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Hybrid Effectiveness-Implementation Study to Improve Clopidogrel Adherence

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STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

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Protocol

Project Title: Hybrid Effectiveness-Implementation Study to Improve Clopidogrel Adherence

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I. Hypotheses and Specific Aims

Clopidogrel is a critical therapy following percutaneous coronary intervention (PCI) with stent placement and reduces the risk of stent thrombosis, myocardial infarction (MI) and mortality (1-7). Despite the importance of clopidogrel following stent implantation, multiple VA and non-VA studies have demonstrated adherence gaps to clopidogrel, both delays in initial filling of the medication at hospital discharge (~16%) and early discontinuation during longitudinal use (up to 30%). These studies demonstrate clear evidence and guideline consensus supporting clopidogrel adherence, adverse consequences of non-adherence, and the care gap that will be the focus of this project.

Non-adherence to clopidogrel is common in the VA. From the VA's Cardiovascular Assessment Reporting and Tracking in the Cardiac Catheterization Laboratory (CART-CL), we found that 22.4% of patients delayed filling clopidogrel following PCI in FY09 with delay defined as filling a clopidogrel prescription > 1 day after discharge. Further, approximately 1/3 of patients discontinued clopidogrel early (< 9 months) prior to the recommended one year treatment duration. Even among patients without an initial delay in clopidogrel filling, almost 40% of patients discontinued clopidogrel by 9 months of hospital discharge. At the hospital level, there is also significant variation in clopidogrel non-adherence. On average at each PCI facility, 18.9% of patients delay filling clopidogrel, and 30-40% discontinue clopidogrel early by 9 months. These findings highlight significant opportunities to improve clopidogrel adherence following stent implantation in the VA.

Therefore, our main objective is to conduct a type 1 hybrid effectiveness/implementation study to test the effectiveness of a successfully-piloted, evidence-based, multi-faceted intervention to improve patient adherence to clopidogrel following PCI. The proposed study will test the hypothesis that a successfully-piloted, evidence-based, multi-faceted intervention targeting veterans following PCI procedure improves adherence to clopidogrel, reduces bleeding, myocardial infarction, stroke, and mortality among these patients, and is cost-effective. The proposed intervention will be based on the Chronic Care Model and will build on our pilot work as well as will leverage the VA's CART-CL, a uniform cath lab procedure reporting tool at all VA cath labs. The study will be evaluated using the RE-AIM framework consisting of the following components, reach, effectiveness, adoption, implementation and maintenance. The intervention will adapt elements of prior successful intervention, including patient education, collaboration between cath lab clinicians and impatient/outpatient pharmacy teams, and tele-monitoring via interactive voice response (IVR) technology. This type I hybrid effectiveness/implementation study will be tested at 16 sites randomized to intervention with an average of 90 patients per site per 6 month period versus usual care.

Specific Aims:

1. To evaluate current practices at VA PCI facilities (n=16) to enhance adherence to clopidogrel, both at hospital discharge and during longitudinal follow-up.
2. To implement the multi-faceted intervention at 16 total sites through 4 roll-out phases (4 sites during each roll-out) in a randomized stepped wedge trial design.

3. To assess barriers and facilitators to intervention implementation during each roll-out phase through semi-structured interviews and incorporate lessons learned from each roll-out phase into subsequent roll-out phases.
4. To determine the effectiveness of a successfully-piloted, evidence-based, multi–faceted intervention versus usual care for improving clopidogrel filling at hospital discharge and adherence to clopidogrel (primary outcomes).
5. To determine the effectiveness of a successfully-piloted, evidence-based, multi–faceted intervention versus usual care for reducing the combined cardiovascular endpoints of bleeding, myocardial infarction, stroke, and mortality (secondary outcomes).
6. To assess the incremental cost-effectiveness of the successfully-piloted, evidence-based, multi–faceted intervention compared with usual care.

II. Background and Significance:

PCI is a common invasive cardiovascular procedure performed in the VA with over 13,000 procedures in FY10. Clopidogrel is a critical adjuvant therapy following PCI with stent placement and is generally recommended for up to 1 year following the procedure (1). This is a class I recommendation in the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, which is the highest level of recommendation in the guidelines (1). Despite the evidence supporting clopidogrel use, studies both outside and within the VA suggest that poor adherence to clopidogrel is common. However, prior interventions targeting non-adherence have not specifically focused on clopidogrel adherence among PCI patients.

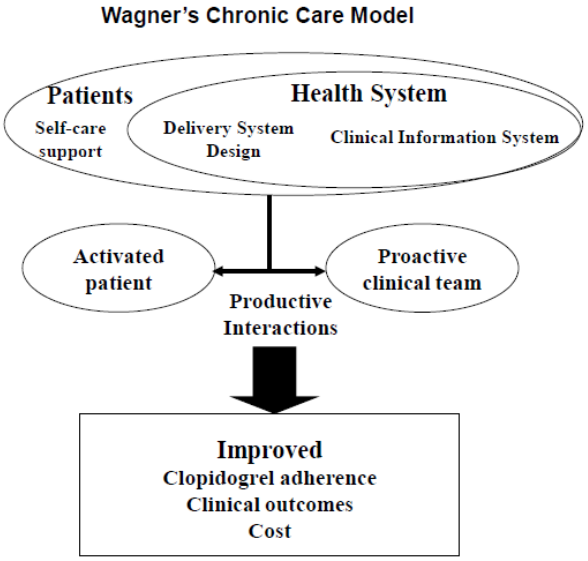
Non-adherence to clopidogrel among PCI patients is common in the VA. From CART, we found that 22.4% of patients delayed filling clopidogrel following PCI in FY09 with delay defined as filling a clopidogrel prescription > 1 day after discharge. Further, approximately 1/3 of patients discontinued clopidogrel early (< 9 months) prior to the recommended one year treatment duration. Even among patients without an initial delay in clopidogrel filling, almost 40% of patients discontinued clopidogrel by 9 months of hospital discharge. At the hospital level, there is also significant variation in clopidogrel non-adherence. On average at each PCI facility, 18.9% of patients delay filling clopidogrel, and 30-40% discontinue clopidogrel early by 9 months. These findings highlight significant opportunities to improve clopidogrel adherence following stent implantation in the VA.

There are many potential reasons for early clopidogrel discontinuation that involve patient and healthcare system factors (8-10). Patients reported the following reasons for discontinuing clopidogrel within 1 month after drug-eluting stent (DES) implantation: 1) misunderstanding the intended treatment duration; 2) conflicting recommendations about intended duration; 3) cost of the medication; and 4) patients' own decision to stop (10). In contrast, patients who continued to take clopidogrel reported the following as helpful: 1) communication such as letters from their physician; and 2) receiving specific instructions on clopidogrel use (10). These findings suggest that there are specific interventions that can be implemented to improve clopidogrel adherence.

