1. TITLE OF PROJECT

   Innovative Immunosuppressive Medication Adherence Mechanisms Among Renal Transplant Recipients

2. FIT INVESTIGATOR

   Name (Last, first, middle): Tsapepas, Demetra, S

   Degree(s): BSc, PharmD

   Position Title: Clinical Pharmacy Manager

   Department, Service, Laboratory, or Equivalent: Department of Pharmacy

   Major Subdivision: Solid Organ Transplantation

   Telephone and Fax (Area code, number, and extension)
   Tel: 212-342-3498 Fax: 212-342-5348 E-mail: det9021@nyp.org

   Has the FIT Investigator received significant peer-reviewed extramural funding as a principal investigator?
   ☐ Yes, if yes, ______________________________________ Granting Agency ____________________ $ Amount
   ☑ No.

   Investigator Mailing Address (street, city, state, zip code):

3. PRINCIPAL MENTOR: Sumit Mohan, MD, MPH Assistant Professor of Medicine

4. TYPE OF AWARD SOUGHT

   _______ R01 _________ K CAREER DEVELOPMENT _______ OTHER

5. POSSIBLE FUNDING AGENCY

   Cardinal Health Foundation

   Other Please Specify

   Grant Number, Grant Name and Website where application materials are found
   E³ (Effectiveness, Efficiency, and Excellence) Patient Safety Grant

6. CATEGORY OF RESEARCH (Used for purposes of assigning investigators to small group and grant proposal groups) Check one.

   _______ BASIC _______ X CLINICAL _______ TRANSLATIONAL T-1

   _______ TRANSLATIONAL T-2 _______ OTHER (SPECIFY______________________)

7. RESEARCH DOMAIN (e.g.: Hematology, Infectious Disease, Pharmacogenetics, Health Outcomes etc)

   PLEASE SPECIFY:

   Solid Organ Transplantation Outcomes

ASSURANCE OF COMPLIANCE

By signing below, I, my Immediate Supervisor/Chair, and Mentor indicate commitment and support for this program application, and acknowledge the resources necessary to fulfill the program requirements, if awarded.

Demetra Tsapepas, Clinical Pharmacy Manager 3/28/2014

Marianne Billeter, Director- Clinical Pharmacy 3/28/2014

Sumit Mohan, Assistant Professor in Medicine 3/28/2014
PERSONAL STATEMENT (NOT TO EXCEED ONE PAGE)

Following completion of my doctor in pharmacy degree from the University of the Sciences in Philadelphia in 2006, I pursued post-graduate training and completed both a pharmacy practice and specialty residency program in solid organ transplantation at NewYork-Presbyterian Hospital. As my career in the field of solid organ transplantation has evolved, I am seeking an opportunity to pursue training in research grant writing.

I am currently the Clinical Pharmacy Manager for Renal and Pancreas Transplantation at NewYork-Presbyterian Hospital and the Residency Program Director of the Post-Graduate Year 2 specialty pharmacy residency program in solid organ transplantation. As a clinical pharmacist and a member of a large multidisciplinary team, I am responsible and involved with providing pharmaceutical care to renal and pancreas transplant recipients. Additionally, I am involved with organizing both student and residency learning programs, pharmacy staff training and management, as well as, serving as the secretary of the Solid Organ Transplant Subcommittee, and pursuing Quality Assurance and Performance Improvement (QAPI) initiatives to optimize safe and cost effective care. Throughout my training and subsequent clinical practice, I have maintained a significant academic interest with regards to research and I continue to be inspired by the pursuit of clinical research and publication as a means to improve patient care and pharmacist involvement in healthcare.

My involvement with professional organizations including the American College of Clinical Pharmacy, specifically the Practice and Research Network for Immunology and Transplantation and the American Society of Transplantation pharmacy community of practice and membership committee, have facilitated collaboration and accelerated pursuit of scholarship. Currently, through a collaboration facilitated by networking in these communities, I am in the midst of producing a manuscript with colleagues to evaluate gastrointestinal prophylaxis protocols for solid organ transplant recipients. I expect that my involvement in these organizations will continue for the duration of my professional career.

I strongly feel that scholarship and the pursuit of education and academic achievement is the lifeblood of the healthcare provider where one develops a self-sustaining drive to become a better practitioner. As such, scholarship and research are a significant focus of my professional life. My Curriculum Vitae outlines in detail previous endeavors through lecturing, publication, participation in national conferences (platform and poster presentations) and development of continuing education opportunities. My major interests include the solid organ transplant population, immunosuppressive strategies and outcomes, infectious disease, and medication adherence.

