the time of lab reporting. The analysis showed that the number of hours hyperkalemic patients spent on potassium supplementation or ACE inhibitors, ARBs, or potassium-sparing diuretics was decreased slightly using a interrupted time-series analysis. Most benefit was found to be due to the alerts at the time of ordering. This study, the subject of a doctoral dissertation by Dr. Ken-Yu Chang, is described in detail below.

3.B.1.A. Effect of lab-medication clinical decision support on inpatient hyperkalemia.

Purpose. This study was conducted to evaluate clinicians' responses to the presence of hyperkalemia before and after implementing laboratory-pharmacy decision support in an inpatient setting. Additionally, efforts were made to explore the factors that might be associated with the changed time course of responses, including patient characteristics, severity of hyperkalemia, renal function, repeated alerts, location of the patients, and alert time.

Methods. Two hyperkalemia-related laboratory-pharmacy CDS rules were implemented at University of Illinois Hospital (UIH), a 450-bed urban teaching hospital in a major academic health center, in June 2003. The synchronous CDS alerted clinicians of abnormal serum potassium level ([K+]) at the time of prescribing ACE inhibitors, angiotensin II receptor blockers (ARBs), potassium supplementation (K-sup), and potassium-sparing diuretics; the real-time asynchronous CDS notified clinicians when abnormal potassium results came back while patients were still on the medication. In May 2010, another once-daily, asynchronous drug-laboratory alert report was implemented to detect any abnormal potassium test result missed and not acted on after the real-time asynchronous alert.

The assessment of synchronous and real-time asynchronous CDS alert was conducted through a retrospective analysis of electronic health record (EHR) data collected from regular clinical care encounters. Clinical actions treating hyperkalemia for patients taking an ACE inhibitor or ARB were identified through patient chart review using the pre-identified action repertoire. Canceling the K-sup order and/or repeating [K+] were expected to be the clinical actions to treat hyperkalemia in patients taking K-sup.

The effect of the synchronous CDS alert was measured by the clinicians' compliance with the synchronous alert, or, in other words, the order cancellation rate after CDS implementation. The alert rate of asynchronous alerts during the post-intervention period was compared with the rate of potential asynchronous alert during the pre-intervention period as the indirect measure of the synchronous alert. The effect of the real-time asynchronous alert was measured by time to the first action (clinicians' action time) and patient time to normal [K+]. Total patient time on K-sup normalized by total patient admission days during the same period and also the patient time on K-sup with [K+] ≥ 5.0 mEq/L (normalized by total patient time on K-sup) were used to measure the combined effect of both alerts on K-sup users. Besides descriptive statistic analysis of the dependent and independent variables, a Cox proportional hazards model was used to assess the modulators of clinician's action time and patient time to normal [K+], and a segmented regression analysis was conducted to evaluate the effect of CDS alerts.

Results. On average, the clinicians' compliance with the synchronous alerts was 88.31% for [K+]↔ACE/ARB and 69.46% for [K+]↔K-sup. As the indirect effect of the asynchronous CDS alerts, the alert rate of the real-time asynchronous CDS for [K+]↔K-sup dropped significantly after CDS implementation (28.8% vs. 30.4%, $p = 0.005$). The change in alert rate was not significantly for [K+]↔ACE/ARB (12.1% vs. 12.5%, $p = 0.752$).

For [K+]↔ACE/ARB alerts, the Cox proportional hazards regression results showed, after controlling for all the covariates, that the action time did not change significantly after CDS implementation. The clinicians' action time decreased as patient [K+] level increased (HR = 1.51 with $p = 0.003$ for 5.7 mEq/L ≤ [K+] ≤ 6.0 mEq/L, and HR = 1.87 with $p < 0.0001$ for [K+] ≥ 6.1 mEq/L). Alerts from ICU patients were responded to more promptly than were alerts for patients from general medical or surgical units (HR = 1.38, $p = 0.032$). However,

the action time was not associated patient age, gender, ethnicity, creatinine clearance level, time of the alert, or whether it was the first hyperkalemic episode during the admission. Patient time to normal [K+] also decreased as alerting [K+] level increased (HR = 1.48 with p = 0.003 for 5.7 mEq/L ≤ [K+] ≤ 6.0 mEq/L, and HR = 1.73 with p < 0.0001 for [K+] ≥ 6.1 mEq/L). It took less time for patients with normal creatinine clearance levels versus those with impaired renal function (HR = 1.71, p = 0.002), but not significantly longer for patients with severe renal insufficiency (HR = 0.90, p = 483). Patient time to normal [K+] was also longer if the patient had a previous hyperkalemic episode during the hospital stay (HR = 0.40, p = 0.002). Alerts from ICU patients and alert time between 5 pm and midnight were also significantly associated with decreased time to normal [K +]. However, patient age, gender, and ethnicity had no effect on the patient time to normal [K+].

