The Impact of Pharmacist Adherence Counseling on Healthcare Utilization
A Systematic Review and Meta-Analysis

April 20, 2015

William N. Kelly, Pharm.D., FISPE — Principal Investigator
Professor of Pharmacy
University of South Florida College of Pharmacy
Tampa, Florida
wkelly@health.usf.edu

John M. Allen, Pharm.D., BCPS – Co-Principal Investigator
Clinical Pharmacy Coordinator
Northside Hospital
St. Petersberg, Florida

Krystal Bullers, MLIS – Researcher
Shimberg Health Science Library
University of South Florida

Kristen Sakmar, MLIS – Researcher
Shimberg Health Science Library
University of South Florida

Branko Miladinovic, PhD
Assistant Professor of Biostatistics
University of South Florida College of Medicine

Benjamin J. Djulbegovic, MD, PhD – Co-Investigator
Professor of Medicine and Oncology
University of South Florida College of Medicine

Table of Contents

Executive Summary .................................................. 2
Goals and Objectives.............................................. 2
Background & Rationale......................................... 3
Methods...................................................................... 4
Workplan & Timeline.............................................. 8
Budget...................................................................... 9
Budget Justification............................................... 9
References ............................................................. 10
Biosketches............................................................. 11
EXECUTIVE SUMMARY

This protocol will guide a systematic review and meta-analysis to assess the evidence on the effect of pharmacists’ medication adherence counseling on the utilization of health services.

GOAL AND OBJECTIVES

The primary objective of this study is to assess the evidence on the effect of pharmacists’ medication adherence counseling on using health services (hospitalization, 30-day hospital readmissions, and physician and emergency department visits). Favorable results, if found, will be used to build a case for pharmacists to make medication adherence counseling a primary job function, and to affect public policy on paying such services as a justified medical expense by health plans and payers. The specific study objectives are as follows:

Objective 1: To identify, using multiple databases and sources, scientific reports — published (in any language) in biomedical journals or online — of pharmacist counseling interventions (with or without other pharmaceutical care practices) designed to improve medication adherence.

Objective 2: To select eligible studies for formal review and analysis based on specific criteria applied to each of the studies and interventions identified in Objective 1. These selected studies must be comparisons of groups exposed and unexposed to the intervention under investigation. The selected studies must report suitable findings, preferably measures of association and variability, about intervention effects on medication adherence and healthcare utilization from randomized controlled trials (RCTs) only.

Objective 3: To systemically collect and summarize quantitative and qualitative information from each study selected in Objective 2, including the following three elements:
   a. characterize the type and features of the intervention (location, intensity and duration), and classify studies accordingly, i.e., into mutually exclusive or overlapping groups;
   b. summarize the design, methodologic features (especially those that might affect or bias results), and relevant population characteristics of each study (e.g., age group, gender, disease states, follow-up period for the study and for the control group, etc.);
   c. abstract or derive as needed, depending on published data and findings, estimates of outcome frequency and the intervention effect (adjusted for confounders) and its variance of each intervention on each outcome in each study, and if available, effect estimates for subgroups in the study population.

Objective 4: To compare and analyze results from all selected studies to evaluate program effectiveness and to characterize the amount and sources of effect heterogeneity across studies. Depending on the available data and differences in presenting results across studies, one or more meta-analyses will be conducted to estimate overall intervention effects and, more importantly, to explain differences in findings (estimated effect heterogeneity) across studies.
**Objective 5:** To draw conclusions about promising or limited strategies of pharmacist adherence counseling; to assess the potential impact of such interventions in the target population; to recommend future research; and, to discuss potential public policy based on the study results.