My philosophy for scholarship, research and publication are driven by a principle once bestowed upon me: the pursuit of scholarship requires that you are constantly accomplishing the following three components; (1) developing research ideas and/or collecting data; (2) drafting a manuscript; and (3) having a current manuscript submission. By following this simple outline, I feel that my plan for scholarship and research is incredibly dynamic and continuously evolving. I am looking to now develop skills for obtaining funding that will enable me to more effectively conduct outcomes research in a manner that coincides with applicability in a challenging and unpredictable healthcare environment.
LETTER OF SUPPORT, IMMEDIATE SUPERVISOR/DEPARTMENT CHAIR OR DEAN (NOT TO EXCEED ONE PAGE)

To Review Committee:

I am writing my support for Dr. Demetra Tsapepas application to the Focused Investigator Training (FIT) program. During the time I have supervised Dr. Tsapepas, she has shown the uncanny ability to generate clinically relevant research questions. Her research is in a breadth of areas including comparisons of medication protocols on patient outcomes, pharmacoeconomic analysis, and utilization of information technologies to enhance patient care. Dr. Tsapepas is able to garner multidisciplinary support to carry out her research endeavors and implement changes to clinical practice when necessary. She is also able to efficiently manage limited resources while carrying out her projects.

Dr. Tsapepas is frequently sought out to help guide new clinical pharmacists with various projects. She is able to help refine the development and analysis of their research projects. Dr. Tsapepas is also a good resource for manuscript development and submission.

I feel that Dr. Tsapepas will personally and professionally benefit from participation in the FIT program. She will be able to refine her skills in protocol development to explore more complex research questions. The FIT program will also help her as she begins to seek external funding for her research. Currently her research is primarily supported with Institutional resources and external funding will be the next step in her research career. NewYork-Presbyterian Hospital will also benefit from Dr. Tsapepas participation in the FIT program as this will enhance her ability to mentor young practitioners in the research process as they begin their careers in clinical pharmacy.

I fully support and highly recommend Dr. Tsapepas for the FIT program.

Marianne Billeter, Pharm.D, BCPS
Director, Clinical Pharmacy Services and Education
NewYork-Presbyterian Hospital
mab9331@nyp.org
(646) 317 – 4922
LETTER OF SUPPORT FROM PRINCIPAL MENTOR (NOT TO EXCEED ONE PAGE)

To Whom It May Concern:

It gives me immense pleasure to write this letter in strong support of Dr. Demetra Tsapepas for the Focused Investigator Training (FIT) program. Demetra's clinical role is that of the Clinical Pharmacy Manager for the Kidney and Pancreas Transplant program at Columbia University Medical Center in New York over the past 5 years. As an attending transplant nephrologist with a focus on outcomes research in renal transplantation at Columbia University Medical Center, I have been responsible for teaching and evaluating medical students, residents, nephrology as well as transplant fellows in addition to teaching outcomes research methodology at several levels. I have collaborated extensively with Demetra both in the clinical setting as well as for clinical outcomes research – and these provide me more than enough opportunity to identify her potential to excel at clinical research.

Over the past 3 years, we have collaborated on numerous projects focused on improving the care of our patients as well as the outcomes following kidney transplantation. These efforts have demonstrated Demetra's intense commitment to improving patient care while underscoring her interest in clinical research. Her interest in research is underscored by the fact that she has co-authored 14 peer reviewed manuscripts in addition to numerous presentations of her findings at the annual American Transplant Congress and the annual meetings of the American Society of Nephrology. We have collaborated on 6 of these manuscripts and at least 10 conference presentations over the last 3 years giving me ample opportunity to observe her commitment to clinical research.

Her commitment to clinical excellence as well as attention to detail and her enthusiasm for clinical outcomes research provide ample evidence of the potential for Demetra to not only excel in her chosen field but to develop in to a thought leader in the field. An example of her ability to integrate her approach to clinical care with her passion for influence patient outcomes is on display in analysis and subsequent publication of “Impact of small variations in the delivered dose of rabbit anti-thymocyte induction therapy in kidney transplantation with early corticosteroid withdrawal” in the journal Transplantation which remains the most widely cited journal in the field. In this analysis, Demetra demonstrated the impact of small errors in the dosing of thymoglobulin as an induction agent is associated with increased rates of rejection and established clinical interventions that prevent this.