The insignificant segmented regression coefficient estimates (p = 0.196 for the difference in the intercept, p = 0.158 for the difference in the slope) confirmed that the real-time asynchronous CDS alerts implemented in June 2003 had no effect in reducing the clinicians' action times when managing hyperkalemia among ACE/ARB users. After controlling for the covariates, the segmented regression results indicated that the asynchronous alert did not help reduce patient time to normal [K+] for ACE/ARB users, either (p = 0.134 for the difference in intercept, p = 0.487 for difference in the slope).

For [K+]↔K-sup alerts, the Cox proportional hazards model showed that [K+] level ≥ 5.4 mEq/L and having unknown ethnicity were associated with decreased action time till K-sup cancellation. Age between 45 and 64 years compared with age 65 years and older, being a woman, having a normal creatinine clearance level, not being the first hyperkalemic episode, being alerted on multiple K-sup orders, and alert time outside of the normal day shift were associated with prolonged action time until K-sup cancellation. When counting repeating [K+] as another action, ages 20-44 years and 45-64 years were both associated with shortened action time compared with ages 65 and older. Being a man, having [K+] higher than 5.3, having normal renal function or severe renal insufficiency, and being the first alert during the admission and located in ICU were significantly associated with shorter action time. It was worth noting that it took longer time to respond to alerts fired between midnight and 7 am (HR = 0.48, p < 0.0001) but shorter time for alerts fired between 5 pm to midnight (HR = 1.54, p < 0.0001).

The multivariate segmented regression results showed that neither the difference in intercept nor the difference in the slope was statistically different, which indicated that the real-time asynchronous alerts had little effect in reducing time to K-sup order cancellation or time to K-sup order cancellation or repeating [K+]. For patient time to normal [K+], the positive and significant slope for the pre-intervention period suggested an upward trend before CDS implementation (coeff. = 1.69, p = 0.024). Even though the asynchronous alert did not decrease patient time to normal [K+] immediately after implementation (p = 0.588), there was a significant difference in the slope (coeff. = -2.50, p = 0.019). This indicated not only a reduction in outcome but also a declining trend during the post-intervention period, because the post-intervention slope estimate was negative. As the combined effect of synchronous and real-time asynchronous alert, there was no significant change in the monthly patient time on K-sup per patient admission days or monthly patient time on K-sup while [K+] was elevated per patient days on K-sup after alert implementation.

Based on the distribution of [K+] level for inpatients at UIH during the period of January 2009–June 2009, the cutoffs of ≥ 5.1 mEq/L and ≥ 5.5 mEq/L were chosen for the once daily report of [K+]↔K-sup and [K+]↔ACE/ARB, respectively. The time analysis of the [K+] posting time suggested that the best time to run the daily report would be between 9 am and 10 am to capture most of the hyperkalemic cases, if not attended already, and to minimize patient time in danger as [K+] was elevated. After discussion with the pharmacy department and the clinical safety team, the time of 2 pm was chosen given the workflow of the existing practice. During the period of June 28, 2011–October 3, 2011, the once-daily report fired 51 [K+]↔ACE/ARB alerts on 34 patients and 44 [K+]↔K-sup alerts on 32 patients. This equaled 0.56 [K+]↔ACE/ARB alerts and 0.45 [K+]↔K-sup alerts per day for a 450-bed hospital like UIH.