**BACKGROUND AND RATIONALE**

Drugs don’t work in patients who don’t take them.¹ Patients, at times, do not have their prescriptions filled; some don’t pick up their medication at their pharmacy; and, nearly half fail to take their medication as prescribed. Poor medication adherence correlates with poorer patient outcomes and 125,000 deaths each year in the United States.² Further, the cost of poor medication adherence is estimated to be $100 billion each year.³

Improving medication adherence correlates with less use of health resources. For example, a study evaluated the impact of medication adherence on healthcare utilization and cost for chronic conditions that are major drivers of drug spending: diabetes, hypertension, hypercholesterolemia, and congestive heart failure in 137,277 patients under age 65.⁴ For diabetes and hypercholesterolemia, high levels of medication adherence were associated with lower disease-related medical costs. For all four conditions, patients who maintained 80% to 100% medication adherence were significantly less likely to be hospitalized compared with patients with lower levels of adherence.

For diabetes, hypertension, and hypercholesterolemia, high levels of adherence with condition-specific drugs were associated with lower medical costs across all the patients’ treated conditions. For all four conditions, all-cause hospitalization rates were lowest for patients who had the highest medication adherence (>80%).

If pharmacist medication adherence counseling is effective, the preferred strategy may be to identify patients at high risk of being admitted or readmitted to a hospital if they do not take their medication as prescribed. Hospitalization is a major economic driver outcome and this event is often traumatic for patients. Ideally, pharmacists would counsel patients about the importance of taking their medication before they leave the hospital, and primary care pharmacists would continue to work with these patients on improving medication adherence once they leave the hospital. However, it must be shown that pharmacist counseling to improve medication adherence reduces healthcare utilization.

Some individual studies show pharmacists can positively impact medication adherence.⁵-⁷ Moreover, systematic reviews about pharmacist provided therapeutic management and patient counseling report favorable findings on clinical and economic outcomes.⁸-¹⁰

As part of a larger, systematic review on the effect of pharmacist direct patient care, pharmacist adherence counseling (data from 1979 – 2008) had a favorable (p <0.05) results in 48.1%, mixed results in 20.4%, no effect in 14.3%, and unclear results in 3.7% of the studies investigated.⁸ One systematic review (with meta-analysis) investigated the impact of any services delivered by
pharmacists, other than drug compounding and dispensing, on health utilization, costs, and outcomes. Overall, physician visits, hospital readmissions, emergency department (ED) visits decreased, however, the interventions were not well-defined. No results were reported specifically for medication adherence counseling, or on utilizing hospital, emergency department, or physician visits.

METHODS

Criteria for Selecting Studies

Types of Studies: Only randomized controlled trials will be analyzed. Written reports in any language — publications appearing in any year and unpublished manuscripts or reports, particularly of ongoing studies where preliminary findings are available -- will be used.

Types of Participants: Studies involving male or female patients of any age.

Types of Interventions: The intervention will be pharmacist-provided medication adherence counseling of patients. The comparison (control) group in each included study will be patients who receive usual care.

Types of Outcome Measures: The primary outcome of interest will be healthcare service utilization (hospitalization, hospital readmissions, and emergency department and physician visits). Mortality will be followed as an academic interest. Medication adherence will be handled as an intermediary outcome of interest as it lies between the intervention and the outcome.

Search Methods for Identification of Studies

Studies included in this systematic review need to be within the time frame covered by the electronic databases used for the search, through January, 2015. The following databases will be used: NLM PubMed (1950); Ovid/MEDLINE (1950); EMBASE (); ABI/ INFORM (1971); Health Business Fulltext Elite (1922); Academic Search Complete (1887); International Pharmaceutical Abstracts (IPA; 1970); LILACS (1982); PsycINFO (1890); Cochrane Database of Systematic Reviews (1988); National Guideline Clearinghouse (1997); Database of Abstracts of Reviews of Effects (DARE; 1991); ClinicalTrials.gov (2000); LexisNexis Academic Universe (1789); Web of Science (1898); and, Google Scholar (1900); ERIC (); Cochrane Central Register of Controlled trials (); CRISP (); Current Controlled Trials (); Database of Abstracts of Reviews of Effects (); Cochrane Methodology Register (); Health Technology Assessment Database (); Economic Evaluation Database (); SOPUS (); Conference papers index (); Proquest Theses & Dissertations (); CINAL (); Database-specific search terms will be used. In addition, reference lists of systematic reviews, meta-analyses, and review articles will be hand-searched to identify additional studies.