Demetra is a highly motivated clinical pharmacist with a passion for improving clinical outcomes. Her interest in pursuing a career that is focused on clinical research represents the ideal candidate that is most likely to benefit from, and implement, from training programs like the FIT program to continue to expand her repertoire of research related skills. As a result, I strongly support her application to the FIT program. Please do not hesitate to contact me if you need further information at 917-450-0834 (cell) or email me at sm2206@columbia.edu

Sincerely,

Sumit Mohan, MD, MPH, FASN
Assistant Professor of Medicine
Division of Nephrology, Department of Medicine
Columbia University Medical Center, New York, NY.
Nondisclosure Agreement

In order to fully participate in the Focused Investigator Training (FIT) Program, I will receive information ("Information") that is proprietary to investigator attendees and participants and should be considered confidential.

I agree to keep confidential the information that I will receive regarding the grant proposals, including, but not limited to any written or verbal communications, any written documents, or any other material that I will receive from ACCP or other attendees in conjunction to the FIT Program. This obligation of confidentiality does not include information which, at the time of disclosure to me, (a) is published, known publicly, or is already in the public domain; (b) is published or becomes known publicly through no fault of my own; (c) is already known by me as evidenced by written records; or (d) is disclosed to me by someone other than ACCP who is not under any obligation of confidentiality.

This agreement shall commence on the day it is executed by me and shall expire at the end of one year from the date of its execution.

Demetra Tsapepas

Investigator's name

Investigator's signature

3/28/2014

Date

Please sign and return electronically to:

Carla Scarborough
cscarborough@accp.com
Adherence to medication therapy is a critical component in the treatment of chronic conditions and is essential to optimize both therapeutic and patient outcomes. The World Health Organization defines adherence as “the extent to which a person’s behavior corresponds with the agreed recommendations from a healthcare provider” (1). Solid organ transplant (SOT) recipients represent a unique patient population requiring indefinite and complex immunosuppressive therapies to sustain allograft function. Poor adherence to immunosuppressive therapy after transplantation is a recognized problem associated with a significant risk of graft loss, increased comorbid diseases, increased medical costs, and even death. Clinicians are in need of effective immunosuppressive adherence intervention programs or tools to promote therapeutic success, improve quality of life, and reduce healthcare utilizations and costs. Health information technology (HIT) and digital health patient engagement tools, such as Glowcap, hold the potential to improve the quality and safety of health care and to improve medication adherence in this setting. Empowerment of patients with simple tools will allow progression of HIT solutions in the realm of enhancing patient engagement, not just patient utilization and lead to innovative practices in healthcare organizations.

The current project is designed as an open label, prospective, randomized, controlled, cross-over, feasibility trial of first-time, adult, renal transplant recipients who are maintained on a tacrolimus-based immunosuppressive regimen at Columbia University Medical Center; target enrollment is 30 recipients. Patients who consent will be randomized to one of three treatment arms: (1) standard of care education, or (2) Glowcap without alerts, or (3) Glowcap with alerts; after three months patients in groups two and three will cross-over to the opposite treatment arm. Adherence will be measured by counting the number of properly taken doses (Glowcap reports), evaluating tacrolimus level variability (>10% variability from target goal deemed as nonadherent), and tacrolimus pill counts and refill history from the outpatient pharmacy where patients with any discrepancy will be deemed nonadherent.

Use of technology with simple-to-use electronic pill bottle caps (GlowCap) is a novel method improving and tracking medication adherence. Identification of methods that can lower the incidence of immunosuppressive medication non-adherence is essential if we are to improve the long-term graft survival and allograft outcomes following renal transplantation. The objectives of this project are to investigate the use of electronic means to engage and remind patients to take their immunosuppressive medications in order to promote adherence and ensure improved allograft outcomes. The current study is the first to combine medication adherence evaluation with objective measures including the actual medication serum concentrations.
## DETAILED BUDGET FOR INITIAL BUDGET PERIOD

**DIRECT COSTS ONLY**

FROM 1/1/2015 THROUGH 6/30/2015

List PERSONNEL (Applicant organization only)

Use Cal, Acad, or Summer to Enter Months Devoted to Project

Enter Dollar Amounts Requested (omit cents) for Salary Requested and Fringe Benefits

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### CONSULTANT COSTS

Statistician

$2,500.00

### EQUIPMENT (Itemize)

- GlowCaps ($25.00 / bottle) x 30 subjects
- Computer and server

$750.00

### SUPPLIES (Itemize by category)

- Office supplies (pens, copies)
- Conference abstract submission
- Conference poster printing
- Publication page fees

