Abstract

This is an application for a K08 Career Development Award for [redacted], an Assistant Professor and clinical pharmacist at Texas Tech University Health Sciences Center School of Pharmacy. His long-term career goal is to be an internationally known expert and independent investigator in the pharmacoepidemiology of therapeutic agents used in patients with type 2 diabetes and chronic kidney disease. The career development aims of this K08 application are to support training in: Aim 1) pharmacoepidemiology, Aim 2) health services research, and Aim 3) analysis of large, complex national databases. This career development award will also support [redacted] path to independence. To achieve this goal, [redacted] has assembled a multidisciplinary mentoring and advisory team with significant experience in extramurally funded clinical research.

Chronic kidney disease (CKD) is a common and well known complication of type 2 diabetes (T2DM). This complication often restricts providers from prescribing metformin, a glucose-lowering agent with known morbidity and mortality benefits in patients with T2DM. This FDA labeled contraindication for metformin using arbitrary serum creatinine cut-points in patients with T2DM and CKD is not evidence based and often necessitates prescribers to initiate or switch patients to other glucose-lowering agents with worse adverse event profiles or that have been associated with poor cardiac outcomes. Guidance in other countries do not endorse the FDA contraindication and allows for metformin use in patients with mild to moderate CKD as measured by estimated glomerular filtration rate. This recommendation is also not based in evidence. Thus, the safety and effectiveness of metformin in patients with T2DM and CKD is largely unknown. [redacted] research will focus on determining the safety and effectiveness through three specific research aims. In Aim 1 he will determine patterns of metformin use in patients with T2DM and CKD. He will analyze complex administrative and clinical data from the national VA database hosted by VINCI. Patterns identified in Aim 1 will inform him of the variables that should be further tested in Aims 2 and 3. Aim 2 will examine associations of adverse events for metformin and other glucose-lowering agents. Specifically, he will study incident hospitalizations for lactic acidosis and primary hospitalizations or emergency department visits for hypoglycemia. In Aim 3, Dr. Alvarez will assess the relationship between metformin and the development of microvascular and macrovascular outcomes. Microvascular outcomes assessed will be the development of proliferative diabetic retinopathy and progression of kidney disease. Macrovascular outcomes will be measured as a composite of non-fatal stroke, acute myocardial infarction, non-traumatic lower extremity amputation and cardiovascular disease death. He will also compare glycemic control between patients prescribed metformin and those on other glucose-lowering agents. Innovative techniques such as combination high-dimensional propensity score and instrumental variable modeling will be used in Aims 2 and 3 to reduce bias often encountered in observational research. The research will form the basis for an R01 or equivalent application to compare metformin usage patterns, safety and effectiveness in patients with type 2 diabetes and chronic kidney disease between those treated in the VA system and the United Kingdom.
Project Narrative/Public Health Relevance: The epidemic of type 2 diabetes (T2DM) and chronic kidney disease (CKD) is on the rise. Unfortunately, metformin, a drug with known benefits in patients with T2DM, has a FDA labeled contraindication in patients with T2DM and CKD. This contraindication is not based on clinical evidence; rather, it is based on previous poor experience with an older drug in the same therapeutic class, phenformin, which has been removed from the market. Despite this contraindication, evidence suggests that patients with T2DM and CKD are still prescribed metformin. It is critical to understand the safety and effectiveness of metformin in this population as it may affect policy and labeling changes on how it is prescribed.
Facilities and Other Resources

Texas Tech University Health Sciences Center School of Pharmacy Dallas Campus (TTUHSCSOP-DFW)

The Division of Clinical Research at TTUHSCSOP-DFW has all the necessary resources to successfully conduct and complete the proposed research and career development activities. TTUHSCSOP-DFW is a partnering institution with The Center for Translational Medicine, funded by the Clinical and Translational Science Awards (CTSA), and has access to additional career development resources through this collaboration. TTUHSCSOP-DFW is also the home for the Center for Clinical Pharmacology, [Pharmacist] is a key member for The Center that has four distinct cores, one of which is the Pharmacoepidemiology and Outcomes Core.

Office Space

TTUHSCSOP-DFW has facilities located at both the VA North Texas Health Care System campus (8,000 square-feet) and Southwest Professional Building (17,000 square-feet) located one block north of the University of Texas Southwestern in the heart of the central Dallas Medical District. [Physician] has a 120 square-foot office at the VA North Texas Health Care System and an 80 square-foot office at the Southwest Professional Building located. Each of his offices are equipped with a desktop computer (Dell Precision T5600, Intel i7 processor, 16 GB RAM, 1TB hard disk), high-speed internet access, printer, fax machine, and a telephone. The office at the Southwest Professional Building has full access to a poster printer for research poster presentations.

Staff

Statistical analysis and data management are capably handled by Christopher Johnson, MPH at the VA North Texas Health Care System. Mr. Johnson has extensive experience with the integrated national VA database and will extract, clean, and analyze all data for the proposed research. Additional statistical support will be provided by Song Zhang, PhD. He is an Assistant Professor at UT Southwestern in the Department of Clinical Sciences. He has expertise in multi-level modeling, propensity score, and instrumental variable analyses. Administrative needs are capably handled by one full-time Senior Administrative Assistant at TTUHSCSOP-DFW.

Other Resources

The Department of Clinical Sciences provides an academic, educational, and cultural home for clinical investigators across all departments and disciplines at UT Southwestern and partnering institutions. The goals of the Department are broad-based and encompass all clinical research throughout UT Southwestern. The mission of the Department is to promote the conduct of high quality patient-oriented research, develop effective mechanisms to facilitate translational research, provide a formal mechanism of institutional recognition for clinical scientists, and accelerate and enhance the training and career development of clinical investigators. The Department includes the Division of Outcomes and Health Services Research (in which Dr. Mortensen has an appointment and Dr. Halm is the Division Chief), Division of Ethics and Health Policy, Division of Biostatistics, Division of Behavioral and Communication Sciences, and the Division of Biomedical Informatics, and offers courses in clinical research, biostatistics, ethics, health services research, and epidemiology. The Department of Clinical Sciences also directs the Clinical Research Scholars Program at UT Southwestern. This program supports the career development of individuals dedicated to a career in clinical investigation, and who aspire to develop into future leaders in clinical research. It is supported, in part, by a KL2 award of the NIH, which is part of UT Southwestern’s Clinical and Translational Science Award (CTSA). The CTSA provides assistance with database management, preparation of IRB documents, grant-writing, budget management, and manuscript preparation, as well as funds for pilot grants are also available through the CTSA. [Physician] will have full access to these resources for the duration of the award.
A. Personal Statement

I am an Assistant Professor at Texas Tech University Health Sciences Center School of Pharmacy and principal investigator for this career development application. My long-term career plan is to study the effectiveness and safety of drugs in patients with type 2 diabetes and chronic kidney disease using large administrative and clinical databases. My background in clinical pharmacy and research training through the KL2 mechanism provides a foundation for achieving this goal; however, large administrative database analysis is complex and sophisticated analytic techniques are needed to ensure that reported results are valid and reliable. Therefore, I have developed a program of practical mentored research experience in conjunction with formal academic training to reach my goal of becoming an independently funded investigator. My research study is designed to examine the safety and effectiveness of metformin therapy in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) by determining: 1) the pharmacoepidemiology of metformin use in patients with T2DM and CKD, 2) if metformin use in patients with T2DM and CKD place them at a higher risk of adverse events and 3) if metformin exposure is associated with an effect on macrovascular and microvascular disease.

I have developed this research plan with my mentors, who will work closely with me throughout the course of this award. I will supplement this mentored experience with formal academic training in pharmacoepidemiology, outcomes and health services research, and analysis of large complex databases. These experiences will provide me with the skills and expertise I need to develop an independently funded R01 by the conclusion of this training award.

B. Positions and Honors

2004-2006 Clinical Instructor, University of Texas College of Pharmacy, Austin TX
2004-2006 Pharmacotherapy Residency, University of Texas Health Science Center at San Antonio, TX
2006-Present Assistant Professor, Texas Tech University School of Pharmacy, Dallas, TX
2009-2013 NIH Clinical Research Scholar, University of Texas Southwestern Medical Center, Dallas, TX

Professional Memberships:
2000 Phi Delta Chi National Fraternity
2000 American Society of Health-System Pharmacists
2002 Rho Chi National Honors Fraternity
2004 American College of Clinical Pharmacy
2007 American Diabetes Association
2007 National Lipid Association

Honors:
2002 Induction into Rho Chi National Honors Fraternity
2002 School of Pharmacy Academic Achievement Scholarship
2003 Bexar County Pharmacy Association Scholarship
2004 Facts and Comparisons Excellence in Clinical Communications Award
2006 Best Resident/Fellow Research Poster American College of Clinical Pharmacy Annual Meeting
2008 Teaching Team of the Year Award Texas Tech School of Pharmacy
2009 NIH Clinical Research Scholar

C. Selected Peer-reviewed Publications

Original Research Articles

Review Articles
Role: PI

5R01NR010828-03 (Mortensen) 2007–2011
NIH/NINR
Impact of Statins and ACE Inhibitors on Outcomes for Pneumonia and Sepsis
Determine the association between outpatient use of medications of interest and clinical outcomes, including 30-day mortality, length of stay, and rates of mechanical ventilation for patients hospitalized with sepsis and community-acquired pneumonia.
Role: PI

XVA 66-002 (Mortensen) 2002–2004
VA/ VISN 17
The Effects of Chronic Outpatient Medication Use on Patients with Community Acquired Pneumonia
The primary aim of this study is to examine the impact of chronic use of ace inhibitors, statins and corticosteroids upon clinical outcomes for patients hospitalized with CAP.
Role: PI

XNV 66-004 (Mortensen) 2002–2003
University of Texas Health Science Center – HHMI grant
Effects of Statins on Clinical Outcomes for Patients with Community Acquired Pneumonia
This is a case-control study of patients with pneumonia comparing prior outpatient use of statins while controlling for other known predictors of pneumonia-related mortality.
Role: PI

F32HS000135 (Mortensen) 1999-2001
AHCPR
Evaluating long-term mortality after community-acquired pneumonia
To assess the impact of an episode of community acquired pneumonia (CAP) on long-term mortality for those who survived the initial episode of pneumonia.
Role: PI

D. Time and effort statement: Research 50%, Administrative 20%, Clinical 15%, Teaching/mentoring 15%
Dear Sir or Madam,

Enclosed is the grant application for a Mentored Clinical Scientist Development Award (K08). This application is in response to PA-11-193.

My long-term goal is to be an expert in the pharmacoepidemiology of therapeutic agents in patients with type 2 diabetes mellitus and chronic kidney disease. Thus, I am requesting assignment of this grant application to The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

My letters of reference are from:

Robert Toto, MD
Associate Dean and Professor
University of Texas Southwestern

Richard Lefti, PharmD, FCCP
Associate Dean and Professor
Texas Tech University Health Sciences Center

Milton Packer, MD
Professor and Department Chair
University of Texas Southwestern

Should you have any questions or concerns, please do not hesitate to contact me at (214) 707-8042 or carlos.alvarez@ttuhsc.edu

Sincerely,

[Signature]

PharmD, MSc, BCPS
Assistant Professor
Texas Tech University Health Sciences Center

CAMPUS:
- ARLINGTON | 1718 Pine Street | Arlington, TX 76010 | T 817.677.0150 | F 817.677.0151
- AMARILLO | Office of the Dean | 1300 S. Outhwaite | Amarillo, TX 79106 | T 806.354.5463 | F 806.354.4813
- DALLAS / FT. WORTH | 5520 Harry Hines Blvd | Dallas, TX 75390 | T 214.648.4444 | F 214.648.4444
- EL PASO | 4800 Albert Pike Avenue | El Paso, TX 79903 | T 915.545.8044 | F 915.545.8043
- LUBBOCK | 3601 4th Street STGP 8162 | Lubbock, TX 79430-8162 | T 806.743.4200 | F 806.743.1200

An FTSO/Executive Action Statement
2. Candidate’s Background

I am committed to a research career studying the pharmacoepidemiology of therapeutic agents used in patients with type 2 diabetes and chronic kidney disease. Through this K award, I will position myself as an independent clinical researcher and future international expert in the area. As a clinical pharmacist, I have a unique perspective on the beneficial and harmful effects of medications in patients’ lives. In this K08 career development award, I propose to investigate the safety and effectiveness of metformin for patients with type 2 diabetes and kidney disease using large population-based datasets.

I graduated from Texas Tech University Health Sciences Center School of Pharmacy in 2004 (Summa Cum Laude) and started my advanced clinical training as a pharmacotherapy resident and graduate student. My advanced clinical training is from the University of Texas Health Sciences Center in San Antonio, one of the nation’s oldest clinical pharmacy programs. I also gained valuable training in basic research skills as a graduate student at the University of Texas at Austin. During this time, I was introduced to translational research and completed projects evaluating the efficacy of inhaled nanoparticles of itraconazole in a mouse model. I presented this work at the American College of Clinical Pharmacy Annual Meeting (winning Best Poster in 2006) and published it in the Journal of Infection (first author). In 2006, I earned my Master of Science degree in Pharmacy, completed my clinical training, and was board certified as a pharmacotherapy specialist. I then began my academic career in 2006 at Texas Tech Health Sciences Center School of Pharmacy-Dallas campus. I was attracted to Texas Tech-Dallas campus’ collaboration with the University of Texas Southwestern. My clinical duties were at the VA North Texas Health Care System, Dallas, where I saw patients with type 2 diabetes and complex medication regimens. My goal in clinic was to ensure patients received the safest and most effective therapies. During this time in my career I began to question some of the established principles about drug safety. I decided to delve even deeper by investigating specific drug safety profiles and outcomes. I collaborated with several of my colleagues to examine the effect of combination therapy with a thiazolidinedione and fibrates on high density lipoprotein concentration in veterans with diabetes. I presented this work at the National Lipid Association Annual Scientific Sessions and ultimately published (first author) in the Journal of Clinical Lipidology. I thus began a career path in clinical investigation.