The search terms for this study are: pharmacist or pharmacist-managed or pharmacy or pharmacy-based or pharmacist-directed or pharmaceutical or pharmacist-led or pharmacist-impact AND adherence or compliance or persistence or educate or counseling or advice or advise or advisory or cost or readmission or rehospitalization or admissions or hospitalization or hospitalisation or effective
or utilization or utilisation or RCT or non-compliance or reminders or resolve or trial or effect or evidence or randomized or randomised or economic or outcomes or risk or improved or benefits or cost or use or improve or polypharmacy or cut or evaluation or pharmacoeconomics or reduced or role or resources or double-blind or contribution or intervention or cognitive or consultations or management or impact or financial or visits or emergency or ER or outpatient or ED in the title.

The search strategy and results will be documented and conducted independently by two academic reference librarians (KB and KS) at the University of South Florida, Shimberg Health Science Library. The results of the independent searches (electronic and manual) will be compared and the raw percentage agreement documented. Differences in search results will be resolved by consensus or, if needed, by a third party.

Data Collection and Analysis

Administration: After removing duplication, an End Note file containing the consensus titles and abstracts of the search will be provided to the reviewers (WK and JA). A data extraction form will be created in MS Excel, and all article information, except outcome results will be captured in this form. Outcome results will be tracked in second Excel spreadsheet for ease of entry into statistical software (STATA).

Selection of Studies: Results of the search will be independently reviewed by two investigators (WK and JA). Titles and abstracts will be reviewed, and if more information is required to determine whether the trial meets the inclusion criteria, the full text will be reviewed.

Inclusion Criteria – To be included in the systematic review, studies will be required to meet all the following criteria: a) a randomized controlled trial (RCT); b) evidence of pharmacist counseling patients about medication adherence (able to discern pharmacist contribution) in the study group; c) a comparison group present with no pharmacist medication-adherence counseling; and, d) one or more the following health utilization rates: hospitalization or readmission, emergency room or physician visits. A note will be made if: 1) the pharmacist counseling was or was not independent of other pharmaceutical care services provided; 2) whether medication adherence or costs were measured; and, 3) the before and after results recorded.

Exclusion Criteria – The following will be considered not appropriate for review in this study: descriptive studies with no comparison group, systematic reviews, meta-analyses, clinical drug trials, commentaries, letters, editorials, books, book chapters, meeting abstracts, case studies, guidelines, online exams, bibliographies, dissertations, lectures, theses, book reviews, and news articles. After eliminating duplications and references not appropriate for the study, the remaining references will be submitted for inclusion/exclusion assessment by two independent reviewers.

Reasons for excluding studies will be documented. Disagreement will be resolved by discussion of the investigators, or by a third party if necessary. Inter-rater agreement will be assessed
with Cohen's kappa statistic and raw percentage agreement.

Data Extraction: Data will be independently extracted from the included studies by two reviewers (WK and JA) and entered into an MS Excel spreadsheet. Data extraction forms will be pilot tested on five studies and revised as needed. When necessary, the authors of the primary studies will be contacted to obtain additional information or data.

The following information will be extracted for the publication: title, primary author, publication source, and publication year. Data extraction for all studies will include: study design, setting, N, duration, follow up, characteristics of the study population (mean age, % male, and disease states), baseline characteristics of the intervention, comparison groups, and the intervention (location, type – with or without other pharmaceutical care – a description, the frequency, duration, and intensity), and when and how adherence was measured. Also, if possible, the source of the outcome data will be recorded, as will the randomization method, allocation procedure, blinding of patients, outcome assessors, withdrawals and dropouts, and analysis.

Results will be extracted for summary measures as healthcare utilization frequency (e.g. incidence rates), estimates of the intervention effect (e.g. incidence rate ratios or differences) with variance estimates or confidence intervals, $p$-values, dropout rate, and reasons for withdrawal).