$250.00

$75.00

$350.00

$500.00

### TRAVEL

American Society of Transplantation 2016 (PI and Mentor)

$3,500.00

### INPATIENT CARE COSTS

$0.00

### OUTPATIENT CARE COSTS

$0.00

### ALTERATIONS AND RENOVATIONS (Itemize by category)

### OTHER EXPENSES (Itemize by category)

- IRB Submission and Review Fee
- Spanish translation per page ($100.00); 5 page consent form

Waived

$500.00

### CONSORTIUM/CONTRACTUAL COSTS

**DIRECT COSTS**

$11,425.00

### TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD

$11,425.00
BIOGRAPHICAL SKETCH

Provide the following information for yourself, your mentor, and other key investigators.
Follow this format for each person.

DO NOT EXCEED FOURS PAGES EACH.

NAME
Demetra Tsapepas

POSITION TITLE
Clinical Pharmacy Manager, Solid Organ Transplantation

eRA COMMONS USER NAME (credential, e.g., agency login)

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)

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<td>Specialty Residency in Solid Organ Transplantation</td>
<td>06/08</td>
<td>Solid Organ Transplantation</td>
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NOTE: The Each Biographical Sketch may not exceed four pages. Follow the formats and instructions below. A sample sketch may be reviewed at http://grants.nih.gov/grants/funding/phs398/phs398.html

A. Personal Statement
The goal of the research proposal is to investigate novel approaches to multidisciplinary care and to enhance cost effectiveness of treatment approaches at our transplant center. I have extensive experience working in the field of solid organ transplantation and have responsibilities in direct patient care, policy and guideline development for medication use, and education of pharmacy students and residents. My strong interest in research stems from involvement in quality initiatives, which are an integral part of practice in the field of solid organ transplantation. I have led and participated in retrospective outcomes analyses as well as prospective pharmacokinetic studies and produced several peer-reviewed publications from each project. My background and experiences in education and research will allow me to effectively mentor and participate in the proposed research. I have laid the groundwork for the proposed research by developing an outcomes database that will be used as a foundation of information that will be evaluated in this study. In addition, I have successfully collaborated with other individuals that are part of our current research team and we have established a stable approach to conducting research.

B. Positions and Honors

Positions and Employment
2013 – Program Director: PGY-2 Pharmacy Residency in Solid Organ Transplantation NewYork-Presbyterian Hospital
2011 – Affiliate Assistant Clinical Professor St. Johns University College of Pharmacy and Allied Health Professionals Department of Clinical Pharmacy Practice

Other Experience and Professional Memberships
2013 – American Society of Transplantation Membership committee, appointed member 2013 – 2016

Honors
2006 – Facts and Comparisons Award for Excellence in Clinical Communications
2006 – B. Morris & Edna S. Kratz Student Achievement Award
2004 – Rho Chi Pharmacy Academic Honor Society, Alpha Tau Chapter, Philadelphia College of Pharmacy
Student Government Association Representative
2003 – Blanche Gardner Whitecar Memorial Academic Scholarship
1999 – L & V Rudolph Academic Scholarship for Biology

C. Selected Peer-reviewed Publications


D. Research Support

Ongoing:
An open research protocol at Columbia University Medical Center: “Renal and pancreas transplant quality dashboard outcomes analysis” is IRB approved
Role: Co-investigator
The above protocol allows our use of a quality derived transplant recipient database with population data for research on management of solid organ transplant recipients. The goals are directed at improving post-transplant outcomes such as those being evaluated in the current research proposal.
BIOGRAPHICAL SKETCH

Provide the following information for yourself, your mentor, and other key investigators. Follow this format for each person. DO NOT EXCEED FOUR PAGES EACH.

NAME
Sumit Mohan

POSITION TITLE
Assistant Professor of Medicine

eRA COMMONS USER NAME (credential, e.g., agency login)
MOHANS

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)

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NOTE: The Each Biographical Sketch may not exceed four pages. Follow the formats and instructions below. A sample sketch may be reviewed at http://grants.nih.gov/grants/funding/phs398/phs398.html

A. Personal Statement
As a clinical nephrologist and epidemiologist, I have a broad interest in kidney disease, renal transplantation and factors that to the identification of factors and processes that can improve clinical outcomes. In particular, I am interested in issues surrounding recovery of renal function, organ allocation and utilization as well as the development of strategies for optimizing organ allocation and lowering disparities among patients with kidney disease with a goal to improving patient outcomes.