In July 2009, I was accepted as one of the National Institutes of Health Clinical Research Scholars at the University of Texas Southwestern Medical Center, funded in part by the KL2 mechanism. During my time as a clinical scholar, I utilized skills I obtained through the program to publish several pharmacoepidemiology studies in Drugs and Aging, American Journal of Geriatric Pharmacotherapy, BMC Infectious Diseases, and several others. While the Clinical Research Scholars program provides basic skills in clinical research, it does not provide advanced structured experiences in pharmacoepidemiology, health services research, and data analysis using large complex databases. The three years of this program are not adequate to complete the career development and research activities needed to provide me the skills and pilot data needed to become a successful independent investigator to compete for R01 or equivalent funding. I have assembled an experienced team of mentors and advisors who are committed to my success. The research and training proposed in this K08 application will lead to an R01 application to compare metformin usage patterns, safety and effectiveness in patients with type 2 diabetes and chronic kidney disease between those treated in the VA system and the United Kingdom (UK). My interest is to determine whether clinical outcomes differ between the UK, a country that uses lower eGFR cut-points for metformin contraindication, and the United States, that uses serum creatinine cut-points. When I receive the K08 career development award, my department chair and Dean have committed to protecting 75% of my full time professional effort (9 person-months) to pursue the research and career development activities outlined in this proposal.
3. Career Goals and Objectives

My long-term career goal is to be an **internationally recognized expert and independent investigator** in the pharmacoepidemiology of therapeutic agents used in patients with type 2 diabetes and chronic kidney disease. I have made important strides in developing my clinical research skills through the KL2 mechanism; however, there are three critical areas where I require additional training, mentoring and practical experience: **Aim 1)** advanced principles of pharmacoepidemiology, **Aim 2)** health services and outcomes research, and **Aim 3)** analysis of large complex national databases. I need to address these deficits over the next 4 years to compete successfully for R01 funding, thus achieving independence as a clinical researcher. In the Career Development and Training Activities section, I lay out the detailed plan to acquire the needed additional training, mentoring and research experience. My short-term career goal, and research proposed in this application, is to conduct a series of studies to better understand the safety and effectiveness of metformin in patients with type 2 diabetes mellitus and chronic kidney disease. I have positioned myself through this K08 proposal to gain the necessary skills to be a successful independent investigator.
4. Career Development and Training Activities

This career development award will provide the necessary training and 75% protected time to engage in mentored research. The remaining 25% each year will be spent participating in clinical, teaching and University service activities.

To gain the knowledge and skills required to achieve my career goals, three educational aims are proposed:

1. Use advanced pharmacoepidemiologic analysis to determine patterns of drug use, and the safety and effectiveness of drugs.
2. Determine patient, provider, and system level factors that influence the prescription of drugs in patients using epidemiologic analysis of health services research.
3. Use large, complex administrative and clinical databases to evaluate pharmacoepidemiological interventions and their impact on clinical outcomes.

Table 1: Career Development Summary

<table>
<thead>
<tr>
<th>Aim 1: Pharmacoepidemiology</th>
<th>Aim 2: Health Services Research</th>
<th>Aim 3: Analysis of Large Complex Databases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Course Work</td>
<td>Epidemiology III</td>
<td>Advanced Design Analysis Methods in Epidemiology</td>
</tr>
<tr>
<td>Mentored Research/Tutorials</td>
<td>Metformin Use Patterns; Lactic Acidosis in Metformin Users/ Mortensen, Pugh, Miller, McGuire</td>
<td>Patient, Provider, System Factors Predicting Metformin Use/Halm, Mortensen, Pugh</td>
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<tr>
<td>Course Work</td>
<td>Advanced Pharmacoepidemiology</td>
<td>Epidemiology IV</td>
</tr>
<tr>
<td>Mentored Research/Tutorials</td>
<td>Lactic Acidosis in Metformin Users/ Mortensen, Pugh, Miller, McGuire</td>
<td>Hypoglycemia in Metformin Users/Halm, Mortensen, Pugh</td>
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<tr>
<td>Manuscript</td>
<td>Pharmacoepidemiology of Metformin Use, Lactic Acidosis in Metformin Users</td>
<td>Mortensen, Pugh</td>
</tr>
<tr>
<td>Grant Application</td>
<td>R03: Comparative Effectiveness of Glucose-lowering Therapy in Patients with T2DM, CKD and CHF</td>
<td></td>
</tr>
<tr>
<td>Course Work</td>
<td>Focused Investigator Training</td>
<td>ICE annual research intensive</td>
</tr>
<tr>
<td>Mentored Research</td>
<td>Micro/Macrovascular Outcomes</td>
<td>Systematic Review: Metformin use in US and UK</td>
</tr>
<tr>
<td>Manuscript</td>
<td>Evaluating Hospitalizations and ED visits for Hypoglycaemia in Metformin Users, Safety of Metformin in Patients with T2DM, CKD and Heart Failure</td>
<td>Multilevel Modeling</td>
</tr>
<tr>
<td>Grant Application</td>
<td>R03, R01: Comparing the Safety and Effectiveness of Metformin Therapy in Patients with T2DM and CKD Among Patients Treated in the United Kingdom and United States</td>
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<tr>
<td>Research</td>
<td>Micro/Macrovascular Outcomes</td>
<td>Systematic Review: Metformin use in US and UK</td>
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<td>Microvascular Outcomes, Macrovascular Outcomes, Systematic Review</td>
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<tr>
<td>Grant Application</td>
<td>R01: Comparing the Safety and Effectiveness of Metformin Therapy in Patients with T2DM and CKD Among Patients Treated in the United Kingdom and United States</td>
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</tr>
</tbody>
</table>

4.1. Coursework:

Introduction to Pharmacoepidemiology (McGill University, Summer week long intensive). Introduce concepts and principles of pharmacoepidemiology in the context of drug evaluation and therapeutic decision-making.

Intermediate Pharmacoepidemiology (McGill University, Summer week long intensive). Introduce more advanced methodological and theoretical concepts in pharmacoepidemiology.

Advanced Pharmacoepidemiology (McGill University, Summer week long intensive). Ecological studies, exposure measures, confounding by indication, drug channeling, designs and analysis issues for cohort, case-control and nested case-control studies as well as the within-subject designs such as prescription sequence analysis, case-crossover and case-time-control studies, including situations with repeated event outcomes and
time-risk functions. The course will also address methodological aspects of computerized databases used in pharmacoepidemiology.

**Advanced Design Analysis Methods in Epidemiology** (University of Texas School of Public Health (UTSPH), Spring 3 hrs/wk). Basic and generalized regression models for binary (logistic), continuous (linear), and count (Poisson) outcomes; longitudinal models; analysis of clustered data; and select data mining methods.

**Advanced Categorical Data Analysis** (UTSPH, Spring 3 hrs/wk). Approaches of maximum likelihood, weighted least squares, and generalized estimating equations applied to the analysis of contingency tables and other categorical outcomes.

**Online Multilevel Modeling Course** (Fall, online course). Analyzing binary responses using multilevel models, including examining latent variables, two-level random intercept and two-level random slope models, clustering effects, and contextual effects. Centre for Multilevel Modeling, University of Bristol.

**Epidemiology III** (UTSPH, Fall 4 hours/wk). Causal inference, measures of disease frequency, measures of association, study design, precision and validity in epidemiologic studies, introduction to stratified and logistic regression analysis, concepts assessing effect modification and confounding, interpretation of epidemiologic study results and manuscript development.

**Epidemiology IV** (UTSPH, Spring 4 hours/wk). Advanced stratified analysis, logistic regression, proportional hazards modeling, meta-analysis, examination of confounding and effect measure modification, strategies for model building and interpretation and presentation of results.

**ICE Research Intensive** (Oregon Health and Science University, Fall 5 day intensive training). Comparative effectiveness research (CER) methodology, examining CER priorities and funding opportunities, propensity scoring, instrumental variables, confounding, and systematic reviews.

**Focused Investigator Training** (American College of Clinical Pharmacy, Summer 5 day intensive training). Mentored program designed for pharmacist-investigators to learn essential steps toward preparing a R01, or similar investigator-initiated application for submission to the NIH or other major funding source. This is hands-on training in which the participant will have their draft grant critically appraised.

### 4.2. Mentors:

My primary mentor Eric Mortensen is Associate Professor of Internal Medicine and Clinical Sciences at the University of Texas Southwestern and Chief of General Internal Medicine at the VA North Texas Health Care System. Dr. Mortensen is a NIH and VA funded researcher in clinical epidemiology and pharmacoepidemiology. He has authored 78 original research articles on drug effectiveness and safety, and extensive experience using VA administrative databases. Dr. Mortensen has successfully mentored 6 junior investigators with a track record of extramural NIH funding. We will meet for at least 1 hour a week to discuss research projects and to ensure my progress towards my career goals. He will help me advance my skills in quantitative research methods, grant and manuscript writing, study design, and implementing protocols. He will also play a primary role in helping me transition into an independent investigator and leader in pharmacoepidemiology. Ethan Halm will be my secondary mentor for comparative effectiveness research and health services research. Dr. Halm is Professor of Internal Medicine and Clinical Sciences, the Walter Family Distinguished Chair in Internal Medicine, and the Division Chief of both General Internal Medicine and Outcomes and Health Services Research at the University of Texas Southwestern. He is a leader in health services, quality and outcomes research and funded by the NIH, Agency for Healthcare Research and Quality (AHRQ), Robert Wood Johnson Foundation, among other institutions. He has successfully mentored 30 individuals including 10 junior faculty members who have competed successfully for grant funding as independent investigators. I will meet biweekly for 1 hour with Dr. Halm to discuss my research and actively participate in the monthly Division of Outcomes and Health Services Research monthly works-in-progress seminar. The purpose of this monthly meeting is to review and discuss upcoming grant submissions, present new methodological and analytic strategies, and present research findings. Participation in this seminar series will allow me to work more closely with Dr. Halm and his research team and provide additional opportunities for collaboration. Mary Jo Pugh is Associate Professor in the Department of Epidemiology and Biostatistics at the University of Texas Health Science Center at San Antonio and a Research Health Scientist for the Veterans Evidence-based Research, Dissemination, and Implementation Center, South Texas Veterans Health Care System in San Antonio, Texas, will serve as my pharmacoepidemiology and drug safety secondary mentor. She is an expert in pharmacoepidemiology of drugs used in patients with chronic diseases. Dr. Pugh has
extensive experience with national VA administrative, clinical and pharmacy databases. She has published over 70 peer reviewed articles in the areas of pharmacoepidemiology, outcomes research, and quality of care. Dr. Pugh has a long-standing relationship with Dr. Mortensen and they have published 27 peer reviewed articles together. She serves as an Associate Editor for BMC Health Services Research and BMC Geriatrics, and is on the Editorial Advisory Board of the Journal of Managed Care Pharmacy. Dr. Pugh and I will talk by telephone for 1 hour biweekly to discuss the principles of pharmacoepidemiology, and methodological and analytic strategies with regards to my research. In addition, we will meet in person at least quarterly.

4.3. Advisors

R. Tyler Miller, my renal epidemiology advisor, is Chief of Medicine at the Dallas VA and the John Fordtran Professor of Calcium Metabolism in the Charles and Jane Pak Center of Mineral Metabolism and Clinical Research. Dr. Miller has been a deputy and associate editor for the Journal of the American Society of Nephrology, and he served on the editorial board of the American Journal of Physiology. Dr. Miller has also sat on many different study sections at the NIH and NIDDK. He has trained many young investigators and is PI of an NIH T32 training grant in nephrology. He will meet with me to discuss the clinical and physiologic aspects of CKD at least once per month to help me better understand the factors within patients that influence treatment outcomes. Darren McGuire, will be my diabetes pharmacoepidemiology advisor. He is Associate Professor of Internal Medicine, Dallas Heart Ball Chair for Research on Heart Disease in Women, Associate of the Donald W. Reynolds Cardiovascular Clinical Research Center, and Director of the Parkland Hospital and Health System Outpatient Cardiology clinics. Dr. McGuire, who studies the effects of a number of therapeutic intervention strategies among patients with diabetes and cardiovascular disease, is senior editor of Diabetes and Vascular Disease Research, associate editor of the American Heart Journal, a Fellow of the American Heart Association (AHA) and the American College of Cardiology, prior Chair of the AHA Diabetes Committee, and a member of the FDA Cardiovascular and Renal Drugs Advisory Committee. We will meet at least 1 hour every 1-2 months to discuss the clinical and policy implications of my research.