Multi-modal interventions that incorporate frequent follow-up, especially with pharmacists and use IVR technology have improved medication adherence (11-20). IVR technology is a computer-based telephone system which initiates calls, receives calls, provides information, and collects data from users. IVR is currently a mainstay in the VA where patients frequently interact with these automated systems to get clinic appointments and/or refill prescriptions. IVR as part of multi-modal interventions have been well received by patients, increased adherence to medications (e.g., statins), and improved clinical outcomes (e.g., blood pressure, diabetes symptoms, health status) (16-20). In addition, we have successfully used IVR as part of a multi-modal, multi-site intervention including pharmacists to improve blood pressure levels among hypertensive patients (21-22). Accordingly, we have designed our intervention to improve clopidogrel adherence that builds on our prior work and other successful adherence interventions from the literature.

Further, we have successfully piloted the intervention to improve clopidogrel adherence following PCI. We developed a software application integrated within CART-CL that assessed whether patients fill their clopidogrel prescription at hospital discharge. If clopidogrel was not filled, patients were contacted to identify barriers to medication filling. During follow-up, automated telephone calls were sent to patients to educate them about the importance of medication adherence and to remind them to refill clopidogrel prior to the refill due date. The software application successfully identified all 15 patients enrolled in the pilot who underwent PCI and whether they filled clopidogrel at hospital discharge at 2 VAMCs. In qualitative interviews about the automated calls, all patients indicated that the refill reminder messages were helpful. A majority of participants indicated that they felt the education/support from the messages or participation in the study was helpful or would be helpful to others. A few patients shared that the messages also supported refilling other medications and reminding them to ask clarifying questions about other medications. Following the successful pilot, our next step is to test the effectiveness of the intervention and study the implementation process across a range of VA facilities.

Building on our prior work and evidence from the literature, we have developed our intervention informed by the Chronic Care Model (CCM) which is a framework that uses clinical information systems to facilitate evidence-based quality improvement (23). We will leverage CART-CL, IVR technology, patient self-management, and team-based care to foster efficient, productive interactions between activated patients and proactive clinical teams to improve clopidogrel adherence. Further the components of the intervention directly address many of the reasons that patients have highlighted as leading to early clopidogrel discontinuation. Figure 1 shows how each of the 4 components of the proposed intervention addresses the CCM.



Intervention component	Clinical information systems	Activated patients	Team-based care
a. CART-CL notifies pharmacist about PCI	X		
b. Pharmacist educates and brings clopidogrel to patient		X	
c. IVR calls to patients	X	X	
d. PACT member contacts patients for delays			X

Figure 1: Conceptual Model

This study will refine the current state of knowledge on improving medication adherence in multiple ways. First, it combines multiple interventions that have been separately shown to be effective in improving medication adherence and addresses causes of clopidogrel non-adherence identified by patients. Second, the intervention focuses on a novel setting (i.e., patients discharged following PCI and transitioning to outpatient care) in contrast to prior adherence interventions that have focused only on patients with stable chronic diseases (e.g., hypertension). Prior work by our group and others suggest that the immediate post-ACS period, and more generally transitions from the inpatient to the

outpatient setting, are particularly 'vulnerable periods' for medication adherence (24). Yet prior interventions have not specifically targeted this setting. Third, the targeted medication in this study has demonstrated short-term benefits and where non-adherence can have immediate adverse outcomes (e.g., stent thrombosis). Prior studies have focused on medications (e.g., hypertension medications) where non-adherence leads to problems longer term rather than the short term. Fourth, the study utilizes existing resources (i.e., cardiac data systems integrated with the VA electronic health record, VA pharmacists and patient-aligned care teams) to implement the intervention, improving the feasibility of broader implementation. Prior adherence interventions have generally required significant additional resources and the majority of quality improvement interventions are not continued following the end of the research project (25). This proposal will extend the current state of knowledge on medication adherence by demonstrating that a successful intervention will need multiple evidence-based components, and designed with plans for implementation in mind. Finally, this study is being conducted as a type I hybrid implementation study and therefore includes extensive study of the implementation process, which will yield both contributions to implementation science and facilitate wider dissemination if the intervention is found to be effective.

It should also be emphasized that the specific aims, design, and intervention proposed are directly and fully supported by key VA operations and research entities, including Patient Care Services (Dr. Rumsfeld, National Program Director for Cardiology), the QUERI program (Dr. Bryson, Director of IHD QUERI), Pharmacy Benefits Management Services (Dr. Valetino, Chief Consultant), the Office of Analytics and Business Intelligence (OABI) (Dr. Steve Fihn, Director), and Patient Aligned Care Team (PACT) (Dr. Schectman, Acting Chief Consultant for Primary Care). As noted in the endorsement letter from IHD-QUERI leadership, this study is also a major component of the IHDQUERI Strategic Plan (26). Further, the goals and methods of this study are also highly aligned with the concepts for improved health care delivery promoted by the Institute of Medicine (IOM), National Heart, Lung and Blood Institute (NHLBI), and the VA. Moreover, the proposed study reflects the QUERI aims including: a) explicit ties between research, QUERI and 'operational' components of the VA (i.e., PCS, OABI and Pharmacy); and b) studies of interventions that might be candidates for national VA implementation. The proposed study also addresses QUERI steps 4 and 5 of implementing interventions to promote best practices and to document its impact on outcomes.

Furthermore, the study will make two important contributions to implementation science. First, we will integrate a structured survey, the organizational readiness to change assessment (ORCA), for use in the formative and summative evaluations (described further in the evaluation plan). The ORCA has previously been psychometrically validated and found to predict implementation effectiveness (27-28). However, it has not been previously tested as a tool to support implementation. Findings from this study will help us understand if and how the ORCA can be used to support other implementation projects, and will contribute to users' materials for the survey. Second, we are using an innovative study design, a randomized stepped wedge design, and building-in iterative formative evaluation to guide implementation of the intervention at sites in subsequent cohorts. As far as we know, this kind of iterative rollout design with planned formative evaluation has not been used in an effectiveness/implementation hybrid study. If it works as planned, and provides useful formative evaluation findings from early cohorts, it may represent an important adaptation of the hybrid design.

In terms of VA patient care, if the intervention is successful, it will increase adherence to clopidogrel by helping patients take their anti-platelet medication routinely as prescribed, the quality of cardiovascular care for veterans since adherence to clopidogrel has been associated with reductions in cardiovascular morbidity and mortality following PCI, and the efficiency of care by using telephone calls and tele-monitoring for communication with patients rather than clinic visits. This study will leverage the automated pharmacy system and tele-monitoring technology for which the VA is a nationally recognized leader. Further, the study will address an important gap in knowledge (i.e., how to improve adherence to clopidogrel medications following PCI) and the findings can inform future interventions to improve adherence to other chronic cardiovascular medications. Finally, since the study is designed to be implemented using existing personnel/staff and current national platforms (i.e., CART-CL and PACT teamlets), it will be generalizable to other VA Medical Centers and veterans.