Assessment of Risk of Bias in Included Studies: The risk of bias of the included studies will be assessed by two independent reviewers (WK and JA). Differences will be reconciled between the reviewers or by a third party. Separate criteria will be used for different study designs. For randomized controlled trials, the following methodologic domains will be assessed: 1) sequence generation; 2) allocation sequence concealment; 3) blinding of participants, personnel and outcome assessors; 4) incomplete outcome data; 5) selective outcome reporting; and 6) and other potential threats to validity (e.g., use of co-interventions and unequal risk-factor distributions at baseline). 11

The raw agreement percentage for reviewers will be documented.

Summary of Findings in Tables: Summary of findings tables included in RevMan 5.2 will be completed to improve the readability of the review (Cochrane Collaboration, 2008). Those tables will include descriptive parameters obtained for each study plus estimates of effect and related measures described below. The GRADE criteria will be used to provide an overall grading of the quality of the evidence for each outcome across studies. 11

Measures of Treatment Effect: Study results will be analyzed using RevMan 5.2 or STATA-IC 13. Effect estimates for continuous outcomes will be expressed as adjusted or weighted mean differences, depending on the similarity of scales measuring an outcome. Effect estimates for outcome events will be expressed as ratios of risks, rates or odds and/or differences of risk or rates, depending on the analysis. Peto "odds ratios" may be used when the estimated intervention effect is weak, outcome events are rare, and there are similar numbers of intervention and comparison subjects in the study. 12
**Heterogeneity of Effect and Meta-Analysis:** Summary estimates of the intervention effect will be combined across studies of similar interventions and outcomes, using standard methods of meta-analysis, provided the data and reported findings are suitable for that purpose. Separate meta-analyses will be used for different outcomes, interventions, study designs, or populations (e.g., women vs. men). Meta-analysis will be used to gain an overall estimate of the intervention effect using inverse-variance weighting and, more importantly, to assess heterogeneity of effect across studies and "explain" that heterogeneity. Heterogeneity will be assessed using three methods: 1) graphical displays of study-specific and overall effect estimates (forest plots); 2) tests of statistical significance, e.g., where \( p < 0.10 \) suggests significant heterogeneity; 3) the \( I^2 \) statistic, where \( I^2 > 0.50 \) may indicate substantial heterogeneity.

**Meta-Regression Analysis** - Meta-regression analysis will be used to predict study-specific effect estimates as a function of study-specific indicators of population characteristics (e.g., age, sex, disease states, patient setting), type and robustness of the intervention, study design, report (published or unpublished), and methodologic features. The goal is to account for variation in the estimated effect across studies. When residual heterogeneity not explained by the predictors is judged to be small, fixed-effects models will be fitted to the summary data, which assume the true effect, conditional on covariates, is the same in all studies.

**Publication Bias** - When residual heterogeneity is judged to be substantial (\( I^2 > 0.50 \)), unexplained variation across studies will be treated as random effects in the model. Funnel plots will be used to detect signs of publication bias, the phenomenon whereby positive findings are more likely than negative findings to be published. To assess the robustness of our results, sensitivity analyses may be done by excluding unpublished studies or studies judged to have a high risk of bias.

If heterogeneity is substantial (\( I^2 > 0.5 \)), a qualitative analysis will be performed using the following criteria for each study and its individual health utilization outcomes:

1. **Favorable:** Determined by a p-value of less than 0.05 indicating significant improvement as a result of pharmacist-provided care.
2. **Not Favorable:** Determined by a p-value of less than 0.05 indicating significant improvement as a result of non-pharmacist-provided care (generally conventional/usual care).
3. **Mixed:** Determined by favorable results on one measurement of a study variable, but not favorable or no effect results on another.
4. **No Effect:** Determined by no significant differences between pharmacist-provided care and comparison (indicated by p-value greater than 0.05).
5. **Unclear:** Unable to determine outcome based on data presented.
6. **Not measured**

**Clinical and Scientific Expertise:** To provide special clinical and scientific expertise, a panel of experts will be recruited and consulted throughout the project to obtain advice, ideas, and feedback on our progress and plans. Experts sought for this purpose will include pharmacists, physicians,
statisticians, and those familiar with RevMan or STATA.