B. Positions and Honors
2006 – Assistant Professor of Clinical Medicine, Columbia University College of Physicians & Surgeons, New York, NY
2006 – 10 Assistant Attending, Harlem Hospital Center
2007 – 10 Associate Program Director, Internal Medicine Residency Program
2010 – Assistant Attending, New York Presbyterian/ Columbia University Medical Center

Other Experience and Professional Memberships
2004 – Member, American Society of Nephrology
2004 – Member, National Kidney Foundation
2005 – Member, International Society of Nephrology
2010 – Member, American Society of Transplantation
2013 – Editorial board member, Transplantation

Honors
2000 Graduate School Faculty Exchange Scholarship, University of Northern Colorado and Manipal University
2007 Teacher of the Year, Department of Medicine, Harlem Hospital Center
2008 Teacher of the Year, Department of Medicine, Harlem Hospital Center
2008 Distinguished Educator Award, Columbia University College of Physicians and Surgeons
2009 Teacher of the Year, Department of Medicine, Harlem Hospital Center
2011 Chair, Data Committee, Fistula First Breakthrough Initiative, Center for Medicare & Medicaid Services
2013 Member, Virginia Apgar Academy of Medical Educators, Columbia University College of Physicians & Surgeons
C. Selected Peer-reviewed Publications


D. Research Support

**Ongoing research support**

**Advancing Research in Transplantation Science Award**

mTOR inhibitors in the prevention of BK Nephropathy: a randomized clinical trial of efficacy and safety. The goal of this study is to compare two different strategies of immunosuppression reduction in the management of renal transplant recipients with BK viremia to prevent the development of BK nephropathy.

Role: PI

**Investigator initiated research grant – Gambro Inc.**

Using NGAL to guide continuous renal replacement therapy cessation.

The goal of this pilot study is to study changes in serum and urine NGAL during continuous renal replacement therapy for patients with acute kidney injury in order to develop a biomarker guided approach to cessation of therapy.

Role: PI
Immunosuppressive Therapy Adherence Among Renal Transplant Recipients
Introduction

Medication use and health care costs in the United States are on the rise. Adherence to medication therapy is a critical component in the treatment of chronic conditions and is essential to optimize both therapeutic and patient outcomes. The World Health Organization defines adherence as “the extent to which a person’s behavior corresponds with the agreed recommendations from a healthcare provider” (1). Solid organ transplant (SOT) recipients represent a unique patient population requiring indefinite and complex immunosuppressive therapies to sustain allograft function. A conventional maintenance immunosuppressive regimen typically consists of a calcineurin inhibitor, an adjunctive antiproliferative agent, and possibly corticosteroids. In an effort to reduce complications associated with immunosuppressive therapies, renal transplant patients frequently require an anti-microbial regimen to prevent infectious complications, antihypertensives, acid-suppressive agents, antidiabetics, and supportive therapies (i.e., aspirin, multivitamins, laxatives, and analgesics).

Poor adherence to immunosuppressive therapy after transplantation is a recognized problem associated with a significant risk of graft loss, increased comorbid diseases, increased medical costs, and even death (2). Nonadherence to transplant regimens due to complexity, large pill burden, and cost introduces the potential for adverse outcomes and must be continuously evaluated to ensure long-term viability of an allograft. Nonadherence incidence estimates vary according to the methodology and evaluation criteria (self-assessment by the patient, physician reports, medication possession, electronic monitoring caps, and pharmacy refill data), but range from 2% to 68% (2-6).

Despite a comprehensive psychosocial assessment by a multidisciplinary care team, the risk of nonadherence in renal transplantation remains high and reasons are multifactorial (7-10). Patient-specific risk factors are influenced by the patient’s attitude, habits, and degree of illness. In addition, poor insight, negative attitude or poor subjective response towards medications, and previous history of medication nonadherence have correlated to poor medication adherence (11). Some studies have cited a lack of social support, younger age, male gender, minority status, low socioeconomic status, and poor social functioning as potential contributors (12-15). Lastly, environmental factors predictive of nonadherence include poor alliance with a therapist or clinician, less outpatient contact, inadequate discharge planning, or a poor aftercare environment (11). Ideally, these factors would be identified prior to transplantation, and patient-specific interventions could take place to reduce the risk of post-transplant nonadherence.