The multivariate segmented regression analysis indicated that there was no significant decrease in the action time to K-sup cancellation immediately after the implementation of once-daily report in May 2010. However, there was a gradually descending trend, given the significant coefficient estimate for the difference in the slope and the negative slope for the post-intervention period. For the action time to K-sup cancellation or repeating [K+], the segmented regression estimates did not confirm the ascending trend for the pre-intervention period but did ascertain the impact of once-daily report in gradually reducing time to either cancel the K-sup order or repeat [K+]. Moreover, the once-daily report did not impact patient time to normal [K+] (p = 0.752 for the difference in the intercept, p = 0.088 for the difference in the slope). The segmented regression analysis also suggested that the once-daily report did not have influence in shortening patient time on K-sup

after normalized on total patient admission days. There was a marginally significant drop in monthly average for patient time on K-sup while [K+] was elevated, but the effect could not be affirmed due to poor model fit.

Conclusion. Clinicians complied with synchronous CDS alerts in managing hyperkalemia in inpatient settings. The real-time asynchronous alert failed to demonstrate its effect in accelerating clinicians' actions but had a potential effect in improving patient outcomes for K-sup users. The once-daily report was effective in detecting potentially hazardous situations that had not been corrected after real-time asynchronous alert, but its impact on changing clinicians' practice behaviors and improving patient outcomes was difficult to establish, given the rare alert rate.

Significance. We have implemented a large set of clinically relevant lab-pharmacy linkages and are in the process of assessing their overall effectiveness.

Future Plans/Sustainability. We will complete a qualitative and quantitative analysis of the phase I and II alerts that have been implemented using a once-daily format at UIH and Stroger and an ad-hoc format at NMH. For all alerts, the alert appropriateness and proportion that produced an action will be determined. In addition, a qualitative analysis of instructive cases to demonstrate the strengths and weaknesses of the method will be completed. For the alerts that fired frequently, particularly those related to potassium, a quantitative analysis using an interrupted time-series model will be performed at each institution to measure the overall benefit of the alerts as related to clinician time to action during potentially dangerous scenarios, and the overall patient time at risk of hyperkalemia will be determined. Also next year, we plan to complete data extraction and analysis of outpatient lab ordering related to certain medications: HMG-COa reductase inhibitors, levothyroxine, ACE Inhibitors, ARBs, and spironolactone. This analysis will determine the appropriateness of lab ordering per FDA recommendations and ramifications on the cost of care based on ordering habits.

The clinical alerts themselves continue to run at each site on an ongoing basis.

3.B.2. Outpatient Lab-Pharmacy Linkage

3.B.2.1. Analysis of large insurance claims data set.

The apparent absence of a large number of lab claims in the database has frustrated our efforts to produce meaningful results from this project, and we may be forced to wind it down with no final deliverable.

3.B.2.2. Utilization of Oral Antidiabetic Medications: Examining Adherence to Clinical Guidelines.

Background and Purpose. The aim of this study was to determine the degree of compliance of physician practice with the ADA guidelines for the use of medications for the treatment of type 2 diabetes and to assess factors influencing these decisions.

Methods. A retrospective cohort study of patients with diabetes managed at one of the clinics that provide routine diabetes care in University of Illinois Medical Center at Chicago was conducted for the period from January 2007 to October 2010. Patients newly starting drug therapy at any one of these clinics were included in the study. Data from electronic prescription medication orders for diabetes were collected. Laboratory data collected included serum creatinine, creatinine clearance, alanine aminotransferase, aspartate aminotransferase, and hemoglobin A1c levels. Patient demographics and all diagnosis data were also collected.

Results. Descriptive analysis of the data showed that physicians at UIMCC were compliant with the ADA guidelines about 72% of the time when they prescribed metformin as first-line therapy, adjusting for any liver or renal impairment status of the patient. The next most widely used drug as first-line therapy was sulfonylureas, followed by insulin. A mixed-effect regression model to identify predictors for prescribing metformin demonstrated that renal function, type of clinic, and hemoglobin A1c levels were statistically significant variables. The liver function markers ALT/AST were perfectly correlated with the metformin prescription and, hence, were not included in the model. Patients with impaired liver function never got metformin. Patients with impaired renal function and higher hemoglobin A1c levels were less likely to receive metformin. Patients seen at the family medicine clinic were more likely to receive metformin than were those seen at internal medicine or geriatric clinics.

Conclusion. This single-site study is the first to document the compliance of physicians with the ADA guidelines and assess the effects of patient's clinical condition on prescribing behavior. It shows that physicians consider label information in their decision-making process. Understanding these factors can help define the second-line therapy toward a more streamlined management of diabetes.