4.4. Meeting Schedule and Evaluation Plan

Advisory Committee: My mentors and advisors will provide guidance on specific topics and assist in the design, implementation, and evaluation of the career development research activities. We have established a formal advisory committee to monitor my progress and help advance my career. I will meet face-to-face every six months with Drs. Mortensen, Halm, Pugh, McGuire and Miller during which I will present my data and discuss future projects. My research and career progression will be evaluated twice a year. At the beginning of each year, I will provide the mentorship team with my annual career and research goals, including coursework, manuscript and national conference submissions, and grant applications. At the end of each year, my mentors will collectively and individually provide a detailed evaluation of my progress. I will present my work at the Outcomes and Health Services Research seminar series at University of Texas Southwestern, Texas Tech University Health Sciences Center Annual Research Days, and General Internal Medicine Grand Rounds. I will also attend and present my research at the annual American Diabetes Association, International Society for Pharmacoepidemiology, International Society for Pharmacoeconomics and Outcomes Research, Academy Health and American College of Clinical Pharmacy meetings. I will submit at least five manuscripts for publication from these projects. My goal is a minimum of 2-3 manuscript submissions per year during the course of this proposed award period.
5 Training in Responsible Conduct of Research

5.1 Previous training. I have completed training in Human Subjects Protection, HIPAA, and good clinical practice through Texas Tech University Health Sciences Center, UT Southwestern, and the Veterans Affairs. Through my Master of Science in Clinical Science program I have also completed the following courses and training: (a) Responsible Conduct of Research (DCS 5107-1 credit hour). In this course, we discussed contemporary ethical issues in biomedical research. We specifically discussed policies regarding human subjects, collaborative research, policies for handling misconduct, and authorship and publication. (b) Ethics in Clinical Sciences (DCS 5105-1 credit hour). Taught by John Sadler who is the Director of the Program in Ethics in Science & Medicine, Chief of the Division of Ethics in the Department of Psychiatry and Chief of the Division of Ethics & Health Policy in the Department of Clinical Sciences. This course covers a vast array of topics in bioethics, including treatment versus research, informed consent, conflicts of interest/duty, handling misconduct and fraud, media relations, and public policy advising. This course was delivered bi-weekly through interactive seminars, 3.5 hours/month, for 12 months, led by faculty in the Division of Ethics (Department of Clinical Sciences) at UT Southwestern and guest faculty.

5.2 Continued Training. During the K08 award period I will continue to receive training in responsible conduct of research through individual meetings with my mentor, Dr. Eric Mortensen, on a weekly basis. Issues we will discuss include, but are not limited to, authorship, human subject protection, navigating the IRB, and data management. He will supervise my instruction in the responsible conduct of research and provide additional guidance, as necessary. I will also participate in Ethics Grand Rounds at UT Southwestern, which take place monthly every 2nd Tuesday at noon. Guest speakers are invited to give formal lectures on current medical ethical issues where interactive discussions are encouraged. I will also complete computer-based modules on ethical topics such as HIPAA Privacy and Patients' Rights and Responsibilities, Human Subject Protection, Good Clinical Practices, and Biomedical Investigator course which are required by Texas Tech University Health Sciences Center, UT Southwestern, and the VA on an annual basis. These modules are intended to carry out the intentions of the 1979 Belmont Report of Ethical Principles and Guidelines for the Protection of Human Subject Research.
March 13, 2013

Dear Study Section Members:

It is my privilege and pleasure to write this letter in strong support for Dr. [Redacted] and his application for a K08 award. I am pleased to serve as his primary mentor for this career development award and agree to spend at least 10% of my time working with him. I am an Associate Professor of Internal Medicine and Clinical Sciences at the University of Texas Southwestern as well as Chief of General Internal Medicine at the VA North Texas Health Care System. My primary areas of research expertise include using large databases and pharmacoepidemiologic methods to identify potential ways to improve outcomes for patients with serious infectious diseases such as pneumonia and sepsis. My interest in using the administrative databases of the Department of Veterans Affairs healthcare system, along with pharmacoepidemiologic methods, to assess whether metformin is associated with worse outcomes in patients with diabetes and chronic kidney disease, clearly fit well with my interests and expertise.

Applicants Qualifications and Potential as a Productive Clinical Researcher: [Redacted] has tremendous potential to be a productive independent clinical researcher. He obtained his Doctor of Pharmacy from Texas Tech University in 2004 and then entered a Pharmacotherapy residency and Master of Science in Pharmacy program at the University of Texas at Austin, both of which he completed in 2006. This program introduced him to the basic principles of clinical and translational research. During this time, his research won Best Resident Poster at the Annual American College of Clinical Pharmacy and was nominated for Best Master’s Thesis at the UT-Austin. From 2006 to 2009 he served as junior faculty member at Texas Tech University, where he served as a clinician educator. Due to his research interests, in 2009 he was selected as a KL2 Clinical Research Scholar at the UT Southwestern and in 2012 rejoined the Texas Tech University Health Sciences Center as an Assistant Professor of Pharmacy Practice on the Tenure track. His research interest is determining the safety and effectiveness of anti-diabetic agents in patients with type 2 diabetes and renal impairment, a proposal of great importance. He has authored 9 peer-reviewed research papers- 2 as primary author and 2 as senior author. He has also presented 10 abstracts at various national/state meetings.

Primary Experience as a Mentor and in the Applicant’s Proposed Area of Research: Over the past 12 years I have mentored 20 medical students, residents, and fellows in addition to 6 junior faculty members. My mentees have collectively published 54 articles in peer-reviewed journals. Four of my junior faculty mentees have been institutional KL2 scholars while the National Heart Lung Blood Institute awarded a K23 to another. I have extensive experience in the area of [Redacted] proposed area of research, which includes pharmacoepidemiology, health services research, and comparative effectiveness research. I am currently Chief of General Internal Medicine at the VA North Texas Health Care System and an Associate Professor of Internal Medicine and Clinical Sciences at the University of Texas Southwestern in Dallas, TX. I have published 77 articles in peer-reviewed journals on topics in pharmacoepidemiology, health services research, and comparative effectiveness research. My research has been supported by the Agency for Healthcare Research and Quality, National Institutes of Health, and Department of Veterans Affairs.

Mentoring Plan: During the career development award period, I will continue to meet with [Redacted] for at least 1 hour per week. I will provide mentoring in project conceptualization, large database analysis, pharmacoepidemiology, statistical analysis, preparing and submitting manuscripts, abstract preparation for scientific meetings, managing project teams, and any other topics of interest he wishes to discuss. Of course, I will increase the time and effort of my interaction with him during grant deadline periods, or as he prepares for national presentations or similar commitments. I will also review and edit [Redacted] manuscripts, abstracts, and future grant applications. [Redacted] will continue to actively participate in the Division of Outcomes and Health Services Research monthly works-in-progress seminar led by Ethan Halm (co-mentor).
previous training, he lacks extensive experience in pharmacoepidemiology, health services research, and comparative effectiveness. I will work with [redacted] and our team of mentors and advisors to assure the proposed career development award will fill these gaps. I am extremely impressed with the drive and commitment that [redacted] has to clinical research. I am fully committed and will work with him to ensure he has academic success, and fulfills his vision to become and independent investigator who has a well funded research program that examines safe and effective treatments for patients with diabetes and chronic kidney disease.

Resources Available to Support Applicant’s Research: [redacted] has a primary appointment with Texas Tech University Health Sciences Center and has secured the support of the Dean in the School of Pharmacy to protect 75% of his time (8 person-months/year) for research. He has already secured $75,000 in start-up funding from Texas Tech that began in 2012 when he was transitioned to the clinical scholars tenure track. In addition, he has access to my experienced research staff- a master’s level biostatistician and research coordinator who will assist him with data analyses and regulatory issues. The administration at Texas Tech has committed resources available to [redacted] such as computers, statistical software and graphics programs, and sufficient office space with administrative support.

Expectations For Productivity: I expect a high level of productivity from [redacted] At a minimum, I expect him to submit 2-3 research manuscripts for publication, and two abstracts to national scientific meetings, every year of the award. In addition, I will also expect [redacted] to participate regularly in the annual scientific meetings of the International Society of Pharmacoepidemiology, American Diabetes Association, and American College of Clinical Pharmacy.

Co-mentors: [redacted] has assembled an outstanding mentor/advisor committee. Each member of the committee is an established clinical researcher with a successful track record in extramural funding. Moreover, each member of the committee was asked to serve based on the specific educational and research aims outlined in [redacted] proposal. Ethan Halm (co-mentor) is an experienced clinical researcher who has successfully mentored junior faculty. He will serve as [redacted] health services research and comparative effectiveness co-mentor. Mary Jo Pugh (co-mentor) is a clinical researcher with multiple VA merit awards in studying pharmacoepidemiology of medications in elderly patients using large VA databases. She will serve as [redacted] mentor in pharmacoepidemiology studies using large national VA databases. Tyler Miller (advisor) is a nephrologist who studies the biophysical properties of diseased renal tissue. He will meet with [redacted] to discuss the clinical and renal epidemiologic aspects of his proposal. Darren McGuire (advisor) is a successful researcher examining cardiovascular outcomes of therapeutic agents in patients with diabetes. He will serve as [redacted] cardiovascular epidemiology advisor.

Plan for Transition to Independent Investigator: I expect [redacted] to submit an NIH R01 or VA Merit Award application in the 3rd year of his K award. This study will compare metformin usage patterns, safety and effectiveness in patients with type 2 diabetes and chronic kidney disease between those treated in the VA system and the United Kingdom. He will also submit an NIH R03 in the 2nd year of his K award to investigate metformin safety and effectiveness in a subgroup of patients with type 2 diabetes, chronic kidney disease and chronic heart failure.

Evaluations of Applicant’s Progress for Award Duration: I believe that all of the key factors are in place for the success of this K08 award: an outstanding junior investigator with a demonstrated early productivity (good record of publications and initial grant funding); high level of interest and motivation; solid support from highly accomplished scientists in a range of disciplines that are relevant for the projects; a well thought out training agenda; and an interesting and scientifically rigorous clinically important research project. I am convinced that within the next 10 years, [redacted] will be an internationally recognized authority on the pharmacoepidemiology of therapeutic agents in patients with type 2 diabetes and chronic kidney disease. All he needs is time, and support of this K08 award, to achieve his potential.

Sincerely,

[Signature]

Eric M. Mortensen, MD, MSc, FACP
May 31, 2013

Dear Study Section Members:

I am writing to enthusiastically support Dr. application for a K08 award. As a practicing general internist with 16 years of experience in conducting outcomes, health services research (HSR) and comparative effectiveness research (CER), I am very excited to serve as a co-mentor to K08 award to evaluate the safety and effectiveness of metformin in patients with type 2 diabetes and chronic kidney disease. Quantifying the risks and benefits of metformin in the large population of patients with renal insufficiency will have major clinical and policy impact. There is great uncertainty about whether metformin should be stopped solely because an arbitrary serum creatinine threshold has been crossed, and the national guidelines on this topic are based on scant evidence.

I am a tenured Professor at the University of Texas, Southwestern Medical Center and the Chief of the Division of General Internal Medicine and Division of Outcomes and Health Services Research. I have known for over three years, and seen him mature as a clinical researcher in our Masters of Science in Clinical Research program. I have co-mentored him on a recently published study using electronic medical record data to predict the risk of ICU arrest and given him feedback on several other research ideas including this K08 award. He was also one of the most thoughtful and diligent students in my Outcomes and Health Services Research masters class last year. Therefore, I can attest to the fact that he has the intelligence, drive, and personality to be successful in the grant. I have mentored over 35 individuals, including on 10 different career development awards and 4 ROIs. My research has been continuously funded for 14 years by the NIH, AHRQ, and the Robert Wood Johnson Foundation. I have published over 110 peer-reviewed articles--the majority of which are HSR and CER. On this K08 award, my role will be as senior HSR and CER mentor--domains critical to his scientific and career development plan. We will meet in person once a month for one hour to discuss his research and training progress, overcome any barriers to success, and identify areas for further training and investigation. He will also actively participate in the monthly Division of Outcomes and Health Services Research works-in-progress seminar which I direct. This will allow him to learn from HSR and CER Investigators UT Southwestern other institutions. I work closely with his other mentor (Dr. Eric Mortensen), participate in K08 advisory meetings every six months, and provide a formal annual K08 evaluation for him.

There are very few clinical pharmacist HSR and CER Investigators nationally, and with the help of this K08 support, I have no doubt that will be well-positioned to fill this important gap in the national clinical research capacity. I will be happy to do everything I can to help him be successful in his K08 award and beyond.

Sincerely yours,

Ethan A. Halm, MD, MPH
Professor of Internal Medicine and Clinical Sciences
Dear Study Section Members,

I am writing to express my strongest support for [redacted], Pharm.D., M.Sc., BCPS, a promising clinical pharmacist, who is applying for a K08 career development award. As a VA Research Scientist at the South Texas Veterans Healthcare System (STVHCS; San Antonio, TX) and an Associate Professor in the Department of Epidemiology and Biostatistics/Geriatrics and Gerontology at the University of Texas Health Science Center at San Antonio, I believe I am well-qualified to comment on [redacted]'s great potential as an independent clinical researcher.

After completing my PhD in Developmental Psychology from Catholic University, I completed a post-doctoral fellowship in Health Services Research/Pharmacoepidemiology at the Center for Health Quality, Outcomes and Economic Research in Bedford, MA. I used my previous experience as a nurse and doctoral-level training (specifically, skill with longitudinal methods) to develop a line of pharmacoepidemiological research in aging Veterans—wth special emphasis on the quality of prescribing. Over the past 13 years I have maintained continuous independent funding from VA Health Services Research and Development, the Centers for Disease Control and Prevention, and several private foundations. This research has led to over 67 peer-reviewed articles, in addition to over 100 poster and platform presentations. Over the last 7 years I have mentored 3 post-doctoral fellows and 4 junior-faculty members; I currently mentor one post-doc and two junior faculty members. Over this period of time I have seen young researchers come and go and have had the opportunity to work with many outstanding individuals. [redacted] is among the most impressive of those with whom I have had the pleasure to work.

I first met [redacted] during interactions with a long-time colleague, Dr. Eric Mortensen with whom I have collaborated on 6 federally funded grants over the past 9 years. In one of our meetings I met Dr. [redacted], and was impressed with his intellect, intellectual curiosity, and insight that leads to important clinical questions and research. His insight and questions led to major changes in a manuscript we developed, and merited inclusion as a co-author. That interaction led to our current relationship, and I am pleased to be a member of [redacted]'s mentoring team along with Drs. Mortensen and Halm.

During the past months, I have worked with the team and have been impressed with the trajectory of development [redacted] career goals, research proposal and training plan have taken. His research question regarding the safety and effectiveness of metformin in patients with type 2 diabetes and chronic kidney disease is important and the techniques he proposes are innovative. Based on the proposal development experience and our interactions I believe that his potential for success is limitless.