**Report Writing:** The final report/manuscript will be consistent with PRISMA statement requirements.¹

**WORKPLAN AND TIMELINE**

The proposed start date for this project is October 1, 2014. Figure 1 shows the estimated timeline for major project activities. We expect to complete the literature searches by March 31, 2014; all data collection by May 30, 2015; the primary data analysis by September 1, 2015; and, a first draft of the results by November 1, 2015. A manuscript describing our objectives, methods, findings, and conclusions will be prepared and submitted to a suitable peer-reviewed journal by December 31, 2015.

**Figure 1: Timeline of Major Project Activities**

<table>
<thead>
<tr>
<th>Activity</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Database search</td>
<td>5 months</td>
</tr>
<tr>
<td>Article acquisition</td>
<td>0.5 months</td>
</tr>
<tr>
<td>Application of inclusion/exclusion criteria</td>
<td>1 month</td>
</tr>
<tr>
<td>Assessment of bias</td>
<td>1 month</td>
</tr>
<tr>
<td>Data extraction and creation of summary tables</td>
<td>2 months</td>
</tr>
<tr>
<td>Consultation with clinical experts as needed</td>
<td>0.5 month</td>
</tr>
<tr>
<td>Data analysis</td>
<td>3 months</td>
</tr>
<tr>
<td>Draft of full report</td>
<td>1 month</td>
</tr>
<tr>
<td>Final report and manuscript for publication</td>
<td>1 month</td>
</tr>
</tbody>
</table>
BUDGET

**Personnel**

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Hours</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>Dr. W. Kelly</td>
<td>480</td>
<td>$65.00</td>
</tr>
<tr>
<td>Co-PI</td>
<td>Dr. J. Allen</td>
<td>160</td>
<td>$50.00</td>
</tr>
<tr>
<td>Co-I</td>
<td>Dr. Djulbegvic</td>
<td>24</td>
<td>$125.00</td>
</tr>
<tr>
<td>Researcher</td>
<td>Krystal Bullers</td>
<td>120</td>
<td>$30.00</td>
</tr>
<tr>
<td>Researcher</td>
<td>Kristen Sakmar</td>
<td>120</td>
<td>$30.00</td>
</tr>
</tbody>
</table>

**Total Personnel:** $49,400

**Benefits & Inflation**

- Salary Inflation (3%) $1,482
- Fringe Benefits (32%) $16,282

**Total Benefits & Inflation** $17,764

**Other Expenses**

- Software – Single user license $750
- Travel (to present manuscript) $2,000
- Copying and Inter-library loan $1,250
- Access to non-USF databases $500
- Translation $1,000
- Texts & user manuals $150
- Statistician (Dr. Miladinovic) $500
- Office Expense $250

**Total Other Expenses** $6,400

**Total Direct Costs** $73,564

**F&A Costs @ 49.5%** $36,414

**Total Project Cost** $109,978

BUDGET JUSTIFICATION

Systematic reviews with a meta-analysis reside at the top of the level evidence hierarchy.

![Evidence Hierarchy Diagram](image)

**Figure 1.** Evidence hierarchy: investigations placed in a superior localization in the hierarchy show greater power of evidence.

9
The study question being addressed by this investigation is of uppermost importance during this time of healthcare reorganization. Moreover, the answer to the research question comes when the pharmacy profession is trying to justify its provider status.

REFERENCES


BIOSKETCHES

**William N. Kelly, Pharm.D., FISPE** is Professor of Pharmacy at the University of South Florida in Tampa, Senior Vice-President for Visante, Inc. He possesses expertise in pharmacopepidemiology, pharmacoconomics, and evidence-based medicine. He has had clinical and executive management responsibility in hospitals and academia, and performed research at the Centers of Disease Control and Prevention (CDC) in Atlanta.