III. Preliminary Studies/Progress Report:

We performed a pilot study called "Pilot Intervention to Improve Clopidogrel Adherence after Drug-Eluting Stent Implantation". This was a pilot feasibility study to improve adherence to clopidogrel after a patient underwent a cardiac procedure that places one or more (DES) in their coronary arteries. We followed eighteen patients at the Denver VA Medical Center for 4 months. Most participants (83%) believed the refill messages were or would be helpful in refilling prescriptions. Two patients with co-morbidities indicated the difficulty of handling multiple tasks and that the reminders would be very helpful. A few shared that the messages also supported refilling other medications and reminding patients to ask clarifying questions about other medications. Most study participants (77%) said the educational calls were or would be helpful.

Therefore, we have successfully tested an intervention that focuses on adherence to clopidogrel following PCI and are now ready to conduct the proposed effectiveness/implementation study to test the effectiveness of a successfully-piloted, evidence-based, multi-faceted intervention to improve patient adherence to clopidogrel following PCI.

IV. Research Methods

Overview: This four-year multi-site site-level randomized stepped wedge trial will test the effectiveness of the intervention to improve adherence and outcomes, and will formatively evaluate and refine the implementation process. This is a randomized stepped-wedge study, modified to allow stratification by clopidogrel adherence. We will randomize 16 VA PCI sites to the multi-faceted intervention through 4 roll-out phases. We will implement the intervention at 4 sites during each roll-out and incorporate a 6-month delay between the start of each roll-out. The rest of the PCI sites that are not randomized will serve as usual care control group. At each site, we will enroll patients over a 6-month period and follow them for 12 months following PCI. The multi-faceted intervention will adapt elements of prior successful intervention and will include the following core components: development of a software application integrated within CART-CL that assessed whether patients fill their clopidogrel prescription at hospital discharge, collaboration between cath lab clinicians and impatient/outpatient pharmacy teams, patient education, and tele-monitoring via IVR technology.

A. Outcome Measure(s):

Initial outcomes will assess understanding current practices as VA PCI facilities to enhance adherence to clopidogrel. We will then assess barriers and facilitators to intervention implementation during each roll-out phase through semi-structured interviews and incorporate lessons learned from each roll-out phase into subsequent roll-out phases.

The primary outcomes of the study include the proportion of patients whose clopidogrel prescription is filled at hospital discharge following the PCI stent placement as well as the proportion of patients who are adherent based on the pharmacy refill data in the year after hospital discharge. Secondary outcomes include hospitalizations for bleeding, myocardial infarction, stroke, and mortality. Additionally, data about the costs of the intervention will be collected to assess the cost-effectiveness of the intervention.

B. Description of Population to be Enrolled:

Setting, sites, and patients:
The project will be conducted at 66 VA PCI sites that were chosen based on PCI volume. The sites are geographically distributed throughout the country. We have divided these PCI sites into quintiles based on the ranks of each site for Clopidogrel delay, so that the highest quintile (5th quintile) represents sites with the highest percent of patients with Clopidogrel delays. The lowest quintile will include sites that do not have delays in Clopidogrel refill, and therefore, will not be randomized. The upper four quintiles will include 13 sites each, and the lowest quintile will include 14 sites. We will randomize 16 sites to the multi-faceted intervention through 4 roll-out phases and compare to 36 control sites.

Each roll out will include 4 sites, one from each of the 4 upper quintiles (those with the highest percent of delay in filling their Clopidogrel prescriptions). Using a 1:1 randomization we will randomize one site in the 5th quintile to the intervention, and the remaining sites in the quintile will serve as usual care controls. We will then randomize the 2nd quintile in the same manner and so on until top 4 quintiles are randomized. We will contact the Cath Lab Director at each randomized site to participate in the study. If declined, another site from the same quintile will be randomized to receive the intervention. We will incorporate a 6-month delay between the start of each roll-out. At each site, we will enroll patients over a 6-month period and follow them for 12 months following PCI. If needed and if the participating sites agree, the enrollment period could be extended for one additional month at sites not meeting enrollment goals. We will document the reasons for site decline to help further understand the implementation contextual factors at the sites.

The intervention will be described in detail in Aim 2.

We will collect the outcomes of interest, adherence to clopidogrel, morbidity (MI, stroke, bleeding) and mortality centrally through data obtained from national VA data sources (i.e., Austin IT Center, CART-CL, and CDW) for both arms of the study.

At the PCI sites, we will include all patients undergoing PCI with either a bare-metal (BMS) or drug-eluting stent (DES) and are prescribed clopidogrel regardless of the intended treatment duration. We will include other potential anti-platelet medications (thienopyridines) used following PCI to accommodate changes in practice (e.g., prasugrel or ticagrelor or ticlopidine). Based on FY10, there were >10,000 patients undergoing PCI with either a BMS or DES at these facilities.

We will include all patients undergoing PCI and receiving clopidogrel at the randomized sites, regardless of gender, ethnicity or race. Based on data from the national CART Program, we anticipate ~23% minorities (African American 16.8%, Hispanic 4.4%, Asian/American Indian 1.4%) and 3.1% women will be included in the study.

C. Study Design and Research Methods:

We are proposing a type I hybrid effectiveness-implementation study of a multi-faceted intervention to improve clopidogrel adherence at VA PCI centers.

An overview of the number of patients and providers involved with interviews and the recruitment process is defined below:

Aim 1 – Identified sites will be stratified into quintiles and randomized to either the intervention or the control arm. We will choose approximately any 3 sites randomized to the intervention to be purposively sampled. We will interview up to 12 providers at each site. The interviews will be used to modify the

email survey that will be sent to all 16 sites targeting key personnel described in detail later in the protocol. After the survey results have been evaluated we will follow up with approximately 2-3 additional qualitative interviews based on results from the survey. A single provider may be interviewed more than once if they happened to have identified specific local barriers or facilitators in their survey responses. Therefore, we plan on collecting up to 96 telephone interviews from the 16 intervention sites. In addition, we will conduct site visits at approximately 2-3 of the 16 intervention sites. During these visits, we will interview up to 10 providers at each site.

Aim 2 – The implementation of the intervention will involve recruiting up to 2,500 patients at 16 sites.

Aim 3 – During the roll-out portion of the intervention we will interview approximately 3-4 clinicians/personnel who are involved with the delivery of the intervention at approximately 2-3 sites in each phase of the roll-out. Follow up interviews will occur at approximately 6 and 12 months. These will include up to 2 interviews with the same personnel we originally spoke with. In addition, we plan to interview approximately 80 patients. Therefore, we plan approximately 176 interviews for this aim.

An overview of the number of patients and providers involved with interviews and recruitment is defined below:

Aim	Interview Participant	Purpose of Interviews	Number of Interviews	Timing of the Interviews
Aim 1	Providers	Modify email survey	Up to 36	Prior to intervention
Aim 1	Providers	Follow-up email survey	Up to 60	Prior to intervention
Aim 1	Providers	Site visits	Up to 30	Prior to intervention
Aim3	Providers	Intervention implementation	Up to 48	During implementation
Aim 3	Providers	Intervention follow-up	Up to 48	6-12 months post implementation
Aim 3	Patients	Intervention follow-up	Up to 80	1-2 months post enrollment
	Total Patient Interviews		Up to 80	
	Total Provider Interviews		Up to 222	

All providers, staff, and patients who are asked to participate in the study and interviews will be offered the opportunity to opt out of being recorded but still participate in the interview.