As a senior pharmacoepidemiologist, my role in [redacted]'s training is to supplement his training in the principles of pharmacoepidemiology, with special focus on the appropriate analysis of large national VA databases using advanced pharmacoepidemiological techniques. I will meet with [redacted] by phone, every two weeks to discuss research progress, design and implementation of his proposed research and professional development and more frequently via e-mail communication. I will also travel to Dallas to meet with him face-to-face every quarter and meet every six months with his advisory committee, and evaluate [redacted] research progress each year of the award.

Based on my experiences to date I have no doubt that [redacted] will become a successful independent researcher, and I feel privileged to be a member of his mentoring team.

Sincerely,

Mary Jo Pugh, PhD, RN
Research Health Scientist, South Texas Veterans Health Care System
Associate Professor, Department of Epidemiology and Biostatistics,
University of Texas Health Science Center at San Antonio

School of Medicine | Mail Code 7933 | 7703 Floyd Curl Drive | San Antonio, Texas 78229-3900
May 20, 2013

Dear Study Section Members,

I write this letter to give my strongest support for [redacted] NIDDK K08 application. He has assembled an outstanding multidisciplinary mentoring team, developed a phenomenal career development and training plan, and has a clinically important research question. Understanding prescribing patterns, safety, and effectiveness of metformin therapy in patients with type 2 diabetes and chronic kidney disease is crucial because of the inadequate evidence that supports withholding a potentially beneficial drug from this high risk population.

I am happy to serve as an advisor on this K08 application and I understand my role as cardiovascular epidemiology advisor. I am Associate Professor and Dallas Heart Ball Chair for Research on Heart Disease in Women at UT Southwestern. I have more than 16 years of experience as a clinical investigator and mentored 24 clinical research trainees. I study cardiovascular disease risk associated with diabetes through epidemiologic and clinical trials investigations, focusing on the development and application of therapies to reduce this risk. I have over 150 peer-reviewed publications, 4 of which pertaining to metformin use in high risk patients. [redacted] and I will meet face-to-face every 1-2 months for 1 hour to discuss his progress and identify training opportunities. The advisory committee will also meet every 6 months to discuss research and career development progress. Every year of the award, I will provide him with a formal evaluation.

[redacted] has outstanding potential to become an independent clinical researcher and I wholeheartedly support his K08 application. I am honored to be a member of his distinguished advisory committee and look forward working with him during the award period.

Sincerely,

Darren K. McGuire, MD, MHSc, FAHA, FACC
Associate Professor
Director- Parkland Health and Hospital System Cardiology Outpatient Clinics
May 31, 2013
NIDDK-D Study Section
Center for Scientific Review, NIH
6701 Rockledge Drive
Bethesda, MD 20892-7814

Dear Committee Members,

I am writing this letter of support for Dr. [redacted] application for a K08 award through NIDDK. He is an extremely promising young investigator whose proposed career development plan and research will position him well for R01 or equivalent funding. As a nephrologist and clinical researcher, I understand the importance of [redacted] proposed research dealing with the safety and effectiveness of metformin in patients with type 2 diabetes and chronic kidney disease. While running a diabetic nephropathy clinic, I was frustrated by the need to stop metformin based on what I believed to be inadequate guidelines. I believe this work has the potential to change practice for the better throughout the US by demonstrating the safety of metformin, probably at reduced doses, in patients with CKD.

I am happy to serve as [redacted] renal epidemiology advisor. I am Chief of Medicine at the Dallas VA, Vice Chair of Medicine at UT Southwestern, and the John Fordtran Professor of Calcium Metabolism in the Charles and Jane Pak Center of Mineral Metabolism and Clinical Research at UT Southwestern. I have over 85 publications and have been continuously funded by the NIH, VA and American Heart Association for 24 years. I have successfully mentored over 15 junior investigators (K awards, fellowship projects, masters, and PhD theses). I was the co-PI for the CWRU T32 training grant in nephrology, was a member of the NIDDK-D study section. I have been involved in basic and clinical research, and will use this expertise to advise [redacted] on the clinical and physiologic aspects of chronic kidney disease. We will meet face-to-face at least once per month and with the other members of his mentoring team every 6 months.

I enthusiastically support [redacted] application for the K08 career development award. He is a gifted researcher with unlimited potential. I am excited to work with him on this clinically important research and honored to be a part of his advisory committee.

Sincerely,

Richard Tyler Miller, M.D.
Chief of Medicine
VA North Texas Health Care System
Professor of Medicine
University of Texas Southwestern Medical School
Vice Chair, Department of Medicine
University of Texas Southwestern Medical School
8. Description of Institutional Environment
8.1 Institutional Collaboration

8.1.1 Texas Tech University Health Sciences Center (TTUHSC). TTUHSC is committed to clinical research as demonstrated by the establishment of the Clinical Research Institute (CRI) in 2010 and through collaboration with The Center for Translational Medicine at the University of Texas Southwestern. The mission of the CRI is to facilitate the conduct of clinical research by TTUHSC faculty. The CRI provides regulatory resources, study design and ethics expertise. Since 2004, TTUHSC has been a partnering institution with The Center for Translational Medicine, supported by the national Clinical and Translational Science Award (CTSA). Junior faculty at TTUHSC have the opportunity to advance their research careers through the Center for Translational Medicine Clinical Research Scholars program, funding in part by the NIH KL2 mechanism, which completed in 2012. _____ primary academic appointment is with TTUHSC, the lead institution in this proposal.

8.1.2 University of Texas Southwestern (UTSW). UTSW Medical Center is ranked among the top academic medical centers in the world. The institution is home to several world renowned faculty members including 5 Nobel laureates and 20 members of the National Academy of Sciences. Ongoing support from federal agencies such as the NIH, along with foundations, individuals, and corporations provide more than $400 million per year to fund about 3,500 research projects. The Center for Translational Medicine at UTSW is member of the national CTSA consortium, a group of 60 medical research institutions that work together and share a common vision to improve biomedical research across the country. They provide resources and infrastructure to enable investigators to perform cutting-edge clinical research. Key functions performed by The Center for Translational Medicine include biomedical informatics, biostatistics, epidemiology and research design, community engagement and research, education and career development, regulatory knowledge and support, research ethics, and access to the clinical and translational research center. _____ has a secondary academic appointment with UTSW in the Department of Clinical Sciences.

8.1.3 United States Department of Veterans Affairs (VA). Study subjects for the proposed research are Veterans from across the country. The VA is committed to successfully implement evidence-based innovations that help to improve the health of Veterans. The VA provides care to 23 million veterans across the U.S. In 2010, there were a total of 80 million outpatient visits in the VA system across the nation. The VA has developed the VA Informatics and Computing Infrastructure (VINCI) for use by researchers to improve the health of Veterans. VINCI is a centralized national research data repository that has several advantages; 1) consistent, defined, and transparent security and standards for access to data; 2) provides tools for analysis and reporting; and 3) tighter and more consistent control over the standards and quality of the data; and 4) provides a high-performance computing environment. VINCI has five distinct objectives 1) build a secure, high-performance computing environment for researchers to access data, 2) construct integrated databases from national clinical and administrative data sets, 3) consolidate processes and procedures for access to data ensuring compliance with VA policies, 4) provide tools to analyze data, report results, and support informatics research, and 5) reach out to the research community to enhance collaboration.

8.2 Environmental Contribution to the Candidate's Success

The resources available at these partnering institutions will provide the PI with a supportive environment for the proposed research and career development activities. Dr. Mortensen, Chief of General Internal Medicine at the VA North Texas Health Care System, will be _____ primary mentor. Dr. Halm, Division Chief of General Internal Medicine UTSW, and Dr. Pugh, Research Health Scientist for the Veterans Evidence-based Research, Dissemination, and Implementation Center, South Texas VA, will serve as his secondary mentors. Dr. _____ advisory committee consists of Dr. Miller, (nephrology) Professor UTSW, and Dr. McGuire, (cardiology) Associate Professor UTSW. This multidisciplinary team will ensure success through access to faculty and resources, such as project assistance and didactic courses. _____ will attend conferences and seminars at each institution. He will attend and participate in the TTUHSC-SOP Annual Research Days, UTSW Health Services Outcomes Research Seminar Series, and Clinical Science Forums, to name a few. These meetings allows young investigators to learn about emerging research, the use of various qualitative, quantitative, and intervention research methodologies, and receive valuable feedback about their research from a multidisciplinary group of nationally-recognized researchers.
Texas Tech University
Health Sciences Center
SCHOOL OF PHARMACY
Office of the Dean
Quentin Smith, Ph.D.

April 1, 2013

Re: Institutional Commitment to Pharm.D.

Dear Sir or Madam,

I enthusiastically write this letter of support for Pharm.D., an applicant to the National Institutes of Health for a K08 Career Development Award.

Pharm.D. is an extremely promising faculty member who has been with Texas Tech University Health Sciences Center School of Pharmacy since 2006. He is a full-time Assistant Professor who recently graduated from the 3-year KL-2 Clinical Scholars Program at UT Southwestern. As a result, the SOP recently transitioned his appointment to the research tenure-track in the Department of Pharmacy Practice. A team of experienced, senior faculty has agreed to mentor development. The mentoring team includes Drs. Mortensen, Halm, and Pugh. To this end, The School of Pharmacy will release from teaching responsibilities so that he can dedicate 75% effort to the development of his clinical research career.

Texas Tech University Health Sciences Center School of Pharmacy is strongly committed to Dr. Pharm.D.'s future success as an independent investigator. We will provide him with resources necessary to guarantee his success, such as:

1. A private office with administrative support at the North Texas VA Health Care System.
2. A visiting professor's office at UT Southwestern
3. Office telephones, photocopying and poster services, and office supplies
4. Administrative support for grant assistance and management through our Office of Sponsored Programs and Office of Sciences
5. Start-up funding to obtain pilot data

Opportunities for obtaining both extramural and intramural funding by making him aware of funding opportunities, providing assistance on grant writing, and promoting his research across departments and at other institutions.

Pharm.D. will be a cornerstone for our developing pharmacoepidemiology program at the School of Pharmacy. We strongly feel that supporting him with a K08 Career Development Award is a good investment and fully expect that his research program will be successful as evidenced by sustained research funding. As a result, we strongly recommend for K08 funding.

Sincerely,

Quentin Smith, Ph.D.
Dean & Professor
University Distinguished Professor

Cynthia Raehl, Pharm.D.
Professor & Chair
Department of Pharmacy Practice
Specific Research Aims: Type 2 diabetes mellitus (T2DM) affects approximately 25 million Americans and leads to serious health consequences, including heart disease, blindness, kidney disease, and lower-limb amputations. Treatment guidelines suggest initiating metformin, a biguanide, as first line drug therapy. Metformin reduces blood glucose, reduces cardiovascular mortality, is inexpensive, and is generally well tolerated. However, patients with concomitant chronic kidney disease (CKD) are often not prescribed metformin due to its listed contraindication in patients with renal impairment, which is based on experience with another medication in the class that is no longer on the market. Patients with CKD are often initiated or switched to other glucose-lowering agents such as thiazolidinediones, sulfonylureas and insulin that have known adverse cardiac effects or cause other severe adverse events such as hypoglycemia. Since metformin is primarily excreted unchanged in the urine, there is concern in patients with CKD for lactic acidosis; which has a case fatality rate of up to 60%. Studies suggest a lack of association between metformin use and lactic acidosis; however, these studies did not focus on individuals with CKD. Multiple clinical guidelines and the FDA caution against the use of metformin in patients with CKD, but choose arbitrary cut points for creatinine clearance (>1.5mg/dL in men and >1.4mg/dL in women) or estimated glomerular filtration rate. Despite this contraindication, evidence suggests that 5% of metformin users have been prescribed the drug with a serum creatinine >1.7mg/dL. Thus, the question remains: Is metformin safe and effective for patients with T2DM and CKD? Therefore, we propose a national retrospective cohort study of patients receiving care at the Department of Veteran Affairs to answer this question. Our central hypothesis is that metformin is safe and effective in patients with T2DM and CKD. Given the beneficial effects of metformin in patients with T2DM, it is essential to determine if this renal contraindication is warranted. In addition to the research described here, the proposed career development plan integrates research training activities in advanced pharmacoepidemiology, health services research and analysis of large complex national databases.

Aim 1. Quantify patterns of use of metformin use in VA patients with T2DM and CKD.
Subaim 1.1: Determine the prevalence and place in therapy of metformin use in patients with T2DM and CKD. This aim will allow us to assess patterns of metformin use in a national VA cohort.
Subaim 1.2: Examine patient, system and provider level factors associated with metformin use. Propensity score and instrumental variable adjustments of Aims 2 and 3 will be informed by these prediction models.

Aim 2. Evaluate the association between metformin use and adverse events in VA patients with T2DM and CKD.
Subaim 2.1: Compare incidence rates of lactic acidosis in patients with T2DM initiated on metformin compared to patients with T2DM initiated on other oral glucose-lowering medications and/or insulin.
Subaim 2.2: Compare the risk of hypoglycemia associated emergency department visits or hospitalizations in metformin vs. metformin non-users.

We will use 3 different approaches to adjust for measured and unmeasured confounders for each subaim (multilevel logistic regression modeling, propensity score modeling, and combination of high-dimensional propensity score modeling and instrumental variable modeling).

Aim 3. Assess the association between metformin use and the development of microvascular and macrovascular events in patients with T2DM and CKD.
Subaim 3.1: Compare the risk of proliferative diabetic retinopathy and progression of CKD in metformin users compared vs. non-users.
Subaim 3.2: Adjusting for risk factors, examine the risk of a composite outcome of non-fatal stroke, acute myocardial infarction, non-traumatic amputations, and cardiovascular disease death in metformin users compared to non-metformin users.
Subaim 3.3: Compare glycemic control between metformin users vs. non-users.