A master's degree thesis was completed on this topic by Ms. Sapna Rao.

3.B.2.3. Seasonal Variation in International Normalized Ratio Among Venous Thromboembolism Patients on Warfarin.

Purpose. The aim of this study was to evaluate the association between seasons and seasonal factors and blood coagulation, as expressed by INR and TTR, in VTE patients on warfarin therapy.

Methods. A retrospective, cohort study of outpatients managed at the antithrombosis clinic of the University of Illinois Medical Center was conducted. One hundred patients with a diagnosis of VTE who were treated with long-term warfarin were included. Data were collected for a 12-month period for the following variables: demographics, INR values, variation in Vitamin K intake, alcohol use, smoking status, concurrent medications, and comorbidities. Temperature, pressure, and humidity data corresponding to patients' dates of INR measurements were extracted from the National Oceanic and Atmospheric Administration. We performed mixed-effects modeling for five outcome variables: mean INR as continuous dependent variable; out-of-range INR (< 2 & > 3); INR < 2; and INR > 3 and TTR, which was modeled as the probability of having in-range INRs, given the total INR measurements for each patient by each season.

Results. Simple descriptive analysis revealed that summer and winter had fewer out-of-range INRs (38% and 34%, respectively) compared with spring and fall (47% each). The mean TTR adjusted for each season and each year was 69.89% in winter and 68.07% in summer, both of which were better than 62.64% in spring. Modeling of our data revealed on the whole that seasonal variation does exist in INR as well as TTR. However, the variation is not necessarily due to seasonal factors of temperature, pressure, and humidity. Likelihood ratio tests showed that seasons significantly improved the fit of the model after controlling for important covariates. In case of TTR, summer ($p = 0.03$, OR = 1.37) and winter ($p < 0.0001$, OR = 1.8) had significantly higher TTRs than did spring. Specifically, the probability of having higher TTR is 0.6 in winter and is 0.53 in summer versus 0.45 in spring, and these differences were statistically significant.

Conclusion. This study is the first to assess the seasonal variation in TTR and to check for the association it may have with temperature, pressure, and humidity. Seasonal variation was proved to exist for mean INR, out-of-range INR, and TTR. Summer and winter had significantly better INR control and TTRs compared with spring. This could mean potentially fewer warfarin-related adverse events in summer and winter compared with spring.

A master's degree thesis was completed on this topic by Ms. Zenobia Dotiwala.

3.B.3. Effectiveness of VTE Prophylaxis Intervention

Purpose. The implementation of a mandatory assessment of risk for venous thromboembolism (VTE) in a health system's electronic medical record (EMR) and clinical decision support (CDS) system was evaluated to measure its effect on the use of pharmacologic prophylaxis and the occurrence of VTE and bleeding events.

Methods. A commercially available CDS system was used in designing the automated CDS intervention. During computerized order entry, the system delivered alerts prompting clinician risk assessment and delivered alerts under circumstances suggesting less-than-optimal prophylaxis. Rates of pharmacologic prophylaxis, clinically diagnosed hospital-acquired VTE, and hospital-acquired bleeding events were measured 1 year before and 1 year after implementation.

Results. After adjustment for patient age, sex, and high-risk comorbidities, the data showed a post-implementation increase in the percentage of patients who received pharmacologic prophylaxis at some time during their admission from 25.9% to 36.8% ($p < 0.001$). The rate of VTE for the entire hospital did not change significantly, but a significant reduction among patients on medical units was observed, from 0.55% to 0.33% ($p = 0.02$). There was no increase in either major or minor bleeding events.

Conclusion. Without increasing the risk of bleeding, a CDS system requiring clinicians to document VTE risk assessment in the EMR promoted improved rates of pharmacologic prophylaxis at any time during an admission and a decreased risk of VTE in general medical patients but not in all adult patients.

Significance. Computerized clinical decision support (reminders) increased VTE prophylaxis in hospitalized patients. Increased prophylaxis was safe, and it effectively reduced the rate of VTE events in the largest subpopulation of patients (on the medicine service where the intervention caused the largest increase in prophylaxis).