A major component and expectation of medication education is highlighting the importance and patient responsibility of adherence to the prescribed medication regimen. Clinicians are in need of effective immunosuppressive adherence intervention programs or tools to promote therapeutic success, improve quality of life, and reduce healthcare utilizations and costs. Health information technology (HIT) and digital health patient engagement tools hold the potential to improve the quality and safety of health care and to improve medication adherence in this setting. Empowerment of patients with simple tools will allow progression of HIT solutions in the realm of enhancing patient engagement, not just patient utilization and lead to innovative practices in healthcare organizations. Use of technology with simple-to-use electronic pill bottle caps (GlowCap) is a novel method improving and tracking medication adherence. The Glowcap issues a series of increasingly insistent reminders for a patient to take their medication. The objectives of this project are to investigate the use of electronic means to engage and remind patients to take their immunosuppressive medications in order to promote adherence and ensure improved allograft outcomes.
Enhancing Immunosuppressive Therapy Adherence Among Renal Transplant Recipients

Specific Aims
HIT has the potential to facilitate and enhance communication between patients and their health care providers. The purpose of this protocol is to evaluate the efficacy of GlowCaps for immunosuppressive medication adherence among renal transplant recipients. Improvement in adherence will be measured by three methods: (1) GlowCap reports recording the timing of each bottle opening, (2) variability in tacrolimus whole blood concentrations, and (3) pill counts and refill information from the transplant specialty pharmacy.

Hypothesis #1: Healthcare technologies will enhance medication adherence and allograft outcomes following renal transplantation.

Aim 1. Patients who are monitored or receiving alerts to take their medications will have a higher rate of medication adherence.

Aim 2. Patients randomized to GlowCap pill bottles will have lower biopsy proven acute rejection rates at 3 and 6 months post-transplantation.

Hypothesis #2: Degree of variability in tacrolimus trough concentrations, pill counts, and medication refill timing are good measures of medication adherence.

Aim 3. Patients with high variability (>10%) of goal trough concentrations will display nonadherence to their medication regimen.

Aim 4. Patients with inconsistent pill counts and refill measures display nonadherence to their medication regimen.

Research Strategy
Our current standard immunosuppression protocol at Columbia University Medical Center (CUMC) includes tacrolimus and mycophenolic acid with early steroid withdrawal. In addition, we use antimicrobial agents such as trimethoprim/sulfamethoxazole (dapsone for sulf allergy), valganciclovir, and nystatin for prophylaxis of opportunistic infections. CUMC has a reputable track record of participation in clinical trials and has also well-established and tested early corticosteroid withdrawal protocols, making us an ideal center for the proposed study. New York Presbyterian Hospital/CUMC performs nearly 250 renal transplants annually with an approximate annual incidence rate for nonadherence of 2%. We propose to identify and enroll 30 renal allograft recipients and randomize these patients to a control arm of standard medication education practices, and one of two treatment arms where patients would be provided with a GlowCap pill bottle to determine if the intervention with an electronic pill bottle improves the rates of medication adherence measured by tacrolimus whole blood trough concentration goal maintenance (C₀) 10–12ng/mL [90% confidence level between 80 and 125% (or 90 and 110%) and less than 10% variability between measurements]. In addition, we will correlate these findings with refill data reports from the outpatient specialty pharmacy. Patients in the two intervention arms will cross over after a period of three months to evaluate the impact of the pill bottle alerts on medication adherence.

Innovation
Identification of methods that can lower the incidence of immunosuppressive medication non-adherence is essential if we are to improve the long-term graft survival and allograft outcomes in renal transplantation. Our proposal is the first attempt to use a randomized control trial study design with a cross-over method to test the improvements of monitoring and intervention for medication adherence using an electronic pill bottle in comparison to the current standard practice of
patient education. Unlike previous studies, our cross-over design will allow for an evaluation of electronic pill bottles that are passively monitoring medication adherence as compared to active intervention to improve medication adherence. In addition, our collaboration with a specialty pharmacy is a unique approach that will allow us to complement our study of efficacy and safety with a concomitant effort to further validate these findings with correlation of tacrolimus trough concentrations as well as pill counts and refill timings.

**Approach**

**Study design**
An open label, prospective, randomized, controlled, cross-over, feasibility trial design will be used. All patients who undergo renal transplantation at CUMC and fulfill the inclusion criteria will be approached for participation in the study. Target enrollment 30 recipients.

**Inclusion criteria**
1. Adult patients over 18 years of age.
2. Renal transplant recipients.
3. Transplanted at CUMC.
4. Participants must live within 50 miles of the transplant center.
5. All participants must be willing and able to provide informed consent.