The proposed work is innovative because it utilizes advanced pharmacoepidemiologic and health services research methods, and the comprehensive VA clinical and administrative data to examine the fundamental question of whether metformin is safe and effective in patients with T2DM and CKD. Results will inform providers, policy makers, and patients about the relative safety of metformin vs. other glucose-lowering medications that are prescribed in patients with T2DM and CKD. My long-term career goal is to develop an independent, federally-funded research program that will develop evidence that will improve the care of patients with T2DM and CKD.
Research Strategy

SIGNIFICANCE. The safety and effectiveness of metformin in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) is largely unknown. While metformin is safe and effective in patients with T2DM and normal renal function, its safety and efficacy in T2DM patients with CKD is largely unknown based on prevalent concerns regarding risk for metformin-associated lactic acidosis in the setting of renal impairment. Current guidance from professional societies regarding the safety and effectiveness of metformin in patients with T2DM and CKD is in conflict with the FDA approved package insert, with societies acknowledging potential utility in patients with more severe renal impairment than product labeling would support. Without clear guidance, patients with T2DM and CKD are commonly prescribed alternative glucose-lowering therapies despite such therapies having similarly sparse data regarding safety and efficacy in the setting of CKD.

1. T2DM is a growing public health concern. Diabetes mellitus (DM) affects 25 million people in the United States (US), T2DM comprises approximately 95% of all cases, and is the leading cause of heart and kidney disease, non-traumatic amputations, and blindness. DM is also the 7th leading cause of death in the US, and the burden of this disease continues to rise.

2. Metformin has demonstrated benefits for patients with T2DM. Metformin, a biguanide, is the first-line pharmacologic treatment of patients with T2DM. Evidence suggests that metformin reduces cardiovascular morbidity and overall mortality in patients newly diagnosed with T2DM, with no such data existing for sulfonylureas and insulin, and controversy regarding such effects with the thiazolidinediones (TZDs). Moreover, unlike sulfonylureas, TZDs, and insulin, metformin is weight neutral (metformin does not increase weight in most patients) making it an attractive option for overweight/obese patients with T2DM. Hypoglycemia, an adverse event that occurs frequently with insulin and sulfonylureas, is rare in patients treated with metformin. Emergency room visits and hospitalizations caused by hypoglycemia occur frequently in patients with T2DM and the problem is compounded when these patients have concomitant kidney disease. Finally, the cost of metformin compared with other, newer oral or injectable proprietary agents is substantially lower.

3. Per the FDA, metformin use is contraindicated in patients with CKD. Despite proven benefits, metformin remains labeled as contraindicated in a large segment of patients with T2DM because many of these patients have concomitant CKD, often a consequence of uncontrolled DM. Patients with CKD represent a subset of patients with T2DM at exaggerated CVD risk. As per the US product label, metformin is contraindicated for patients with impaired renal function defined as serum creatinine >1.5mg/dL (men) and >1.4mg/dL (women). Since it is eliminated unchanged by the kidneys, it is feared that elevated metformin concentrations in patients with CKD may increase the risk for lactic acidosis. Despite these explicit serum creatinine cut-points, the perception of metformin use in patients with CKD is changing. In a statement authored by the American Diabetes Association and the European Association for the Study of Diabetes suggests using an estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73m² as a contraindication to metformin use. Guidance in other countries also use eGFR cut-points of <30 mL/min per 1.73m² or <45 mL/min per 1.73m² as contraindications to metformin use; however, these cut-points are arbitrary. Metformin's labeled contraindication in patients with CKD is not based on clinical evidence. Rather, it is based on case reports of lactic acidosis with phenformin, a predecessor to metformin in the biguanide class that was withdrawn from the market in 1977 due to fatal cases of lactic acidosis. Pharmacodynamically, increased phenformin concentrations reduce peripheral glucose oxidation and raise peripheral lactate production with a direct linear correlation between phenformin and lactate circulating concentrations; a correlation not observed with metformin.

5. Safety assessment of metformin in patients with CKD has not been evaluated in context with its effectiveness. A series of meta-analyses by Salpeter, et al. have assessed incidence of fatal and nonfatal lactic acidosis, correlated with blood lactate levels for patients on metformin therapy. In their most recent meta-analysis, data from 347 studies, accounting for 125,000 patient-years, there was no difference in the incidence of lactic acidosis between metformin vs. non-metformin users. The upper 95% confidence limit for true incidence of lactic acidosis per 100,000 patient-years (i.e. worst case scenario) was 4.3 vs. 5.4 cases in the metformin and non-metformin groups, respectively. Furthermore, there was no difference in circulating lactate levels, either as mean treatment levels or as a net change from baseline, for metformin vs. non-metformin users. However, these meta-analyses evaluated clinical trials that carefully selected patients, often systematically excluding those with CKD, or observational studies in which metformin safety assessment was not the primary objective. Bodmer, et al. conducted a nested, case-control study of more than 50,000 patients with T2DM. They found 6 cases of lactic acidosis, yielding a crude incidence rate of 3.3 vs. 4.8 cases per
100,000 patient-years in metformin vs. sulfonylurea exposed patients, respectively. However, this observational analysis is potentially impact by confounding by indication, with CKD patients more likely to be treated with sulfonylurea who are known to be at increased risk lactic acidosis. None of these studies evaluated the risk of metformin in context to its benefit.

6. Metformin continues to be prescribed despite its labeled contraindication for use in patients with CKD. Evidence suggests that metformin is used in some patients despite labeling contraindications with respect to renal function. Emslie-Smith, et al. conducted a retrospective cohort study of more than 1,800 patients with T2DM in Scotland and found that 3.4% of patients prescribed metformin had a local exclusion of a serum creatinine ≥1.7 mg/dL. Similarly, in a study of patients with T2DM in the U.S., 4.5% of patients treated with metformin had creatinine levels >1.4 and >1.5 mg/dL in women and men, respectively. Nevertheless, metformin is withheld from many patients with CKD because of the labeled contraindication.

7. Public health significance. Metformin is presently contraindicated by product labeling in a large subpopulation of patients with T2DM and CKD, though an evidence basis underpinning such contraindication is nonexistent. Studies suggest that patients are commonly switched from metformin to other glucose-lowering medications as CKD advances, despite absence of safety and efficacy data in the renally-impaired cohort for any alternative glucose lowering therapies. The growing epidemic of T2DM and consequent CKD in the US necessitates further investigation on what if any CKD contraindications for metformin are warranted, balanced within the context of demonstrated safety, tolerability and clinical efficacy of metformin.

8. Summary: The proposed research will identify patterns of use, and examine safety and associations with clinical outcomes of metformin exposure in patients with T2DM and CKD. These studies will inform healthcare providers, patients, and policymakers with regard to the associations between metformin and safety/efficacy outcomes according to CKD status, and frame hypotheses that may be assessed in future controlled trials.

INNOVATION

1. Advanced Analytic Technique. One major innovative feature of this proposal is the use of new analytic techniques. Large administrative, clinical and pharmacy databases are frequently used to estimate causal effect of drugs on rare patient outcomes, when such rare events preclude rigorous controlled clinical-trials assessment. Criticisms of traditional techniques in pharmacoepidemiologic studies, such as logistic regression, include selection bias, confounding by indication/disease severity, endpoint ascertainment bias, and other unmeasured confounding. Moreover, multivariable logistic regression modeling is often limited by the relatively small number of candidate variables included in the model and is susceptible to over-fitting. Overall, this approach leads to biased estimates and spurious conclusions. Other methodologies have been developed and are available to mitigate these problems.

Patients who are prescribed metformin are inherently different from those patients who are not prescribed metformin, in that they have an indication for therapy and more specifically, lack contraindications for such therapy. Typically in pharmacoepidemiologic studies, this indication is associated with the outcome under study. Unless the indication can be measured, uncontrolled confounding and selection bias may occur. Choice of therapy, selection of a dose, or the decision to continue a drug may be difficult to measure using longitudinal databases, and most often not quantitated at all. The proposed research will use a novel approach to account for measured and unmeasured confounding, thereby reducing selection bias. This two-step approach involves high-dimensional propensity score (HDPS) matching followed by instrumental variable (IV) selection and modeling. Propensity score analysis has been developed as an effective tool for adjusting large numbers of confounders. Propensity scores are known as a multivariate balancing tool to estimate the probability of starting treatment A versus treatment B. HDPS is unique because it takes a systematic approach to identify potential covariates from a very large pool of candidate variables. This systematic approach takes seven steps: 1) specify data sources; 2) identify empirical candidate covariates; 3) assess recurrence; 4) prioritize covariates; 5) select covariates; 6) estimate exposure propensity score; and 7) estimate the outcome model. HDPS analysis has resulted in improved effect estimates when compared with adjustment limited to predefined covariates and minimized the potential for selection bias. HDPS would address much of the measured confounding.

This research proposal would also include an IV analysis to address the unmeasured confounding that is prevalent in pharmacoepidemiologic studies. An instrument is a variable that is causally related to the exposure of interest, only weakly related to the uncontrolled risk factors of concern, and is not itself in the causal chain. Consequently, an instrument is an external factor that affects an outcome only through its effect
on treatment. By controlling for the instrument, it is thought that one can control for the indication for treatment. This novel method has the potential to impact how investigators analyze data in comparative effectiveness research.

APPROACH

1. Preliminary Feasibility Study. Our objective was to prove the feasibility of the proposed research using national VA data. We examined a national cohort of patients treated at VA Health Care Systems between CY2005 to CY2013. There were a total of 12.9 million unique patients who received care at 130 different VA medical centers. The majority of these patients were white (73.9%; 9,728,701) males (89.7%; 11,642,624) with a mean age of 55 years old. Of these, 18% (2.3 million) had a diagnosis for T2DM and 5.5% (424,161) of patients with a diagnosis for T2DM also had a diagnosis of CKD. Patients with T2DM were identified using ICD-9 codes of 250.xx and CKD was identified by ICD-9 codes of 585.xx, 250.4x, 403.9x, 583.x on two separate encounters. A total of 0.22% (29,052) patients in the full cohort and 0.63% (14,671) of patients diagnosed with DM had incident lactic acidosis. In patients that had both DM and CKD diagnoses, 2.1% (8,927) had incident lactic acidosis. Lactic acidosis was identified by ICD-9 code 276.2 in the hospital discharge diagnosis.

Using national VA data identifying metformin users by keyword search, we found that 50% of patients (1.1 million) diagnosed with T2DM were prescribed metformin. Of the 1.1 million patients with T2DM and prescribed metformin, there were 2,795 cases of incident lactic acidosis. In patients with T2DM and concomitant CKD, 24% (102,403) of individuals were prescribed metformin. Of these patients, there were 636 (0.6%) cases of incident lactic acidosis. This is in contrast to 7,660 (2.3%) cases in patients not exposed to metformin. The odds of lactic acidosis for patients with T2DM taking metformin was lower when compared to those not taking metformin (OR 0.91; 95% CI, 0.85-0.97). The odds remained lower in patients with concomitant CKD taking metformin (OR 0.26; 95% CI, 0.24-0.28) (Table 1).

To determine if variations in prescribing may be used as an instrumental variable we examined metformin prescribing patterns by station, Veterans Integrated Service Network (VISN), and region. The mean percentage of patients with T2DM and CKD prescribed metformin by station was 24.1% (range 10.3%-45.9%) with less variation by VISN (mean 24.3%, range 20.5%-28.5%) and region (mean 24.4%, range 22.5%-27.3%). These data coincide with prior published observations with regard to metformin prescribing in patients with labeled contraindications.24

2. Research Design and Methods

a. Overview of study design. We propose to conduct a retrospective cohort study using over 10 years of data from VA patients with T2DM who received a new prescription of any glucose lowering medication from FY 2003-13. We aim to 1) quantify patterns of use of metformin use in VA patients with T2DM and CKD, 2) evaluate the association between metformin and adverse events in VA patients with T2DM and CKD, and 3) assess the association between metformin and the development of microvascular and macrovascular events in patients with T2DM and CKD. Associations of metformin use and hospitalization with incident lactic acidosis, hospitalization or ED visits for hypoglycemia, macrovascular and microvascular events will be examined, controlling for other factors that influence the risk of dependent variables.

b. Study subjects and setting.

i. Study Subjects. All adult patients (≥18 years) with T2DM and CKD treated at VA medical centers with a new prescription for any glucose lowering medication during FY 2003-13. T2DM will be identified using a validated algorithm that uses both administrative claims and pharmacy data.31,32 Patients with CKD will be identified using a validated algorithm that uses a combination of ICD-9-CM codes from all health care encounters (diagnosis groups: chronic renal insufficiency, diabetic nephropathy, hypertensive nephropathy, acute renal failure, and miscellaneous other renal disease)33 or clinical laboratory data (estimated glomerular filtration rate is < 60 mL/min/1.73m² for 2 consecutive readings >3 months apart).34 We will exclude patients who are receiving dialysis or had a kidney transplant as identified by inpatient or outpatient ICD-9-CM or CPT codes since progression to these renal endpoints are considered outcomes in this proposal.
c. **Data Source.** We will obtain national VA data (FY2003-13) from the VA Corporate Data Warehouse (CDW) and use the VA Informatics and Computing Infrastructure (VINCI) to host and analyze the data. The CDW includes all data from Veterans Health Information Systems and Technology Architecture (Vista), inpatient and outpatient administrative data sets (MedSAS), cost information (DSS), and other non-Vista data through Text Integration Utilities. Data included in the CDW includes inpatient and outpatient diagnosis/procedure codes, pharmacy, and laboratory data. To capture events that occur at other institutions in patients ≥65 years of age we will obtain claims data from Medicare through the VA-CMS data system.