Future Plans/Sustainability. The research project is complete, but the clinical intervention is in ongoing use at UIHHSS. The results have been published:

Galanter, W. L., Thambi, M., Rosencranz, H., Shah, B., Falck, S., Lin, F.-J., Nutescu, E., Lambert, B. L. (2010). Clinical decision support to improve venous thromboembolism risk assessment, prophylaxis, and prevention at a university teaching hospital. *American Journal of Health-System Pharmacy*, 67, 1265-1273.

3.B.4. The Effectiveness of Medication-Laboratory--Linked Computerized Alerts for Gadolinium and Radiocontrast Imaging in Patients with Chronic Kidney Disease (CKD)

Purpose. To determine whether computerized alerts linking lab data to radiology test order entry could reduce the completion of orders for gadolinium and radiocontrast in patients with decreased renal function.

Methods. We implemented computerized alerts warning clinicians of the presence of a creatinine clearance (CrCl) < 45 mL/min when ordering radiocontrast. Based on an FDA warning on the use of gadolinium-based magnetic resonance contrast agents (GBCA), an alert was added to warn when GBCA was ordered when the estimated glomerular filtration rate (eGFR) was < 60 mL/min. We assessed the effect of alerts on rates of order cancellation and completion and built logistic regression models to examine associations between cancellation rates, study completion, and covariates.

Results. Alerts led to cancellation of a portion of both types of contrast orders, though compliance with the radiocontrast alerts was higher than with GBCA: 33.9% vs. 19.3% ($p < 0.0001$). Cancellation was strongly negatively associated with eGFR: Patients with eGFRs between 30 and 60 mL/min were less likely to have orders canceled compared with patients with eGFRs < 10: 77.0% vs. 47.5% ($p < 0.0001$). Attending physicians were more likely than residents to comply with alerts: 47.1% vs. 28.2% ($p < 0.0001$). Compared with orders by residents, orders by attendings were less likely to result in completed studies: 33.1% vs. 53.7% ($p = 0.04$).

Conclusions. Computerized alerts succeeded in producing cancellations of potentially harmful GBCA and radiocontrast orders. Analysis and better understanding of specific clinician, test, and patient factors related to alert overrides may help refine and better target similar future interventions.

Significance. Computerized clinical decision support effectively reduced the rate at which hospitalized patients with chronic kidney disease were exposed to gadolinium and radiocontrast, both of which are nephrotoxic and can cause rare but serious adverse effects.

Future Plans/Sustainability. This project is complete, and the results were submitted, revised, and resubmitted to the Journal of the American Medical Informatics Association (but ultimately were not published):

William L. Galanter, Connie Jung, Shengsheng Yu, Gordon D. Schiff, Bruce L. Lambert, Ph.D. Medication-laboratory--linked computerized alerts for gadolinium and radiocontrast imaging in hospitalized patients with decreased renal function: Effects on orders and study completion (to be submitted)

An editorial related to this project has been published separately:

Galanter, W. L., Moja, J., & Lambert, B. L. (2010). Using computerized provider order entry and clinical decision support to improve prescribing in patients with decreased GFR. *American Journal of Kidney Diseases*, 56(5), 809-812.

The clinical intervention continues to be used on an ongoing basis at UIHHSS. The plan is to follow through until the main manuscript above has been published.

3.B.5. An Analysis of Computer Alerts Suggesting Oral Medication Use During Computerized Order Entry of Intravenous (IV) Medications

Purpose. Compliance with computer alerts suggesting oral medication use during computerized order entry of IV medications was analyzed.

Methods. Using automated computerized clinical decision support (CDS) to suggest converting IV medications to oral alternatives can reduce medication costs for hospitalized patients, but prescriber noncompliance limits the effectiveness of such interventions. Clearer understanding of the factors associated with noncompliance to alerts may facilitate the design of more effective CDS systems. Electronic medical record data were retrospectively analyzed to measure the rate of compliance with a CDS alert that suggested converting to an equivalent oral form of a drug at the time of ordering the IV formulation. Multiple logistic regression was used to examine the associations among medication type, clinician characteristics, hospital service type, time of order, and compliance with the IV-to-oral conversion recommendation. The main

outcome was compliance with the alert, measured at the level of the individual medication order.

Results. The mean +/- SE overall compliance rate was 18.7% +/- 0.6%. Compliance varied among the medications, with methylprednisolone having the lowest (8%) and famotidine having the highest (32%) rates ($p < 0.05$). Nurses had the highest compliance rate (35%), whereas pharmacists had the lowest (10%) ($p < 0.05$). Medical house staff (19%) and medical faculty (21%) complied at similar rates. The intensive care units had lower compliance rates than did the medical-surgical ward (15% versus 21%, $p < 0.05$).