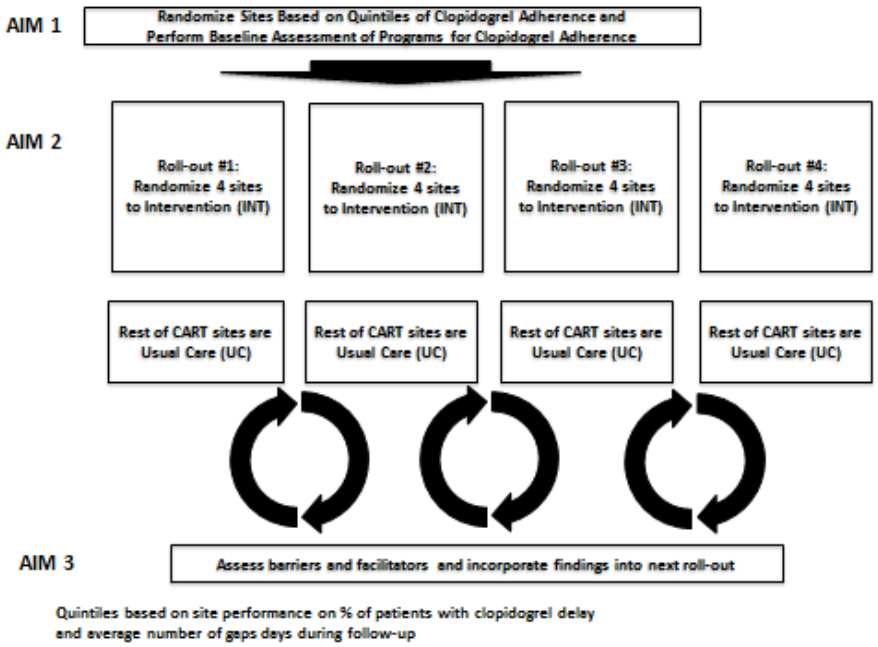
Telephone interviews will originate from Denver, and both telephone and site visit in person interviews will use VA-approved audio-conferencing software to record the interviews. Electronic data files will be encrypted/password-protected on computer servers maintained in a secure environment per VA security regulations. To protect confidentiality, all study records will be stored on an access-controlled secure data server, and access to the study records will be limited to project staff.

Data from interviews will be recorded directly to the secure server, with field notes recorded in text files saved directly to the secure data folder. Likewise, audio recordings of the interviews will be made using the VA-approved audio-conferencing software in order to facilitate secure audio recording. Such software uses a toll-free conference dial-in line with the capability of generating a digital audio recording

of the call. Audio recordings are made directly to the meeting organizer's computer and can be directed to any network drive. In this case the secure data drive is in Denver. Telephone lines dialed into the conference line are displayed on the audio-conferencing software window, and so participation in the call can be monitored (i.e., a third party calling into the interview, intentionally or inadvertently, will be visible to the study team). Interview participants will be sent the conference call number and code at the time the interview is scheduled.

We will sequentially rollout the intervention through 4 phases to 16 sites to test the effectiveness of the intervention to improve adherence and outcomes. The conceptual overview of the study is outlined in Figure 2. We will randomize sites to the intervention stratified by quintiles of site performance based on percent of patients with delay in filling clopidogrel at hospital discharge and average number of gap days during follow-up. Prior to each roll-out, we will evaluate current practices at sites randomized to the intervention (n=20) to enhance adherence to clopidogrel (aim 1). This information will be used to inform implementation and modification of the intervention if needed at sites (aim 2). Next, during each roll-out phase, we will conduct qualitative interviews with a sample of sites from each cohort to understand barriers and facilitators of implementation. Because of the sequential roll-out study design, we will be able to incorporate these findings into subsequent roll-out phases in an iterative implementation process, building on prior experiences (aim 3). We anticipate that follow-up interviews will be most intensive in early cohorts where the learning curve is steepest, and less intensive in later cohorts, by which point the most common barriers should be understood.

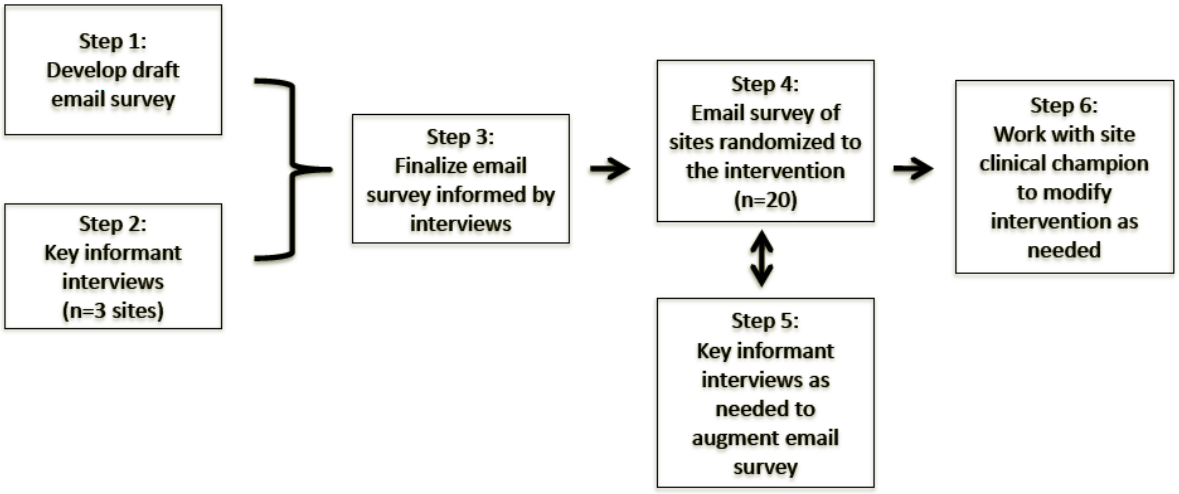
Figure 2: Study Design Overview



Aim 1: Through email surveys and targeted qualitative interviews, evaluate current practices at VA PCI facilities (n=16) to enhance adherence to clopidogrel, both at hospital discharge and during longitudinal follow-up among intervention sites.

Overview of Aim 1: We will conduct an email survey supplemented with key informant interviews at the 16 sites randomized to the intervention to understand the following: 1) potential clinical champion(s) interested in leading implementation of the intervention; 2) perceived local barriers and facilitators to implementing the intervention; and 3) perceived readiness to change and change culture. These 6 steps of Aim 1 are outlined in Figure 3.