i. **Research variable definitions.** 1) **Exposure variable:** The exposure variable will be metformin use, as defined by prescription fills from pharmacy records. Prescriptions for metformin alone or in combination with other agents will provide the basis to define exposure. Each person-day of follow-up will be classified into mutually exclusive exposure categories according to metformin use. Classification will be based on dispensing dates and days supply. Current use is defined as the period between prescription start date and end of days supply. Indeterminate use is defined as the first 89 days after end of current use. Former use begins at 90 days after end of current use and ended at 364 days after last current use. Ever-use is defined as person-days with any history of current use or any past use (back to 365 days before cohort entry). Non-use is defined as person-days with no current use and no past use (back to 365 days before cohort entry). We consider current use the most physiologically relevant exposure for safety. In Aim 1 we will determine metformin usage patterns for each exposure classification in patients with T2DM and CKD. Moreover, we will explore patient, provider, and system level factors associated with metformin use. For the purpose of the primary safety outcome we will compare risk during current use with risk of non-use. For the primary effectiveness outcome we will compare risk for patients who ever-used metformin with those of non-use. 2) **Primary outcomes** in Aim 2 will be adverse drug events. Specifically, incident lactic acidosis and emergency department (ED) visits or hospitalization for hypoglycemia. In Aim 3, our primary outcomes will be microvascular and macrovascular disease. Composite microvascular and composite macrovascular disease outcomes will be assessed. Microvascular disease is comprised of proliferative diabetic retinopathy, and progression of CKD. Macrovascular disease is comprised of cardiovascular disease (CVD) death, lower extremity amputation, non-fatal stroke, or non-fatal acute myocardial infarction (AMI).

ii. **Outcomes:**

<table>
<thead>
<tr>
<th>Outcome Variables</th>
<th>How Measured</th>
<th>Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic Acidosis</td>
<td>ICD-9-CM code 276.2 in discharge diagnosis OR serum lactate &gt;5 mEq/L; diabetic ketoacidosis will be excluded (ICD-9-CM code 250.1)</td>
<td>Inpatient discharge data, Laboratory data</td>
</tr>
<tr>
<td>ED visits or hospitalizations for hypoglycemia</td>
<td>Validated algorithm that uses ICD-9-CM codes</td>
<td>Inpatient discharge data, ED discharge data, Medicare claims</td>
</tr>
<tr>
<td>Proliferative diabetic retinopathy</td>
<td>ICD-9-CM code 362.0X and 250.50</td>
<td>Ambulatory data</td>
</tr>
<tr>
<td>Progression of CKD</td>
<td>eGFR progression to greater CKD stage as defined by KDOQI OR ≥25% decrease in eGFR from baseline OR progression to end stage renal disease as indicated by: 1) new dialysis initiation (CPT codes 90835, 90937, 90945, 90947, 90993), 2) renal transplant (ICD-9-CM codes V42.0, 3) eGFR &lt;15mL/min per 1.73 m²</td>
<td>Laboratory data, Ambulatory data</td>
</tr>
<tr>
<td>Lower extremity amputations</td>
<td>ICD-9-CM codes from AHRQ's Prevention Quality Indicators</td>
<td>Inpatient discharge data, Ambulatory data</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>ICD-9-CM codes from AHRQ's Inpatient Quality Indicator (IQI) 176</td>
<td>Inpatient discharge data, Medicare claims</td>
</tr>
<tr>
<td>AMI</td>
<td>ICD-9-CM codes from AHRQ's IQI 176</td>
<td>Inpatient discharge data, Medicare claims</td>
</tr>
<tr>
<td>CVD death</td>
<td>Death concomitant with or within 30-days following an incident major adverse CVD event, such as AMI, unstable angina, coronary revascularization, stroke, arterial embolism, pulmonary embolism, ruptured aortic aneurysm, aortic dissection, heart failure, or cardiac arrhythmia</td>
<td>Inpatient discharge data, VA vital status file</td>
</tr>
<tr>
<td>Glycemic Control</td>
<td>Achieving the 2013 NCQA HEDIS measure of HbA1c &lt;8%</td>
<td>Ambulatory data</td>
</tr>
</tbody>
</table>

iii. **Potential confounders** assessed in our models will include:

1. **Patient demographics:** Age, sex, ethnicity/race, socioeconomic status as assessed using the VA priority score, geographic location and distance to VA facility.
2. Risk factors for lactic acidosis: Age, sepsis, CKD severity, alcohol abuse, chronic obstructive pulmonary disease, liver disease, myocardial infarction, chronic heart failure, and coronary artery bypass graft surgery.

3. Hypoglycemia risk factors: Age, alcohol abuse, previous hospitalization or ED visit for hypoglycemia, chronic heart failure, CKD severity, and liver disease.

4. CVD risk factors: Age, sex, tobacco use, hypertension, hypercholesterolemia, low HDL-C, obesity, and family history of premature atherosclerosis.

5. Facility characteristics: Facility size, urban/rural setting, geographic location, and Community Based Outpatient Clinics/VA hospital setting.

6. Other Drugs: Prescriptions for nucleoside-analog reverse transcriptase inhibitors (lactic acidosis), isoniazid (lactic acidosis), sulfonylurea and insulin use (hypoglycemia), angiotensin converting enzyme inhibitors and angiotensin receptor antagonist (renal disease progression and CVD), and beta-blockers, aspirin and statin drugs (CVD).

d. Statistical analysis

i. General analytic approach. We will examine the association between metformin use and incidence of lactic acidosis, hospitalizations/ED visits for hypoglycemia, composite CVD outcome, and composite microvascular disease complication outcome in patients with T2DM and CKD using three techniques: multilevel logistic regression, propensity score models, and a combination of HDPS and IV analysis.

ii. Aim 1. Descriptive analysis of metformin use in patients with T2DM and CKD. For subaim 1.1, we will characterize the prevalence of metformin use in patients with T2DM and CKD including dose and concomitant glucose lowering medications prescribed. We will also characterize metformin use on the definitions of exposure outlined in d.ii. National secular trends will be analyzed to determine the prevalence and incidence of metformin use and initiation in this population. For subaim 1.2, provider, system, and regional factors of metformin prescribing will be analyzed using multiple logistic regression models. These factors will be used to inform the multilevel modeling, propensity score modeling, HDPS, and IV analysis described in the aims below.

iii. Aim 2. Using multilevel logistic regression, propensity score models, HDPS and IV analysis; we will determine the association between metformin use and adverse events in patients with T2DM and CKD. Adverse events will be defined as incidence of lactic acidosis or hypoglycemia requiring ED visit or hospitalization. For subaim 2.1, we will assess incidence of lactic acidosis in patients using metformin compared with patients receiving non-metformin oral glucose lowering therapy or insulin. For subaim 2.2, we will assess hospitalizations or ED visits for hypoglycemia in patients using metformin compared with patients receiving non-metformin oral glucose lowering therapy or insulin.

1. Multilevel Logistic Regression Model. The association between metformin use and the observed primary adverse event variable will be adjusted by measured covariates. We will also include a multilevel component to adjust for clustering by site and region.

2. Propensity Score Analysis. This technique has emerged as a tool for adjusting multiple confounders. A propensity score is the estimated probability of initiating metformin versus other glucose lowering medications, conditional on all observed pretreatment patient characteristics. Demographic factors (age, race, and sex), CKD stage, baseline HbA1c, comorbid burden, and other covariates will be selected for inclusion in propensity score models. We will adjust for measured covariates in 3 ways, 1) propensity scores as a continuous covariate in a multiple logistic regression model; 2) propensity score stratified by quintile fit into a stratified multiple logistic regression model; and 3) propensity score matching by probability for metformin vs. other glucose lowering drug prescription using a logistic regression modeling. We will perform nearest number matching with a caliper of 0.0001. Robust standard errors will be calculated to account for potential heteroskedasticity.

3. High Dimensional Propensity Score Matching and Instrumental Variable Analysis. We will use HDPS to balance measured and unmeasured confounding in metformin exposed versus non-exposed patients. First, we will specify our data sources and define our data dimensions used. Examples of data dimensions are ambulatory care and hospital ICD-9-CM diagnosis and procedures. An additional important dimension we will assess is concomitant medication use. We will also assess predefined covariates such as age, sex, race, year of entry and comorbid burden. Baseline characteristics will be identified 12 months prior to study entry. Second, within each dimension, codes will be sorted by their prevalence. Prevalence will be
measured as the proportion of patients having a specific code at least once during the 12 month baseline period. Third, for the most prevalent codes within each dimension, we will assess how frequently each code was recorded for each patient in the baseline period. We will evaluate frequency by dividing each code into 3 binary variables: code occurred >1 time, >median number of times, and >75th percentile number of times. Fourth, we will prioritize covariates across data dimensions by their potential for controlling confounding that is not conditional on metformin exposure and other covariates using the equation in Figure 1. The confounded or apparent relative risk (ARR) is a function of the imbalance in prevalence of a binary confounding factor among metformin users (Pc1) and non-metformin users (Pc2) as well as the independent association between a confounder and the study outcome (RRc0). The fraction on the right side of the equation in Figure 1 represents the multiplicative bias term (BiasM). We will sort the most prevalent codes in each data dimension by the magnitude of log(BiasM) in descending order. Fifth, we will select the top 10% of covariates identified in step 4. Additionally we will include predefined covariates such as age, sex, race, year of entry and comorbid burden. Sixth, we will estimate metformin exposure propensity scores using multivariable logistic regression. Each patient will have a propensity score to estimate the predicted probability of metformin use conditional on all the empirically chosen and predefined covariates. Seventh, we will match metformin users to non-metformin users using a 1:2 ratio. We will estimate the outcome in our matched cohort using logistic regression where metformin use and an IV are used as the independent variables. IVs are used to address unequal distributions of unobserved covariates. IVs operate best when the variable of interest is associated with metformin treatment and not associated with outcomes. Regional differences in metformin prescribing could be used as a potential IV. Patients receiving treatment within one of the VA Community Based Outpatient Clinics as opposed to an academic VA hospital may also represent an IV.

iv. Aim 3. Using the same techniques in Aim 2, we will determine associations between metformin use and development of microvascular and macrovascular disease. For the purpose of this research in subaim 3.1, microvascular disease is defined as either proliferative diabetic retinopathy or non-traumatic lower limb amputations as outlined in section d.ii.4. The presence of microvascular disease will be analyzed as a composite binary outcome. In subaim 3.2, macrovascular disease will also be analyzed as a binary composite outcome and defined as having cardiovascular disease (CVD) death, non-fatal stroke, or non-fatal acute myocardial infarction (AMI). Glycemic control in those patients prescribed metformin versus those receiving non-metformin glucose-lowering therapy will be assessed in subaim 3.3. Glycemic control will be defined as achieving the 2013 NCQA HEDIS measure of HbA1c <8%. We will also assess HbA1c as a continuous variable using a repeated measures model.

e. Power analysis. Power is calculated to test the association between metformin exposure and lactic acidosis. Our preliminary analysis discovered 424,181 patients with T2DM and CKD (CY2005-CY2013). We assume this is an underestimate considering the use of only administrative data as seen in previous studies. Moreover, we plan on expanding our time period to include FY2003-CY2013 and incorporating laboratory data to ascertain the cohort. We will assume to have 550,000+ patients in the proposed study cohort among whom we assume one fourth will be exposed to metformin. Based on preliminary analysis, we observed that the incidence rate of lactic acidosis is 0.8% and 2.3% in the exposed and non-exposed groups, respectively. To detect the aforementioned difference between the two groups, a cohort of 2288 patients can achieve a power of 80% with a two-sided type I error of 5%. A cohort of 2768 patients can achieve a power of 90%. Thus we believe the 550,000+ patients will be sufficient to detect the effect.

3. Experimental problems. a) External validity. The VA population is distinctive and generalizability of results may be probed. The VA consists of mostly Caucasian males; however, it is worth noting this population has several advantages. The VA population has approximately a 20% diabetes prevalence that provides a rich source of patients for inclusion into our studies. This was confirmed in our preliminary analysis of the last 8 years of data. Moreover, patients within the VA system tend to stay in the system long term. This is especially true if they have high priority status. This allows us to collect longitudinal administrative, clinical and pharmacy data with confidence. We will conduct sensitivity analysis according to VA priority status. Because Veterans with priority status 1-3 stay in the VA system long-term and tend to obtain most prescription medications through the VA pharmacy we will examine this group compared with priority status 4-8 within the VA. b) Confounding by indication. This occurs when a condition or variable is present in the unexposed patient, but is also an indication for the exposure of interest. Confounding by contraindication is a particular problem in this...
proposal. As an example, patients with higher stage CKD will most likely not have high prevalence of metformin use compared to those patients with lower stage CKD. Severity of CKD is a risk factor for lactic acidosis and associated with higher rates of metformin discontinuation. We will conduct sensitivity analysis of patients by CKD stage and adjust in our mathematical models. Case ascertainment. This can be a significant problem for retrospective cohort studies that use administrative claims data. We propose finding cases with algorithms using multiple administrative and clinical sources within the national VA database. We will also use Medicare claims data to ascertain events that may occur at other institutions such as ED visits for hypoglycemia, and hospitalizations for stroke and AMI.