Conclusion. CDS alerts to convert 12 IV medications to oral alternatives were developed and implemented in an urban tertiary hospital. Compliance rates for the alerts were relatively low and varied by medication, location, and clinician type.

Significance. This information should provide useful for further modifications of alert-based interventions designed to decrease medication costs through increased use of oral medications.

Future Plans/Sustainability. This project is complete. The clinical intervention continues to be used on an ongoing basis at UIHHSS; results have been published:

Galanter, W. L., Liu, X., Lambert, B. L. (2010). An analysis of computer alerts suggesting oral medication use during computerized order entry of intravenous medications. *American Journal of Health-System Pharmacy*, 67, 1101-1105.

Project Area 4. N-of-1 Trial Service

4.A. Specific Aims

The specific aims of this project were as follows: (1) to establish an N-of-1 clinical trial service that will serve clinicians at UIC Hospital and John Stroger, Jr. Hospital of Cook County; (2) to integrate the N-of-1 trial service with the activities of the P&T committee by granting permission to use certain nonformulary drugs only if the requesting physician agrees to carry out an N-of-1 trial to evaluate the effectiveness of the drug; (3) to identify and describe the circumstances (i.e., types of drugs, patient populations, diagnoses, reimbursement schemes) in which N-of-1 trials are most cost effective; and (4) to learn more about the effectiveness of drugs for which these trials are performed.

4.B. Studies and Results

Coordinated N-of-1 clinical trial teams were established at both UIC Hospital and John Stroger, Jr. Hospital of Cook County to facilitate ongoing protocol development and implementation. The UIC Investigational Drug Service team established and committed to ongoing participation at both institutions for the provision of clinical trial drug therapy. The Investigational Drug Service developed a support service to assist with drug study blinding and compounding. Our first protocol: **"N-of-1 randomized trials to assess the efficacy and tolerability of gabapentin versus pregabalin in the treatment of diabetic peripheral neuropathy,"** was approved and implemented at each institution. Current study recruitment efforts are listed below:

Institution	Screened	Recruited	Enrolled	Completed	Gender	Ethnicity
Stroger	---	---	5	4	M-3, F-1	Hisp - 1 AA - 1 Indian - 1 Caucas - 1
UIC	150	3	0	0	M-2, F-1	AA - 3

The results, interestingly, led to gabapentin being the preferred drug treatment of choice or the patient not being able to differentiate between the two agents; thus, the more cost-effective treatment regimen could be prescribed. In addition, we confirmed the extent to which these agents are not well tolerated.

4.C. Significance

N-of-1 trials establish a sound scientific basis upon which to customize therapy for individual patients. They also hold the promise of being used as a mechanism to switch otherwise reluctant patients from expensive to less expensive therapies that can be shown to be equally effective and tolerable for individual patients.

4.D. Future Plan/Sustainability

Overall, this project did not succeed. We were not able to efficiently carry out N-of-1 trials, nor were we able to create a sustainable N-of-1 trial service linked to local formulary decisions. Nevertheless, there were some enduring products that are in the process of completion and dissemination.

N-of-1 randomized trials to assess the efficacy and tolerability of gabapentin versus pregabalin in the treatment of diabetic peripheral neuropathy. This study was closed out at both institutions. Results have been compiled and analyzed. The plan is to abstract and publish the data accordingly.

Using N-of-1 clinical trials in diabetic peripheral neuropathy. This project led to a meta-analysis of published N-of-1 trials. A subset of N-of-1 trials for pain, including diabetic peripheral neuropathy, will be compiled and disseminated. The plan is to abstract and publish the data accordingly.

Our Investigational Drug Service team has developed a support service model to assist with study drug blinding and defray costs.

Dose optimization strategies to individualize drug therapy in diabetic peripheral neuropathy. Using telemedicine strategies, the protocol leveraged telemedicine techniques to optimize individual dose preferences and monitor for adverse drug effects. Results will be abstracted, presented, and published. Protocol will be shared accordingly.