Figure 3: Overview of Aim 1



Steps 1 and 2:
We will conduct key informant interviews with a purposeful sample of sites to further understand existing processes and barriers to ensuring clopidogrel adherence for PCI patients. Using the findings from these interviews we will modify the draft email survey (Appendix 1). The sites will be selected based on the outcome (i.e., clopidogrel adherence rates) and structural factors that may influence implementation of the intervention (e.g., facility complexity, region, cardiology-related resources available). These structural factors will be obtained from the recently completed Survey of Cardiovascular Specialty Care Services. This was a comprehensive survey of all VA facilities about the availability and type of cardiology services, processes of cardiac care, and cardiology related structures of care.

We anticipate conducting interviews with approximately 10-12 individuals at ~3 sites. Semi-structured interview guides (see Appendix 2 for draft guide) will be designed for use during these interviews and a two-page content summary form will be completed following each interview. This summary will include the context of the interview, emerging themes or issues that arose in the interview, areas for clarification, and other comments about the interview or interview guide. The goals of these interviews are: 1) to inform development of the structured survey and 2) to provide preliminary information about how the intervention will integrate into existing care processes. Interviews will last up to one hour. During the process of conducting the qualitative interviews, the study team will review preliminary results in order to ensure that subsequent interviews are iterative and focus on emerging themes that will effectively inform the intervention.

Step 3: Finalize survey: In order to analyze the qualitative content and adequately inform the design and conduct of the email survey, we will use an iterative, inductive and deductive toolkit of analytical strategies, drawing particularly on qualitative content analysis and reflexive team analysis. Analysis will

commence as the interviews commence and will continue alongside and informing data collection. Interviews will be digitally recorded and transcribed, and will be analyzed using qualitative content analysis methods. Analysis of transcripts will begin with repeated readings to achieve immersion followed by initial coding using an emergent rather than *a priori* approach, in order to emphasize respondent perspectives and de-emphasize team member speculations. ATLAS.ti v 6.2 (Scientific Software Development, GmbH, Berlin) will be used for data organization and management during analysis. This software will only be used by the qualitative analyst at the analysis site only. Words, sentences, and paragraphs will be treated as coding units or "meaning units". After initial coding is completed, the resulting shared set of codes will be applied to the transcripts, code categories will be developed, and emergent themes will be identified. Throughout the analysis, new findings will be continually checked and compared with the rest of the data to establish new codes, themes or patterns. The resulting information will be used to inform, modify, and finalize the email survey to be sent to PCI sites.

The ORCA questionnaire (Appendix 1) will be included as part of the email survey and is comprised of three scales corresponding to core elements of the Promoting Action on Research Implementation in Health Services (PARIHS) framework: 1) Strength and extent of evidence for the clinical practice changes represented by the QI program, with four subscales; 2) Quality of the organizational context for the QI program, with six subscales; and 3) Capacity for internal facilitation of the QI program, with nine subscales. Each subscale is comprised of three to six items assessing common dimensions of the given scale. The ORCA scale has previously been validated and baseline scores have been positively correlated with measures of implementation effectiveness (27-28).

Steps 4 and 5: Conduct survey and interviews at intervention sites: We will send these surveys to sites randomized to the intervention targeting the Cath Lab Director, Cath Lab manager, pharmacists (both inpatient and outpatient), Chief of Primary Care and/or PACT leadership (Step 4). We will disseminate the survey via Site PIs. We will use a Web-based survey tool (such as RedCap and/or other VA-approved survey tools), housed on the VA Intranet, so that surveys can be completed online behind the VA firewall. The goals of this survey are to identify the following: 1) potential clinical champion(s) interested in leading implementation of the intervention at that site; 2) perceived local barriers and facilitators to implementing the intervention; 3) perceived readiness to change and change culture using the Organizational Readiness to Change (ORCA) scale. We will follow prior methods for conducting email surveys by the CART Program that have achieved response rates of >80%. We will also follow-up these surveys with qualitative interviews targeting key informants identified from the email survey to gather more in-depth information about specific local barriers and potential solutions that can be implemented to address the barrier as well as clarifications to responses on the email survey (Step 5). We envision that this may entail 2-3 interviews per site.

In addition, we will conduct qualitative interviews with clinicians and providers at the sites from the lowest quintile to learn about their practices, current and past experiences of working with patients taking the anti-platelet medicine, and their perceptions of how care should be delivered to patients taking the anti-platelet drugs. These interviews will provide additional insights into existing processes. We will notify a facility medical director of these sites of our intent to conduct the interviews. We will request a response within seven days if a facility director decides to opt out from the interviews.

We will conduct site visits for ~2-3 sites (out of 16 possible sites) for the purpose of exploring whether site visits reveal different types of information or quality of information than telephone interviews. Relative to telephone-based interviews, site visits are expensive and time-intensive, and potentially more burdensome for participants. However, there is some reason to believe that telephone interviews may omit critical information. Specifically, site visits provide information about physical layout, staff interactions, and general atmosphere. They provide greater opportunity for chance observations. There is also evidence that non-verbal, interpersonal cues dramatically influence interpretation of the content of communication. For all of these reasons, telephone interviews (though they represent the current methodological standard in implementation science) could introduce measurement bias. To assess potential differences, we will compare subjective ratings by investigators on the quality of interview data

between telephone and site-visit based interviews and will compare and contrast the themes that emerge to determine if the site visits elicit different or additional themes.

Step 6: Work with site clinical champion to modify intervention as needed: Working with the site clinical champion, who are the site PIs responsible for conducting the study locally, we will then use the survey data on barriers and facilitators to clopidogrel adherence, and organizational readiness, to inform implementation of the intervention. We will generate summary findings to guide the discussion of specific issues related to local implementation and determine whether modifications are needed (Step 6). For example, if pharmacist respondents at a given site perceive that medication adherence is not a priority for their leadership, project staff and the site clinical champion will engage leadership to discuss goals of the project as well as the importance of improving adherence to clopidogrel. In addition, we provide examples of potential problems that may be identified during the survey/interviews and provide solutions to address the barrier.

In addition, we will include a process improvement component by utilizing A3 tool which is used for identifying problems in current processes, identifying suggestions for improvement and communicating these to the management/supervisors. We will present this tool to the participating sites to explore local issues and solutions to improve adherence to anti-platelet medications that could be sustained once the study is finished. We will work together with a local study coordinator to facilitate and guide the completion of the A3 tool by local members of the health care team. We will work to communicate the local solutions to the site PIs and the local leadership team.

***Aim 2: Implement the multi-faceted intervention at 16 total sites through 4 roll-out phases (4 sites during each roll-out) in a randomized stepped wedge trial design*.**

Overview of Aim 2: This is a randomized stepped-wedge study, modified to allow stratification by clopidogrel adherence. We will randomize 16 VA PCI sites to the multi-faceted intervention through 4 roll-out phases. We will implement the intervention at 4 sites during each roll-out and incorporate a 6-month delay between the start of each roll-out. The rest of the PCI sites that are not randomized will serve as usual care control group. At each site, we will enroll patients over a 6-month period and follow them for 12 months following PCI. If needed and if the participating sites agree, the enrollment period could be extended for one additional month at sites not meeting enrollment goals.