4. Timeline of Publications and Grant Submissions

<table>
<thead>
<tr>
<th>Table 3: 4-Year Timeline of Publications and Grant Submissions</th>
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<tbody>
<tr>
<td><strong>Work Plan</strong></td>
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<td><strong>Manuscripts</strong></td>
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<tr>
<td><strong>Grant Submissions</strong></td>
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5. Next Steps

Research and training proposed in this application will provide the foundation for further studies of metformin use in patients with type 2 diabetes and chronic kidney disease. The findings from this research will be the underpinnings of a R01 submission that compares metformin use in the United Kingdom (UK) and United States (US). Guidance for metformin use in patients with kidney disease is different in the UK as compared to the US. The UK recommends limiting metformin prescribing in patients with an estimated glomerular filtration rate <30mL/min/1.73m². This is in contrast with the US, package insert, that recommends limiting metformin use in patients with serum creatinine >1.5mg/dL (men) and >1.4mg/dL (women). Additional studies are needed to determine if these vastly different approaches to therapy are either safe or effective.
HUMAN SUBJECTS

1. Risk to Subjects

Human Subjects Involvement and Characteristics. This study examining the safety and effectiveness of metformin therapy in patients with T2DM and CKD from Veterans is observational. As a matter of course, all women and minorities will be included in this study. Current estimates indicate that approximately 5% of veterans are women and approximately 68% are white. The observational component will include all Veterans who were prescribed metformin, or other glucose-lowering therapies in FY2003-FY2013. Based on preliminary data from FY2005-FY2010 we expect approximately 430,000 individuals to meet the criteria. The age range for individuals in this population is 18-110 years. Health status of this population ranges from relatively healthy individuals with few diagnosed conditions other than diabetes to individuals who are unemployable due to service-connected disability or extreme disease burden. There will be no intervention or contact with the patients under study for this component.

Sources of Materials. Data for the proposed study will be obtained from: 1) data extractions from the VHA national and administrative databases hosted by VA Informatics and Computing Structure (VINCI). Information from the VHA national and administrative databases and the electronic medical record involves existing patient data. VINCI is an initiative to improve researchers' access to VA data and to facilitate the analysis of those data while ensuring Veterans' privacy and data security. VINCI provides both onsite and remote access through an interface to secure VA data servers. VINCI also hosts analytical applications such as SAS, STATA, R, and SPSS. All data will be securely stored and all analysis of data will be conducted on the VINCI environment. Access to this data is restricted to those with a primary appointment with the VA, without compensation (WOC) appointment, or approved by the national VA office.

Potential Risks. This will be an observational study only with no intervention conducted for research purposes. Since there is no contact with the Veterans there is no therapeutic risk or risk of physical injury as a result of this research. There is no contact with Veterans, therefore the potential risk posed by the study is minimal.

In general, however, the most salient risk to Veteran participants in the proposed work is the potential for a loss of confidentiality. Patient/participant identifiers or PHI will not be disclosed outside of the VA unless required by federal law, including the Federal Privacy Act and its regulations. Authorized representatives from the IRB may also review patient information for the purpose of monitoring compliance. Otherwise, confidentiality will be strictly maintained throughout the study within known limits to confidentiality (as mentioned previously) and the measures to ensure confidentiality will be described in the IRB-approved study information sheet. Any study findings will be reported in aggregate only for all scientific presentations and journal articles resulting from this research; no individual patients or participants will be identified. Data security procedures to protect patient identifiers and PHI are outlined below.

2. Adequacy of Protection from Risk

Recruitment and Informed Consent. IRB approval will be obtained at Texas Tech University Health Sciences Center, UT Southwestern Medical Center and North Texas VA Health System requesting a waiver for written consent for the study. The research team will request this waiver for written consent for two reasons: first, obtaining written consent would constitute the only contact with the study participants and second, we cannot practically accomplish this study's objectives in a timely manner by obtaining written consent for 430,000 Veterans.

Protection Against Risk. Because the proposed study does not involve intervention (i.e., physical interaction with subjects, manipulation of their environment, or performing medical-type treatment procedures), data collection regarding complications or adverse events related to treatment is not applicable. However, we will promptly record and report to the IRB any Unanticipated Problems Involving Risk to Subjects or Others (UPIRSO) that come to our attention.

The research team will protect all PHI by (a) maintaining up-to-date training required for all research team members engaged in research, (b) monitoring implementation of good data security practices by all study staff on an ongoing basis, (c) storing data behind the VA firewall on protected, limited-access research servers at all times, (d) using secure data transfer methods to obtain PHI, such as limited access password-protected and user-specific direct data transfer behind the VA firewall (the preferred method; used by CDW) or PKI-protected email (Public Key Infrastructure, a method of encrypting email preferred by ARC for cost data) or commercial carrier conveyance of encrypted datasets on CD's (if required by a data source), (e) limiting PHI
requested/obtained to the minimum needed to meet study objectives, and (f) reporting only aggregate results with no sub-group smaller than 11 persons and no ages greater than 90 years.

3. Potential benefits of research to subjects and others.

Study participants are not likely to benefit directly from their participation. It is anticipated that patients with diabetes and chronic kidney disease, as well as administrators and clinicians, will benefit from the knowledge gained through this research. Because risks to the subjects are minimal, the proposed research has a reasonable risk-to-benefit ratio.

4. Importance of knowledge to be gained.

The safety and effectiveness of metformin in patients with T2DM and CKD is largely unknown. Metformin is the first line therapy in patients with T2DM and no renal insufficiency because of its known benefits and minimal risks. The FDA approved labeling of metformin lists renal insufficiency as a contraindication to therapy. This is based on no evidence; rather, this contraindication is based on previous case reports of lactic acidosis with phenformin which was removed from the market in 1977. This research will use VA data to determine if metformin is safe and effective in patients with T2DM and CKD.

5. Data and safety monitoring plan.

All investigators and research assistants and other staff (including administrative staff) have received or will receive training in the protection of human research participants in the form of a Texas Tech University Health Sciences Center on-line tutorial, or an approved equivalent tutorial. All investigators and staff in the study will remain updated on issues related to patient rights and data safety through educational programs and updates provided by Texas Tech University Health Sciences Center, UT Southwestern, North Texas VA Health Care System and its IRB.
15. **Inclusion of Women and Minorities.** Women and minorities will not be excluded from the proposed research. The selection criteria, in this retrospective study using extant data, are inclusive of patients 18 years and older. The percentage of women and minorities included in the study will be a direct reflection of the population of patients who receive VA clinical services.

15.1. **Inclusion of Women.** My preliminary analysis of patients from CY 2005-CY 2013 shows that 10.3% of all patients are female. The inclusion of women in this study is limited by the demographics of the military, and thus the veteran population. However, a recent study of VA patients showed a 70% increase in the trend of female veterans utilizing health services at VA health systems from 2000 to 2008.\(^5^4\)

15.2. **Inclusion of Minorities.** The Department of Veterans Affairs reported the United States veteran population as 79.4% white, 11.3% black, 5.7% Hispanic, 1.8% Asian/Pacific Islander, 0.8% American Indian/Alaska Natives, and 1.0% classified as "other".\(^5^5\) This is consistent with what we found in our preliminary analysis and what was found by the US Census Bureau.\(^9^8\)
17. **Inclusion of Children.** The proposed research study includes persons 18 years or older. Thus, some persons under age 21 may be included. We do not include children under age 18, as 1) the study intends to study the use and safety of prescription metformin among adults with diabetes and kidney disease and 2) the VA clinical population contains extremely few children under 18 years of age.
APPLICATION NUMBER: 1 K08 DK101602-01

Program Contact:
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(301) 594-7692
hydej@niddk.nih.gov

Principal Investigator:

Applicant Organization: TEXAS TECH UNIVERSITY HEALTH SCIS CENTER

Review Group: DDK-B
Diabetes, Endocrinology and Metabolic Diseases B Subcommittee

Meeting Date: 01/12/2014
Council: JAN 2014
Requested Start: 04/01/2014

Council:
JAN 2014

RFA/PA: PA11-193
PCC: DJH CARE

Project Title:
Safety and Effectiveness of Metformin Therapy in Patients with Type 2 Diabetes an

SRG Action: Impact Score: 16

Human Subjects: 30-Human subjects involved - Certified, no SRG concerns
Animal Subjects: 10-No live vertebrate animals involved for competing appl.
Gender: 1A-Both genders, scientifically acceptable
Minority: 1A-Minorities and non-minorities, scientifically acceptable
Children: 1A-Both Children and Adults, scientifically acceptable
Clinical Research - not NIH-defined Phase III Trial

<table>
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<tr>
<th>Project Year</th>
<th>Direct Costs Requested</th>
<th>Estimated Total Cost</th>
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ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

ADMINISTRATIVE NOTE
SCIENTIFIC REVIEW OFFICER’S NOTES

RESUME AND SUMMARY OF DISCUSSION:

This application was submitted in response to program announcement PA-11-193 entitled “Mentored Clinical Scientist Research Career Development Award (Parent K08)”. Strengths of the application include: the extremely important research topic; the strong productive candidate who is well-positioned to become a national leader in this area; the supportive letters of reference; the mentoring team; the compelling preliminary data; the research environment; and the outstanding institutional support for the candidate. Weaknesses of the application were few and include: certain aspects of the career development plan; the definition of chronic kidney disease is not clear and it is often undocumented; ethnicity in the study population was not well-considered; and the rationale for the hypoglycemic arm is not clearly articulated. In addition, there is an opportunity to include consideration of the protective effects of metformin particularly in breast and colon cancer. These weaknesses were considered minor and did not significantly decrease the merit of the application. Overall there was a high level of enthusiasm among the review committee for this application. This application is rated Exceptional to Outstanding.

DESCRIPTION (provided by applicant): This is an application for a K08 Career Development Award for [name], an Assistant Professor and clinical pharmacist at Texas Tech University Health Sciences Center School of Pharmacy. His long-term career goal is to be an internationally known expert and independent investigator in the pharmacoepidemiology of therapeutic agents used in patients with type 2 diabetes and chronic kidney disease. The career development aims of this K08 application are to support training in: Aim 1) pharmacoepidemiology, Aim 2) health services research, and Aim 3) analysis of large, complex national databases. This career development award will also support [name] path to independence. To achieve this goal, [name] has assembled a multidisciplinary mentoring and advisory team with significant experience in extramurally funded clinical research. Chronic kidney disease (CKD) is a common and well known complication of type 2 diabetes (T2DM). This complication often restricts providers from prescribing metformin, a glucose-lowering agent with known morbidity and mortality benefits in patients with T2DM. This FDA labeled contraindication for metformin using arbitrary serum creatinine cut-points in patients with T2DM and CKD is not evidence based and often necessitates prescribers to initiate or switch patients to other glucose-lowering agents with worse adverse event profiles or that have been associated with poor cardiac outcomes. Guidance in other countries do not endorse the FDA contraindication and allows for metformin use in patients with mild to moderate CKD as measured by estimated glomerular filtration rate. This recommendation is also not based in evidence. Thus, the safety and effectiveness of metformin in patients with T2DM and CKD is largely unknown. [name] research will focus on determining the safety and effectiveness through three specific research aims. In Aim 1 he will determine patterns of metformin use in patients with T2DM and CKD. He will analyze complex administrative and clinical data from the national VA database hosted by VINCI. Patterns identified in Aim 1 will inform him of the variables that should be further tested in Aims 2 and 3. Aim 2 will examine associations of adverse events for metformin and other glucose-lowering agents. Specifically, he will study incident hospitalizations for lactic acidosis and primary hospitalizations or emergency department visits for hypoglycemia. In Aim 3, [name] will assess the relationship between metformin and the development of microvascular and macrovascular outcomes. Microvascular outcomes assessed will be the development of proliferative diabetic retinopathy and progression of kidney disease. Macrovascular outcomes will be measured as a composite of non-fatal stroke, acute myocardial infarction, non-traumatic lower extremity amputation and cardiovascular disease death. He will also compare glycemic control between patients prescribed metformin and those on other glucose-lowering agents. Innovative techniques such as combination high-dimensional propensity score and instrumental variable modeling will be used in Aims 2 and 3 to reduce bias often encountered in observational research. The research will form the basis for an R01 or equivalent application to compare metformin usage patterns, safety
and effectiveness in patients with type 2 diabetes and chronic kidney disease between those treated in the VA system and the United Kingdom.

**PUBLIC HEALTH RELEVANCE:** The epidemic of type 2 diabetes (T2DM) and chronic kidney disease (CKD) is on the rise. Unfortunately, metformin, a drug with known benefits in patients with T2DM, has a FDA labeled contraindication in patients with T2DM and CKD. This contraindication is not based on clinical evidence; rather, it is based on previous poor experience with an older drug in the same therapeutic class, phenformin, which has been removed from the market. Despite this contraindication, evidence suggests that patients with T2DM and CKD are still prescribed metformin. It is critical to understand the safety and effectiveness of metformin in this population as it may affect policy and labeling changes on how it is prescribed.

**CRITIQUES**

Note: The critiques below were prepared by the reviewers assigned to this application. These commentaries and criterion scores do not necessarily reflect the position of the authors at the close of the group discussion, nor the final majority opinion of the group, although reviewers are asked to amend their critiques and criterion scores if their position changed during the discussion. The resume and other initial sections of the summary statement are the authoritative representation of the final outcome of group discussion. If there is any discrepancy between the peer reviewers' commentaries and the individual criteria scores or the overall priority/impact score on the face page of this summary statement, the overall priority/impact score should be considered the most accurate representation of the final outcome of the group discussion.

**CRITIQUE 1:**

Candidate: 2
Career Development Plan/Career Goals /Plan to Provide Mentoring: 1
Research Plan: 2
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 1
Environment Commitment to the Candidate: 1

**Overall Impact:**

The strengths of this application are several including a strong candidate with high level of productivity and credentials that position him to become a leader in pharmacoepidemiology. The research plan addresses an important area in a rapidly growing high CVD risk population of diabetic and CKD regarding the safety, efficacy and benefits of metformin in these patients where metformin use is restricted without any scientific bases for the exaggerated fear of lactic acidosis. Therefore, performing this proposal will yield important clinical data that will help inform clinicians and policy makers and it will provide an opportunity for career development of the candidate to evolve as an independent investigator in a unique way as a pharmaco-epidemiologist. Mentoring team are strong as well as commitment and institutional support for the candidate. A few issues with the proposal such as rationale for the hypoglycemia arm of the study and the method of estimation of GFR need to be clarified. Also further details regarding future directions into R01 also need to be further explained.