**Exclusion criteria**
1. Patients with previous transplant(s).
2. Patients on a non-tacrolimus based immunosuppressive regimen.
3. Patients receiving medications that have known drug interactions with tacrolimus at any time post-transplantation.
4. Patients who take medications more than two times daily at any point in the study.
5. Patients who are blind and/or deaf.
6. Patients with significant cognitive deficits.

Patients who consent will be randomized to one of three treatment arms: standard of care education, or Glowcap without alerts, or Glowcap with alerts using a predetermined randomization schedule.
Group 1:
- The GlowCap bottle will not be used in this treatment arm.
- Patients will learn the importance of medication adherence during teaching sessions as part of our standard of care at the transplant center.

Group 2:
- The GlowCap bottle will passively track medication adherence over the course of the study.
- The pill cap will collect data, but will not provide any visual or auditory alerts for the subject and they will be monitored randomly at any point in the study period.
- Patients will learn the importance of medication adherence during teaching sessions as part of our standard of care at the transplant center.
- After 3 months, patients will cross-over into group 3.

Group 3:
- The GlowCap bottle will passively track medication adherence over the course of the study.
- Subjects in this group will receive daily visual, auditory, and phone call reminders to take their medication via the GlowCap system if they fail to take their tacrolimus at the scheduled dose time.
- Subjects will receive Weekly and Monthly Progress Reports by email and mail, respectively. Reports will include information about medication adherence and target goals. Monthly Progress Reports will also be sent to the subject’s primary care physician.
- Subjects will choose, a friend or family member who will receive a Weekly progress report by email.
- After 3 months, patients will cross-over into group 2.
Outcome measures

Adherence measurement: investigators will measure adherence by counting the number of properly taken doses throughout the study.

Tacrolimus level variability: tacrolimus levels will be deemed variable if there are levels with differences of >10% higher or lower than the mean of all tacrolimus trough concentrations.

Pill counts and refill data: tacrolimus pill counts will be assessed on a weekly basis and refills monthly. Patients with any discrepancy will be deemed nonadherent.

Data and Safety Monitoring

Our proposed safety-monitoring plan for this study consists of continuous, close monitoring by the Principal Investigator in conjunction with a named Safety Officer. There will be prompt reporting of all adverse events to the Safety Officer as well as prompt reporting of unanticipated problems, serious adverse events, and other risk-related events to the Columbia University Medical Center IRB, in accordance with their reporting policy. This plan is deemed appropriate because the study does not involve high risk or vulnerable populations; it is a single site study of short duration.

The Safety Officer will act in an advisory capacity to monitor patient safety and evaluate the efficacy of the interventions described in this study for all subjects.

Safety Monitoring Endpoints: Safety monitoring will involve the regular monitoring of vital signs, physical exam along with the standard blood and urine testing consistent with the care of a renal transplant patient. All these adverse events are currently monitored for, as part of the standard of care. Adverse events will be reported as incidence rates per treatment group.

Definitions of Adverse Events

An "unanticipated problem" is any incident, experience or outcome during the study that: A. Is unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approved protocol and informed consent document, and (b) the characteristics of the subject population being studied; and B. Related or possibly related to participation in such research (i.e., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures in such research); and C. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized. All unanticipated problems will be reported promptly to the IRB. All unanticipated problems will also be reported to the safety officer and the funding entity.

Statistical Analysis

Analysis of categorical data will be performed using Chi squared and Fisher’s exact test as appropriate. Continuous variables will be compared using the t-test. The rates of nonadherence from pill counts and medication refill times will be compared using Chi squared analyses and the tacrolimus level variability between the groups that will be compared using the t-test. Comparison of allograft and patient survival will be performed using time-to event analyses and compared using the Log rank test and a Cox proportional hazards model.
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Power Analysis
This study is designed to identify if electronic pill bottle (GlowCap) alerts will improve immunosuppressive medication adherence rates. Currently, at CUMC, approximately 2% of patients are nonadherent despite standard medication teaching and demonstration of the importance of immunosuppression. A sample size of 30 patients will be enrolled in this feasibility study so that we are able to determine how to best proceed with a larger study design.