Setting, sites, and patients: We will exclude sites with low PCI volume, less than 20 PCI procedures performed during the last fiscal year (n=3). The sites are geographically distributed throughout the country. At the PCI sites, we will include all patients undergoing PCI with either a bare-metal (BMS) or drug-eluting stent (DES) and are prescribed clopidogrel regardless of the intended treatment duration. We will include other potential anti-platelet medications used following PCI to accommodate changes in practice (e.g., prasugrel or ticagrelor or ticlopidine). Based on FY10, there were >10,000 patients undergoing PCI with either a BMS or DES at these facilities. In addition, we will only include patients discharged to home setting. Patients discharged to nursing/assisted living facilities, other hospitals, or any other facility where their medications are managed will be excluded.

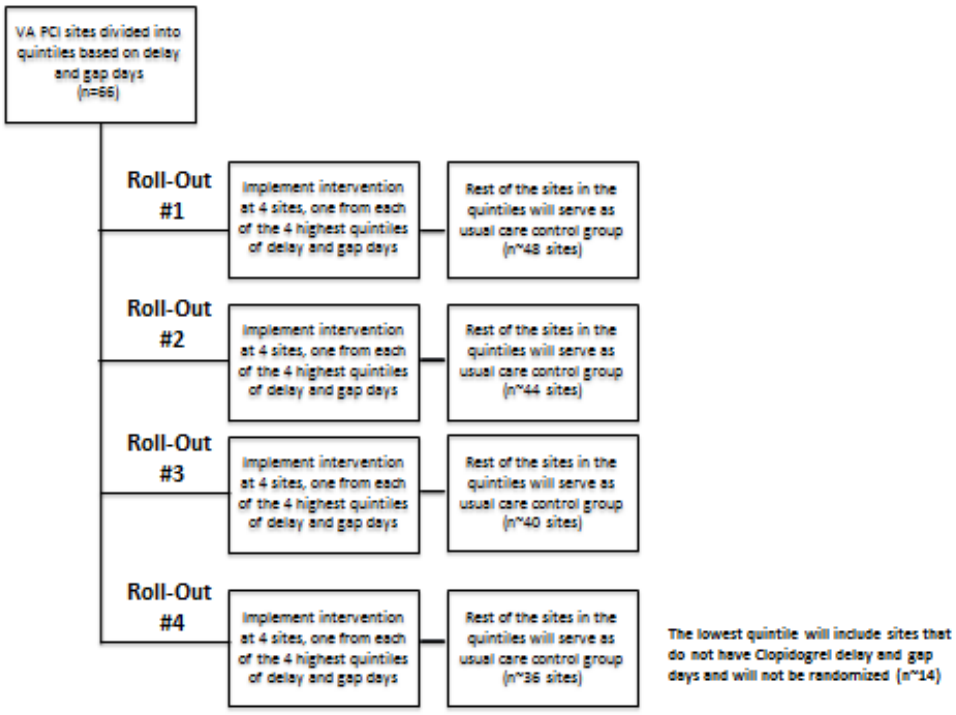
Study design: Given the serious and prevalent nature of the clinical problem under study and the characteristics of the intervention to be tested, we believe that a randomized trial at the site level is the most appropriate design. The intervention is focused on changing processes of care (e.g., process for getting clopidogrel to patients at hospital discharge) which are clustered by sites and therefore to avoid contamination, we will focus the randomization at the site level. Target enrollment is 16 sites for the intervention and the remaining 36 PCI sites will serve as usual care controls.

Recruitment: Of the 66 sites eligible for randomization, we have ranked each site according to the percent of patients with delay in clopidogrel filling at hospital discharge, and the average number of gap

days (i.e., days without clopidogrel based on clopidogrel refill data) during follow-up for FY10, FY11, and FY12 using CART data. Next, we have divided these PCI sites into quintiles based on the ranks of each site for clopidogrel delay and average gap days so that the highest quintile (5th quintile) represents sites with the highest percent of patients with clopidogrel delay and the greatest average number of gap days among its patients. We will sequentially randomize sites from each quintile beginning with the 1st quintile (Figure 4). During each roll-out, we will randomize 4 sites, one from each of the 4 top quintiles, to the intervention with the remaining sites in the quintiles serving as usual care controls.

We have chosen to randomize and include sites from the different quintiles because there may be lessons learned from sites in each quintile during our interviews prior to and following implementation of the intervention that may inform sites that have similar practices during wider implementation/dissemination. Further, these sites will provide different insights into barriers and facilitators not present in other quintiles. If for some reason a site is unable to participate following randomization to the intervention, we will randomize another site to replace the ineligible site. This will result in slight imbalance in the numbers of usual care sites across quartiles which can be accommodated in the planned analyses.

Figure 4: Overview of Aim 2

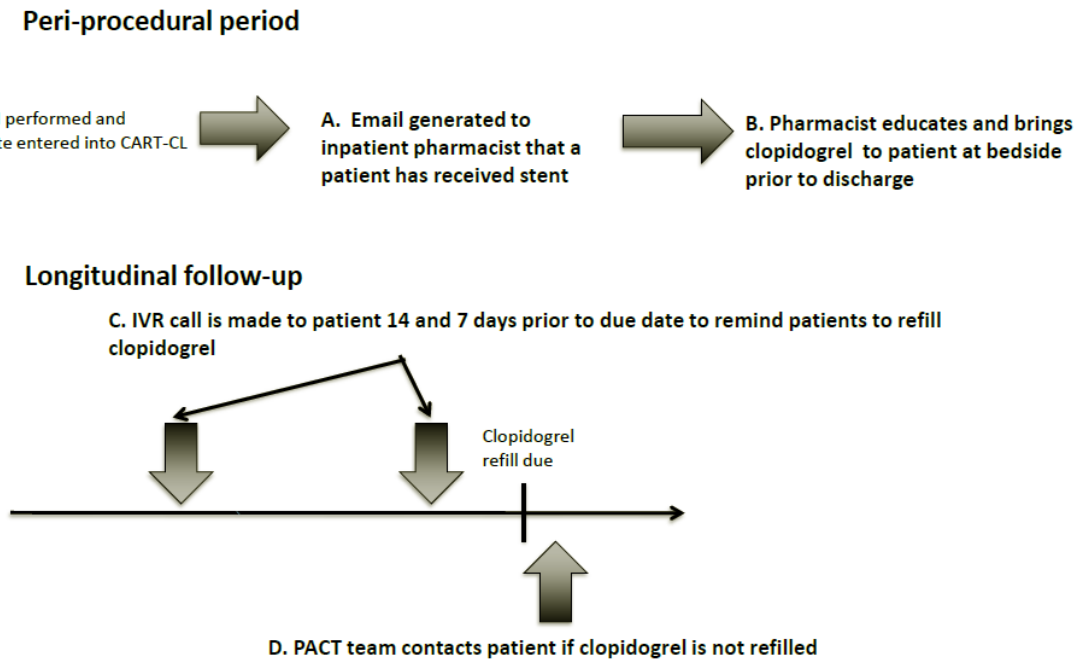


Randomization Process: Unit of Randomization, Sequence Generation, Allocation Concealment, Implementation, and Blinding: The unit of randomization is the site or PCI facility. Sites that are not randomized to the intervention will serve as usual care control groups in this randomized stepped-wedge study design. The process of randomization will be centralized and stratified by quintiles of