He earned a BS degree in pharmacy from Ferris State University, and a doctor of pharmacy (Pharm.D.) degree and at the University of Michigan, where he also completed a clinical pharmacy residency program. He completed a fellowship in Executive Management at the Leonard Davis Institute of Health Economics (the Wharton School) at the University of Pennsylvania. He has also completed graduate work in pharmacoepidemiology and biostatistics at the University of Michigan, and McGill and Emory Universities, and is a fellow of the International Society for Pharmacoepidemiology.

Dr. Kelly has published over 80 peer-reviewed manuscripts and 10 chapters in books, and has presented his work nationally and internationally. He is also the author of four books:

- “*Prescribed Medications and the Public Health: Laying the Foundation for Risk Reduction*”(Haworth Press, 2007)
- “*Leadership & Management in Pharmacy Practice*” (CRC Press, 2014)

**John M. Allen, Pharm.D., BCPS** is an Assistant Professor at the University of South Florida (USF) College of Pharmacy. Dr. Allen practices in the Medical Intensive Care Unit at Tampa General Hospital. Dr. Allen also holds a joint appointment as an Assistant Professor within the Department of Internal Medicine, at the USF, Morsani College of Medicine. Dr. Allen’s research has been presented locally and nationally.

Dr. Allen graduated with his Doctor of Pharmacy degree (Magna cum laude) from Florida A&M University (FAMU) in Tallahassee, FL. He then completed PGY-1 residency in pharmacy practice and PGY-2 residency in critical care at the Tampa General Hospital. He is a Board Certified Pharmacotherapy Specialist.
**Krystal Bullers, MLIS, AHIP** is the Emerging Technologies Librarian and College of Pharmacy Liaison for the University of South Florida Shimberg Health Sciences Library in Tampa Florida. She is accomplished in the art of information retrieval and is responsible for teaching drug information and literature evaluation skills to USF College of Pharmacy students throughout the Drug Information and Evidence Based Practice series of courses.

She earned a BA degree in history from Nyack College in Nyack, New York and a Masters in Library and Information Science from the University of South Florida. She is a credentialed member of the Academy of Health Information Professionals. She serves on the Library and Information Services Section Communications Committee of the American Association of Colleges of Pharmacy and as archivist for the Florida Health Science Libraries Association.

**Kristen Sakmar, MA** is the Graduate Medical Education (GME) librarian for the University of South Florida Shimberg Health Sciences Library in Tampa, FL. She has been the GME librarian for the past 7 years. She teaches PubMed, search strategies, information retrieval skills, and EndNote to USF Health students, staff and faculty. She attended the Systematic Review Workshop: Nuts and Bolts for librarians at the University of Pittsburgh, to stay current with the search practices for EBM.

**Branko Miladinovic, PhD** is Assistant Professor of Biostatistics at the Division of Evidence-based Medicine and Outcomes Research at the University of South Florida. Dr. Miladinovic’s current research focuses on systematic reviews/meta-analysis, prognostic models, extreme value distributions, instrumental variable analysis and Bayesian methods.

**Benjamin J. Djulbegovic, MD, PhD** is a Distinguished Professor and Professor of Medicine and Oncology at the University of South Florida. His major academic research interest lies in evidence-based medicine, decision-analysis, clinical reasoning, systematic reviews /meta-analysis and comparative effectiveness research, ethics and design of clinical trials, practice guidelines, outcomes research, impact of clinical trials and the role of uncertainty in medicine. He has extensively published and taught on these subjects. His work on regret in decision-making and the role of uncertainty in the conduct of clinical trials received national and international rewards and has received attention of the press all over the world. Dr. Djulbegovic’s research has been funded both by private entities and the NIH (he has been continuously awarded multiple R01 grants - the most prestigious and competitive federal grants - during last 10 years).