1. **Candidate:**

**Strengths**

- The candidate is a clinical pharmacist and an assistant professor Texas Tech University Schools of Pharmacy. His interest in research is well established and solid. He has great potential to become an independent productive pharmacoepidemiology investigator. Because of his research interest he was selected for K12 Clinical Research scholar at the UT Southwestern in 2012 and he joined Texas Tech as a tenured assistant professor.
• He has multiple publications in related areas of research including 3 first authorship with 2 in collaboration with the primary mentor and the secondary mentor. He is also a first author on book chapters and review articles.

• The candidate represents a rare breed among pharmacist investigators and is well positioned to fill this void at a national level.

Weaknesses
• None noted

2. Career Development Plan/Career Goals & Objectives (K24 Plan to Provide Mentoring):

Strengths
• Strong, focused and well described with course work and specific goals for training in pharmacoepidemiology, health services research and analysis of large complex databases

• Mentoring plan is well described by both the candidate as well as the primary mentor with specifics provided and timetables.

Weaknesses
• Career path to independence needs further details.

3. Research Plan:

Strengths
• Addresses and important area of research with questions that needs to be answered regarding the most important medication currently available for diabetes that has been shown to be safe with long track records since 1950's and effective with favorable CVD risk profile. However, pattern of use, safety and associated clinical outcomes with the metformin use in patients with diabetes and concomitant CKD is largely unknown and that is the bases of this research project.

• The PI will analyze the VA large cohort utilizing ICD-9-CM codes and using advance statistical techniques including the High Dimensional Propensity score (HOPS) to address the measured confounders as well as the Instrumental Variable (iv) for the unmeasured confounders. These techniques will offset the over fitting observed with the basic logistic regression models.

• Feasibility data are provided and looks promising with adequate sample size, these preliminary results indicate that the incident lactic acidosis is lower in the diabetic patient on metformin and in diabetic patients with CKD on metformin, compared to non-metformin users.

Weaknesses
• The rationale for hypoglycemia arm is not clear. Metformin is an insulin sensitizer and is not known to cause hypoglycemia as a monotherapy. Furthermore, CKD itself is associated with higher rate of hypoglycemia in diabetic and non-diabetic subjects due to decreased insulin clearance, decreased caloric intake due to anorexia, decreased gluconeogenesis among other factors. This issue was not adequately addressed.

• Definition of CKD was not adequately addressed and it is a well-known fact that many patients with diabetes and CKD are not labeled or referred to nephrology care till late stages. This will limit the use of the ICD- codes. The PI addresses this issue on page 77 and will use either ICD code or clinical and laboratory data to calculate eGFR. In that case details are not provided as to which formula will be used MDRD versus CKD-EPI etc.

• It would be a great opportunity for the candidate to assess the cancer association with the use of metformin given the accumulating data of protective association, particularly with colon and breast CA, common cancers among diabetic populations.
4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Strengths:
- The candidate assembled a group of seasoned investigators led by Dr. Mortenson, MD who is an expert in pharmacoepidemiology methods using large databases. The co-primary mentor, Dr. Ham is the chief of the division of outcomes band health services research. Both have strong track records of funding, publications and successful mentoring experiences. Furthermore, the team is supported by well-seasoned researcher with necessary expertise to execute the project. Specifically in CVD pharmacoepidemiology, Dr. Darren McGuire and in CKD, Dr. R. Tyler Miller who is an experienced renal epidemiologist as well as Dr. May Jo Pugh who possess expertise in biostatistics and epidemiology.
- Very strong and well-structured letter of support from the primary mentor delineating the mentoring plan and offering resource and mentoring support to the candidate.

Weaknesses
- Some of the mentors have limited active funding.

5. Environment and Institutional Commitment to the Candidate:

Strengths
- Ample research support available to the investigator to conduct his proposal including resources at the Texas Tech Clinical Research Institute, the Center for translational research as well as department of Veterans Administration including the well-developed VA Informatics and Computing Infrastructure (VINCI).
- Strong and well-structured joined letter of support from both the Dean and the Chairman of the Department of Pharmacy delineate clearly 75% commitment time for research and specific commitments in terms of space, administrative support as well as startup money for pilot studies. Institutional commitment is also demonstrated through his Tenure track appointment that is not contingent upon this funding mechanism.

Weaknesses
- None noted

Protections for Human Subjects:
Acceptable Risks and Adequate Protections
- data analysis without patient contact, observation of HIPPA rules and protection of all PHI is described.

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):
- Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:
G1A - Both Genders, Acceptable
M1A - Minority and Non-minority, Acceptable
C1A - Children and Adults, Acceptable
- Persons between 18 and 21 years will also be including representing children by NIH standards.

Vertebrate Animals:
Not Applicable (No Vertebrate Animals)
Biohazards:
Not Applicable (No Biohazards)

Training in the Responsible Conduct of Research:
Acceptable

Comments on Format (Required):
- computer based

Comments on Subject Matter (Required):
- responsible conduct/ ethic

Comments on Faculty Participation (Required; not applicable for mid- and senior-career awards):
- mentioned with primary mentor

Comments on Duration (Required):
- for 12 months

Comments on Frequency (Required):
- weekly meetings with mentor and monthly every second Tuesday for the ethics grand round

Select Agents:
Not Applicable (No Select Agents)

Resource Sharing Plans:
Not Applicable (No Relevant Resources)

Budget and Period of Support:
Recommend as Requested
- Recommend the 4 year support requested by the candidate.

CRITIQUE 2:
Candidate: 1
Career Development Plan/Career Goals /Plan to Provide Mentoring: 1
Research Plan: 2
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 1
Environment Commitment to the Candidate: 1

Overall Impact:
This is a well written proposal which will examine whether the FDA labeled contradiction for using serum creatinine cut points of >1.5 mg/dl and >1.4 mg/dl for men and women in T2DM patient with CKD, which is the contention of the applicant to be arbitrary, is justified. The contra indication is based on the premise that use of metformin is patients with CKD may result in greater incidence of lactic acidosis. The applicant’s preliminary data argues against this. The enthusiasm of this reviewer for this application is based on numerous salutatory effects that are associated with treatment of T2DM with metformin. Should the finding corroborate no increase lactic acidosis in T2DM patient with CKD and creatinine values above the cut point, then treatment practice for the patients will be changes and glucose homeostasis (as well as other conditions) will be improved. Another salient feature of this application is excellent mentoring team that the applicant has gathered to help him through this investigation.
1. Candidate:

Strengths

- The candidate obtained his doctor of pharmacy in 2004 from Texas Tech University of Pharmacy and then did a two year pharmacotherapy residency at Texas Health Science Center at San Antonio. During that time he also obtained a MSC from UT, Austin. He subsequently became an assistant professor at Texas Tech School of Pharmacy which has an affiliation with UT-SWMC through a CTSA. He was a clinical scholar at UT-SWMC (funded in part by KL2 mechanism) from 2009-2013 and obtained a MSCS from that institution. He has an excellent record of publication with nine peer-reviewed paper, two as the first author and two as the senior author. The letters of references clearly identify him as a very promising future independent investigator who will significantly contribute to the field of pharmacoepidemiology.

Weaknesses

- None noted.

2. Career Development Plan/Career Goals & Objectives

Strengths

- It is clear that this candidate's goal is to become not only an expert in dependent investigator, but an internationally recognized one, and it is very likely that he will succeed. The prior training and experience have been excellent and the proposed work is very well planned and presented. Both formal course work and didactic plans are well presented. The monitoring and evaluated plan is also well established to with more than adequate interaction between the mentoring team and the candidate.

Weaknesses

- None noted.

3. Research Plan:

Strengths

- The research plan is very well outlined. The candidate will conduct a retrospective cohort study from VA data FY 2003-13. These VA patients will have T2DM and have received new prescription of any glucose lowering medication. The candidate will quantify pattern of use of metformin in these patients with T2DM and CKD. He will then evaluate the association between metformin and adverse events in these patients. He will also assess the association between metformin and the development of microvascular and macrovascular events in these patients. ICD-9 codes will be used to measure outcome variables. Multiple logistic regression model, propensity score analysis and high dimensional propensity score matching and instrument variable analysis will be used to assess the association between metformin and abnormal primary adverse events variables. Adjustment to covariates will be made. The propensity score analysis cohorts for adjustment of multiple confounders and the thigh dimensional propensity score is used to balance measure and unmeasured cofounding in metformin exposed versus non-exposed patients. Overall the research plan is very well described.

Weaknesses

- My only concern is that no mention is made with respect to potential effect of made with respect to potential effect of ethnicity. From the data presented in the inclusion enrollment report, it appears that there are sufficient member of patients in the VA population to examine whether blacks or AA and Hispanics have different adverse effects than the white patients. I believe that this investigation can be accomplished in 3 years.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):
Strengths

- The mentors research qualifications in the area of the investigations are excellent and very appropriate. Each mentor clearly addresses the applicants potential and each is looking forward with great anticipation to conduct this research. The course work and didactic elements are well described. Each mentor has excellent publication record and ample evidence of tutoring previous mentees. Expertise with respect to T2DM, CKD, CV, HSR and CER are clearly evident from the mentors background.

Weaknesses

- None noted.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- The environment at UTSWMC and TTUS of pharmacy and the VA is excellent for the conduct of this investigation. The commitment from the chair and the dean for this candidate to outstanding.

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and Adequate Protections

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable
M1A - Minority and Non-minority, Acceptable
C1A - Children and Adults, Acceptable

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- adequate

Comments on Subject Matter (Required):

- adequate

Comments on Faculty Participation (Required; not applicable for mid- and senior-career awards):

- adequate

Comments on Duration (Required):

- adequate
Comments on Frequency (Required):
  
  • adequate

Select Agents:
Not Applicable (No Select Agents)

Resource Sharing Plans:
Not Applicable (No Relevant Resources)

Budget and Period of Support:
Recommended budget.

CRITIQUE 3:
Candidate: 1

Career Development Plan/Career Goals /Plan to Provide Mentoring: 2

Research Plan: 3

Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 1

Environment Commitment to the Candidate: 1

Overall Impact:
This is a new application for a K08 award from a promising clinical pharmacist who has a goal of defining the appropriate use of metformin in people with diabetes and chronic kidney disease. The research question is important and cogently formulated. It is driven by the fact that current recommendations regarding limiting metformin use in CKD are not supported by data. The mentors and career development plan are strong, the approach for acquiring new skills in the process of conducting a retrospective study is compelling, and there is evidence of strong institutional support. Minor weaknesses included the lack of metrics for defining independence and some potential problems with the study design, but these do not detract substantially from a very strong application.

1. Candidate:

Strengths
  
  • The candidate, a clinical pharmacist, has definite potential to develop as an independent and productive investigator.
  
  • The candidate's academic, clinical, and research record is of high quality.
  
  • There is a clearly articulated commitment to meeting the program objectives.
  
  • Letters of reference address the candidate's potential, accomplishments, and commitment to research, and provide evidence that the candidate has great potential for developing into an independent scholar.

Weaknesses
  
  • None apparent.

2. Career Development Plan/Career Goals & Objectives:

Strengths
  
  • The plan is quite detailed and is likely to contribute to the candidate's development.
  
  • Content, scope, and duration are appropriate.

Weaknesses
• Aside from the metric of writing grants, it is not clear how the candidate will be judged as ready to be independent.
• The plan seems to involve a very large amount of didactic work in the first two years of the program. The clock time involved in these courses is not defined.

3. Research Plan:
Strengths
• The proposed question, whether metformin use should be limited in those with renal dysfunction, is highly relevant to the mission of the NIH.
• The design and methodology are appropriate and well described.
• The plan is appropriate for the objectives of the candidate and appears to be a suitable vehicle for career development.

Weaknesses
• Lower extremity amputations will be used as an outcome for microvascular complications but this may be simplistic. This assumes that these will be neuropathy-related, but that assumption is probably not warranted.
• Macrovascular outcomes variables do not include some of the more standard determinants that could be extracted from the VA database. These would be angina, re-vascularization of any type, etc.
• Only two adverse events will be pursued, lactic acidosis and hypoglycemia. One would predict that gastrointestinal side effects would be very common, and might confound other effects such as hypoglycemia.
• The propensity score does not include family history of diabetes. At least some metformin use may be driven by the desire to prevent diabetes.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):
Strengths
• The mentors are qualified in the areas of health services research and comparative effectiveness research, pharmacoepidemiology, and management of large data sets.
• Each suitably addresses the candidate’s strengths.
• Elements of the career development plan are appropriately described.
• There is clear evidence of research productivity and peer-reviewed support.

Weaknesses
• Plans for defining progress toward independence could be better developed.

5. Environment and Institutional Commitment to the Candidate:
Strengths
• There is clear commitment to ensure 75% effort on the part of the candidate for this program.
• The institutional commitment to this candidate is strong. The candidate has been shifted to the tenure track, a start-up package of $75,000 has been provided, and other aspects of support are clearly defined.
• The environment for scientific and professional development is of high quality.
Weaknesses
- None apparent.

Protections for Human Subjects:
Acceptable Risks and Adequate Protections
- An appropriate description of risks and benefits is provided.

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Inclusion of Women, Minorities and Children:
G1A - Both Genders, Acceptable
M1A - Minority and Non-minority, Acceptable
C1A - Children and Adults, Acceptable
- Inclusions are mentioned appropriately.

Vertebrate Animals:
Not Applicable (No Vertebrate Animals)

Budget and Period of Support:
Recommended budget.

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE
INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE
INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE
INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE

SCIENTIFIC REVIEW OFFICER'S NOTES:
The plans outlined in the application to obtain training in the responsible conduct of research are adequate to satisfy this requirement. See NIH notice NOT-OD-10-019 for information regarding this requirement. http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-019.html. In the event of an award, NIDDK staff must verify that the training requirement will be met.

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.
Recommended direct cost levels are estimated and are subject to further adjustment based on the Institute's standard budget calculation practices.

The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the
overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.