Timelines
With the sample size required and our current transplant rate, we expect to complete patient recruitment within 6 months. Interim analysis will be performed after the recruitment of 9 patients (3 in each group) for safety endpoints. Completion of data collection and adjudication of endpoints will be timed to allow prompt data analysis at the completion of the stimulated follow up of 6 months for the last patient. We intend to present findings from our study at the American College of Clinical Pharmacy, the American Transplant Congress, the American Society of Nephrology in addition to publishing the results of our study as a manuscript in a relevant journal.

- Estimated date first patient enrolled: January 2015
- Estimated date of enrollment of the last patient: June 2015
- Estimated date of last follow up: December 2015 (6 months from date of last enrollment)

Potential Pitfalls and solutions
1. Inadequate recruitment
   Recruitment goals will be reviewed every month to ensure that we are on track to complete enrollment within the first 6 months. In the event that we are not, we will consider extending our recruitment duration to 12 months.

2. Patient disparities
   There are a variety of sociocultural, economic, human factors, and environmental issues that could lead to differential benefits across populations. For example, the benefits of HIT may disproportionately accrue to individuals and populations cared for by health care organizations that are best positioned to implement and use new technologies. Meanwhile, a digital divide persists among older adults, racial and ethnic minorities, physically disabled, poor, and those with limited English proficiency. GlowCaps are relatively simple to use, however patients that have issues with using the bottles will be provided additional training and information and will be requested to have a family member present for education as well.

3. Loss to follow up
   Given the duration of follow up and the likelihood that this is an early complication after transplantation, it is anticipated that all patients will continue to be followed with a low loss to follow up rate. In the rare event that a patient does not want to return to their primary transplant center for follow up, records will be obtained, with permission from the primary nephrologist in the community.

4. Potential confounders
   Some patients may receive medications that could interact with tacrolimus for treating infections or blood pressure and as a result potentially confound the outcomes. While efforts will be made to try to minimize these events by discussing alternative therapeutic options with the treating physician, we will record/report these events and perform our analysis on an intent-to-treat basis.

5. Cross-over between treatment arms
In the event that a patient is not responding to the strategy that they are assigned to, the treating physician may either switch them to a strategy in the other arms or to a completely different strategy. All patients who experience a cross-over and/or changes in therapy will be deemed as treatment failures in an intent-to-treat analysis. However, they will continue to be followed and changes in therapy will be reported as part of the overall analysis.

**Description of Facilities**

**Department of Pharmacy at NewYork-Presbyterian Hospital**

The Department of Pharmacy at NewYork-Presbyterian Hospital is supported by highly trained pharmacists and clinicians who work closely with other health care providers to ensure optimal pharmaceutical care to patients. The Department of Pharmacy continually embraces visionary thinking, thoughtful management and new technology to maintain its distinction as a leader in operational and clinical excellence. Policies, guidelines, programs and services ensure that patients receive appropriate pharmaceutical care as measured against accepted standards. The quality, effectiveness, and appropriateness of the services are monitored and reviewed by departmental committees and the Formulary and Therapeutics Committee.

**Renal Transplantation at Columbia University Medical Center**

Established in 1969 by Mark Hardy, the kidney transplant program at CUMC has a long history of innovation. Currently headed by David Cohen and Lloyd Ratner, it remains dedicated to providing every possible opportunity for transplantation, and to overcoming the most significant challenges in kidney transplantation. The team at CUMC has developed innovative strategies to increase access to transplantation for the sickest patients, and those with immunologic incompatibilities. The programs are national leaders in developing treatment strategies that have facilitated ABO incompatible transplantation, transplantation across positive cross-match, desensitization protocols and paired exchange transplantations. CUMC is a national leader in performing multiple paired living donor kidney transplantation, a revolutionary approach that may dramatically improve opportunities for patients in need of kidney transplants to find a compatible donor.

**Data Confidentiality**

All data will be kept in a password-secured database. All patients will be assigned an alphanumeric code as a subject number. A separate code sheet linking the subject number to the medical record number and patient name will be kept in a separate password-protected file. The separate code sheet and any/all protected health information will be accessible only to the principal investigator. The code sheet will be destroyed at the completion of the study.

**Privacy Protections**

The consent form discloses to potential participants the individuals and/or agencies that are able to look at and copy research records; namely, the investigator, study staff and other medical professionals who may be evaluating the study - Authorities from Columbia University and New York Presbyterian Hospital, including the Institutional Review Board - The United States Food and Drug Administration (FDA) - The sponsor of this study, including persons or organizations working with or owned by the sponsor. Information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. In addition to confidentiality disclosures described in the consent form, subjects will also be given a study specific HIPAA Form which must be signed before participating in this study.
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References