Project Area 5. Pharmacoeconomics: Empowerment Tool for Formulary Process

5A. Specific Aims

We proposed to utilize the nationally recognized UIC College of Pharmacy Center for Pharmacoeconomic Research to support and advance the formulary process.

5.B. Studies and Results

5.B.1. Cost-effectiveness of Strategies for Diagnosing Heparin-Induced Thrombocytopenia (HIT)

Purpose. Heparin-induced thrombocytopenia (HIT) is an immune-mediated complication of heparin therapy. Accurate diagnosis reduces the need for unnecessary treatment, which can result in bleeding complications. The objective of this study was to identify the most cost-effective strategy (enzyme-linked immunosorbent assay [ELISA] vs. ELISA/Serotonin Release Assay [SRA]) for diagnosing HIT from the health system perspective.

Methods. Multiple decision-analysis models were constructed using TreeAge Pro software following the ISPOR task force guidelines for modeling. The 2008 American College of Chest Physician's Guidelines were used to inform HIT treatment approaches. A systematic literature search was used to identify all model inputs, such as the effectiveness of argatroban, heparin, and warfarin; weighted costs and disutilities for overall thrombosis and bleeding complications; and costs of acute events and long-term complications. The mean age-adjusted quality of life of a healthy patient was estimated using life tables. Costs and quality-adjusted life years (QALYs) were discounted at 5%. Base-case values were determined using Monte Carlo simulation, and sensitivity analyses were conducted. The net benefit of each strategy was analyzed at different willingness-to-pay (WTP) thresholds ($0 to $150,000) to determine the most cost-effective strategy.

Results. In the base case, ELISA resulted in lifetime costs and utilities of $9028 and 10.5413 QALYs compared with $8849 and 10.5428 QALYs for ELISA/SRA. ELISA was dominated by ELISA/SRA. ELISA/SRA was the most cost-effective strategy for WTP thresholds between $25,000 and $150,000; ELISA was optimal for WTP thresholds under $25,000. ELISA/SRA remained cost effective when thrombosis and bleeding complication costs and probabilities were varied. ELISA was the most cost-effective strategy when specificity was greater than 92.7%. The results were consistent for both prophylactic and treatment doses of unfractionated heparin.

Conclusion. For the base-case scenario, ELISA/SRA is the optimal testing strategy. Healthcare providers need to take into account the turnaround time for ELISA and SRA results to generalize the study findings.

An abstract of this study has been published: Patel V, Touchette D, Yang Y, Galanter W et al. Cost-Effectiveness of strategies for diagnosing heparin-induced thrombocytopenia. *Value Health*. 2010. Volume: 13 Issue: 3 Pages: A209-A209

5.B.2. Economic Analysis of Alvimopan for Prevention and Management of Post-Operative Ileus

Purpose. To determine whether alvimopan for the prevention of postoperative ileus in patients undergoing small- or large-bowel resection by laparotomy is associated with lower total costs compared with standard care.

Design. Pharmacoeconomic analysis using a formal decision model

Data source. Four phase III clinical trials, two pooled analyses, and one meta-analysis

Patient population. A cohort of patients who underwent bowel resection with primary anastomosis by laparotomy and received either standardized, accelerated postoperative care (usual care) or usual care plus alvimopan

Measurements and results. Clinical outcomes, obtained from pooled analyses of published studies, were time to discharge order written, postoperative nasogastric tube insertion, postoperative ileus-related readmission within 7 days, and occurrence of nausea and vomiting. Cost inputs included drugs, nursing labor, readmissions, and hospitalizations. Costs were assessed by determining the net cost of alvimopan use and subsequent reduction in length of stay. Sensitivity and scenario analyses were conducted. Costs for alvimopan were $570 based on an average of 9.5 doses. Given the 18.4-hour mean reduction in time to discharge order written, use of alvimopan reduced hospitalization costs by $2021. The mean difference in overall cost of care, as determined by Monte Carlo simulation, was $1168 (95% certainty interval, -$437 to $5879), favoring the use of alvimopan. In the sensitivity analysis, association of alvimopan with lower costs was robust to several changes in key parameters, including cost and number of doses of alvimopan, time to discharge order written, readmission rates, and hospitalization cost. In the scenario analyses, alvimopan use yielded a net cost of $226 when no difference in time to discharge order written was assumed. In the scenario analysis using data from a study that did not enforce opioid use, alvimopan resulted in a cost saving of $65/patient.