clopidogrel delay at hospital discharge and average gap days during follow-up. Following randomization, we will approach sites about their willingness to participate in the intervention as well as conduct the baseline assessment. If for some reason a site is unable to participate in the study, we will randomize another site from the same quintiles to replace that site. During each roll-out, we will implement the intervention at 4 sites, one from each quintile, leaving the remaining sites as usual care controls. Through the 4 roll-outs, we will have a total of 16 intervention sites and 36 usual care sites. All the randomized sites will be contacted for their willingness to participate in the study. Sites that agree to participate will be assessed at baseline. We will collect the outcomes of interest, adherence to clopidogrel, morbidity (MI, stroke, bleeding) and mortality centrally through data obtained from national VA data sources (i.e., Austin IT Center, CART-CL, and CDW) for both arms of the study.

Intervention Components: The intervention, building upon the successful pilot, will comprise the following 4 components (Figure 5):

Figure 5: Intervention Components



A) A Site Study Team will be formed at each intervention site. The Study Team will have up to 10 members and will include Directors of the CATH Labs, pharmacists, pharmacy techs, PACT nurses, and physicians. All members of the Site Study Team will be members of the research team and will be IRB-trained. As standard of care, after a patient receives a PCI with a stent, clinicians enter a procedural report in CART-CL. Completion of the procedural note will trigger a secure email to a member of the Site Study Team notifying them that a patient received a stent.

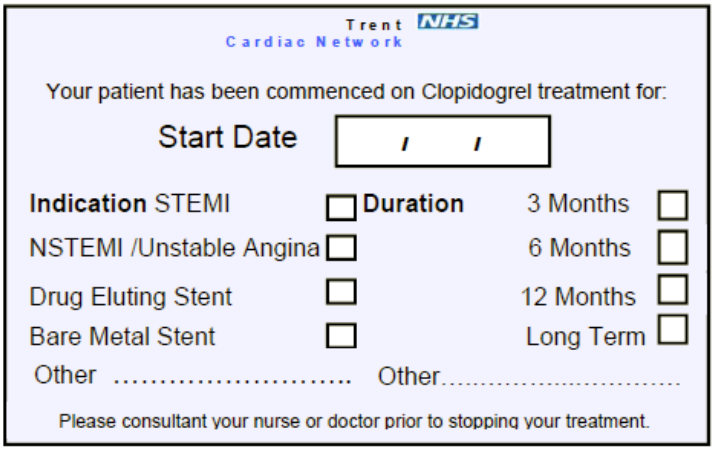
We will set up folders on a secure VA server where information about a patient receiving a stent will be entered by the CART-CL program. Each intervention site and its identified study staff will have access to the specific folder, not visible to other sites. A general email, notifying a study

team member that a PCI procedure has been performed, will be sent to a Site Study Team member. The email will contain no PHI. Upon receiving the email, a Site Study Team member will access the secure site-specific folder to obtain the details about the patient study participants.

B) Once notified, a member of the Site Study Team, which may include a pharmacist, a nurse, a doctor, or whoever the site determines to be the appropriate person to fulfill the requirements of the site and the study, will review the chart to see the anticipated discharge date for the patient. Before approaching, patients will be given adequate time to recover from the procedure and sedation. The Site Study Team member will bring the first prescription of clopidogrel to patients' bedside prior to hospital discharge. A member of the Site Study Team will discuss the verbal consent with the patient participant and provide the information sheet about the study. If the patient chooses not to participate they can refuse at this time or in the future and will be instructed where to call if the patient would like to opt-out from participating in the study. A Site Study Team member will educate patients on the importance of and adherence to clopidogrel following PCI as well as bring clopidogrel to patients' bedside prior to hospital discharge. We will keep a master list of all patient participants and document those who opt-out and reasons, if they are known, to help further understand the contextual factors

We will provide well-developed education materials from the ACC/AHA that describes the importance of and adherence to clopidogrel following PCI. Further, we will provide patients with a clopidogrel treatment wallet card, which outlines the intended duration of clopidogrel treatment following PCI. An example is provided below (Figure 6), and is currently used in the United Kingdom. This is similar to the cards that patients currently receive following PCI that outlines the type and location of their stents and will serve as another reminder about the importance of continuing clopidogrel therapy.

Figure 6: Clopidogrel wallet card



We will use existing staff and no new staff will need to be added so that if the intervention is effective, it can be continued without additional resources. At some sites, someone other than a pharmacist may be designated to educate patients and bring clopidogrel to the bedside. We will work with each site to identify and train the designated individuals to perform this step of the intervention. This component is intended to activate patients, which is an integral part of the CCM.

C) IVR reminder calls to patients around time of clopidogrel refill and to facilitate refills: Building on our prior developed IVR calls from the pilot study, we will further refine the calls so that patients

will receive an IVR reminder call 14 and 7 days prior to the anticipated refill date for clopidogrel. During these calls, patients will have several options: 1) to connect to the pharmacy refill line so that they can refill clopidogrel at the same time; 2) to request a call from a pharmacist if they have questions regarding their medications; and/or 3) to cancel future IVR reminder calls if they obtain clopidogrel outside of the VA, have been instructed to stop the medication by their physician or for some other patient-specific reason.

During the call, we will provide the patient with their clopidogrel prescription number in case they would like to be connected to the pharmacy line to refill clopidogrel at the same time. The call at 7 days will not occur if a refill has been made in the interim. In addition, we will also make sure that the patient is not deceased or is not filling their clopidogrel prescription at an outside pharmacy by looking for clopidogrel in the "Non-VA Medication List" that is part of CPRS. If either is the case, we will discontinue the IVR calls. In our qualitative interviews from the pilot, patients were positive about these refill reminder calls. The IVR calls will occur for up to 12 months following hospital discharge given current recommendations for clopidogrel treatment duration but will be modified based on patient's clinical needs. This component leverages clinical information systems of the CCM and is intended to activate patients.

To accomplish this step, we will obtain data on date of clopidogrel fill and the number of days supplied from the Corporate Data Warehouse (CDW). Based on these data, we will be able to trigger the IVR calls to deliver the reminder messages to patients 14 and 7 days prior to the clopidogrel refill date. If a patient has refilled their prescription prior to the 7 day reminder call, we will turn off the reminder call. We have successfully used pharmacy data (date of clopidogrel fill and days supplied) to trigger IVR calls in our pilot. The CDW pharmacy data is refreshed on a daily basis and therefore will reflect any interim refills made by patients.