Conclusion. Alvimopan was cost saving for the prevention of postoperative ileus in patients undergoing bowel resection by laparotomy, although these potential cost savings were highly dependent on a difference in time to discharge order written. This finding is not applicable to the less-invasive laparoscopic surgical approach, for which quality data on alvimopan use are lacking. Limitations of this analysis included use of time to discharge order written as a proxy for length of stay and difficulty interpreting study results due to inconsistent reporting and conduct of the clinical trials evaluating alvimopan. More research is needed to determine the cost-effectiveness of alvimopan.

This study has been published.

Touchette DR, Yang Y, Tyriaki F, Galanter WL. Economic analysis of alvimopan for prevention and management of post-operative ileus. *Pharmacotherapy*, 2012 Feb; 32(2):120-8.

5.C. Significance

The pharmacoeconomic projects described above all seek to improve the efficiency of pharmaceutical care. The projects all serve to provide information for use by decisionmakers to improve the efficient use of medications.

5.D. Plan

These projects are completed with no plans to continue them.

CERT and CERT-Affiliated Publications

Alexander, G.C., Lambert, B.L. (2012). Is treatment heterogeneity an Achilles' heel for comparative effectiveness research. *Pharmacotherapy*, 32(7):583-5.

Dotiwala, Z. (2011). Seasonal variation in international normalized ratio among venous thromboembolism patients on warfarin. Master's Thesis, Department of Pharmacy Administration, University of Illinois at Chicago.

Duhig, J. E. (2011). Medication guide comprehension and health literacy. Doctoral dissertation. Department of Pharmacy Administration, University of Illinois at Chicago, Chicago, IL.

Galanter, W. L., Moja, J., & Lambert, B. L. (2010). Using computerized provider order entry and clinical decision support to improve prescribing in patients with decreased GFR. *American Journal of Kidney Diseases*, 56(5), 809-812.

Galanter, W. L., Liu, X., Lambert, B. L. (2010). An analysis of computer alerts suggesting oral medication use during computerized order entry of intravenous medications. *American Journal of Health-System Pharmacy*, 67, 1101-1105.

Galanter, W. L., Moja, J., & Lambert, B. L. (2010). Using computerized provider order entry and clinical decision support to improve prescribing in patients with decreased GFR. *American Journal of Kidney Diseases,* 56(5), 809-812.

Galanter, W. L., Thambi, M., Rosencranz, H., Shah, B., Falck, S., Lin, F.-J., Nutescu, E., Lambert, B. L. (2010). Clinical decision support to improve venous thromboembolism risk assessment, prophylaxis, and prevention at a university teaching hospital. *American Journal of Health-System Pharmacy*, 67, 1265-1273.

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Gibbons RD, Segawa E, Karabatsos G, Amatya AK, Bhaumik DK, Brown CH, Kapur K, Marcus SM, Hur K, Mann JJ. Mixed-effects Poisson regression analysis of adverse event reports. *Stat Med*. 2008 May 20; 27(11): 1814–1833.

Gibbons RD, Amatya AK, Brown CH, Hur K, Marcus SM, Bhaumik DK, Mann JJ. (2010). Post-approval drug safety surveillance. *Annual Review of Public Health*. 31:419-37.

Gibbons RD, Hur K, Brown CH, Mann JJ. (2009). Relationship between antiepileptic drugs and suicide attempts in patients with bipolar disorder. *Archives of General Psychiatry.* 66(12):1354-60.

Patel V, Touchette DR, Yang Y, Nutescu E, Kim K, Vidanovic V, Galanter W. Cost-effectiveness of strategies for diagnosing heparin-inducted thrombocytopenia. ISPOR 15th Annual International Meeting, Atlanta, GA; May 2010. Value Health. 2010. Volume: 13 Issue: 3 Pages: A209-A209.

Rao, S. (2011). Utilization of oral anti-diabetic medication: examining adherence to clinical guidelines. Doctoral dissertation. Department of Pharmacy Administration, University of Illinois at Chicago, Chicago, IL.

Schiff, G.D., Galanter, W.L., Duhig, J.A., Lodolce, A.E., Koronkowski, M., Lambert, B.L. Principles of conservative prescribing. (2011). *Archives of Internal Medicin*e, 171(16), 1433-1440.

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