D) PACT member will contact patients who delay refilling clopidogrel: For patients who do not refill their clopidogrel prior to the refill due date, we will notify the patient's PACT team about the delay in clopidogrel filling so that a PACT team member can contact patients to identify potential barriers to refilling the medication. A specific goal of the PACT initiative is to have teamlets actively follow-up with their patients following hospitalization or referrals to coordinate care. By working with Primary Care to involve PACT teamlets, we will help make their jobs easier and improve the feasibility of the implementation as well as longer term maintenance. During the initial interviews at each site, we will work with the site champions to identify the person(s) that these notifications should be delivered to. At some sites, it may make sense to send these reminders to the primary care providers, pharmacists or a designated individual in cardiology. We will adapt the intervention to local practices while maintaining the key component of the intervention, which is that a key person/group is informed of the delay in clopidogrel filling and can follow-up with patients to ensure that the medication is refilled and taken. This component uses team-based care to interact with activated patients under the CCM.

We have identified key aspects of the intervention that are essential and will not change, but realize that for successful implementation and long term maintenance, we will need to have flexibility in aspects of the intervention. The elements of the intervention that are not modifiable include: 1) Notification that PCI procedure has been performed; 2) Patient education and having clopidogrel brought to the bedside prior to discharge; 3) IVR reminder calls about clopidogrel refills; and 4) Contacting patients who do not refill clopidogrel. However, the manner in which these components are delivered and the specific person(s) delivering the component can be modified according to local site preferences and personnel availability. In addition, in certain situations, it may be more feasible to approach potentially eligible patients for participation before their procedures (such as weekend and/or same day discharges, etc). In this case, a member of the site study team will approach and inform the patients about the study and will obtain permission to contact the patient after their procedure if they are eligible to enroll, and the permission to record the interview will be requested at the time of the interview. In addition, when no study team members are available to approach eligible patients, a member of a patient's healthcare team will deliver Clopidogrel to the bedside since it is an approved drug and is part of standard of care,

will supply the patients with patient information sheet without discussing it, as well as obtain permission to call the patient. A member of the healthcare team will document in the CPRS that they gave information sheet to a patient and permission to call the patient was obtained. A member of the research study team will call the patient and complete enrollment over the phone. In our initial survey/interviews at sites (aim 1), we will explore these issues to better understand potential barriers and implement processes that facilitate implementation of the intervention, and long term maintenance.

Aim 3: During each roll-out of the intervention, assess barriers and facilitator to implementation of the intervention through semi-structured interviews and incorporate the lessons learned from each roll-out phase into subsequent roll-out phases.

Overview of Aim 3: This aim will involve in-depth, key informant interviews (~3-4) with representatives from a sample of sites (~2-3) in each cohort of the roll-out phase. We will work with the site champion to identify and interview key clinicians/personnel involved in the delivery of the intervention and the interviews will be designed to understand barriers to and facilitators of intervention implementation. In addition, we will interview patients to obtain feedback regarding the IVR calls as well as other aspects of the intervention. The sequential roll-out design will enable incorporation of knowledge gathered from these interviews into subsequent roll-out phases. If additional qualitative data are needed to achieve thematic saturation, the point at which interviews no longer produce new themes about barriers and facilitators, additional interviews will be conducted. In addition, we will conduct follow-up interviews at 6 and 12 months following intervention implementation to assess maintenance and identify issues that arise after initial implementation and any local solutions.

Focus of the qualitative interviews: The goals of these interviews are: 1) to identify issues, facilitators or barriers to the implementation of the intervention and 2) identify strategies that may be useful in the refinement of subsequent roll-out phases (see Appendix 3).

For patients, we will inquire about perceived strengths and weaknesses of the intervention components, focusing on: 1) the education process prior to hospital discharge; 2) having clopidogrel brought to the bedside; 3) the clopidogrel wallet card; and 4) the content of IVR calls and ease of being connected to the pharmacy line (see Appendix 3).

These interviews with providers and patients will last up to one hour. Throughout the analysis of the qualitative interviews, the team will review the preliminary results in order to ensure that subsequent interviews are iterative and focused on emerging themes that will effectively inform the intervention.

Timing of the interviews: We will conduct these interviews approximately 1-2 months after the start of the intervention at each site to allow for sufficient time for study personnel to gain experience with conducting the study. Following the interviews, we will summarize the findings so that the lessons learned from each roll-out can inform the next roll-out phase. Below, we outline some potential barriers that may be identified during these interviews and potential solutions to address the barrier. We will work with the site clinical champion to identify solutions.

Qualitative interview methods: All interviews will be recorded using VA-approved audio-conferencing software and will be transcribed verbatim by study personnel and, when needed, by a VA approved professional transcription service. De-identified recordings of the interviews will be uploaded to the HIPAA-compliant web-based platform, which is tightly controlled and monitored. Moreover, the platform automatically tracks user access and makes it available for review, monitoring and reporting. Confidentiality and anonymity will be maintained; only study investigators and the internal VA transcriptionist will be aware of participant identities. Professional transcription service will not have access to the participant identities. Each participant in the study will be assigned a unique coded identifier, and only this identifier will be directly associated with any other data. A file containing only individual contact information will be maintained separately to allow coordinators to conduct follow-up

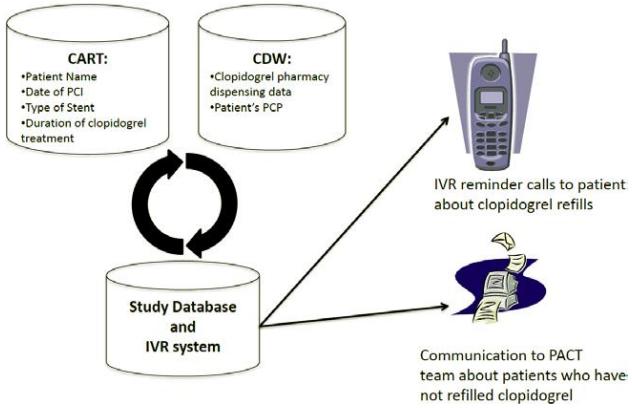
contacts if needed. The contact information file and all de-identified data will be stored in password-protected files on secure servers in the VA. Only investigators will have access to the files.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

We will employ well-developed and well-tested data management procedures to ensure accurate and efficient data collection and analysis, as we have done for our prior/current IVR projects and in several other IHD-QUERI studies. Some CART data for this study will be pulled from the database established under 06-1149. Different elements of the proposed study database system are in current use (e.g., hypertension IVR [Improving Blood Pressure in Colorado]; and MEDICATION [IIR 08-302]), and are easily adaptable to the current proposal (i.e. this study deals with a different aspect of cardiovascular disease). There are internal error checks (e.g. detection of pre-specified out-of-range data values and incorrect skip patterns), data definitions, and missing data checks. As part of the database, pharmacists will have the ability to document that education was provided to the patient, that clopidogrel was brought to the patient's bedside prior to hospital discharge, and to confirm phone numbers that the patient can be reached at. The system will also allow for tracking of number of patients enrolled per site based on the PCI procedures inputted into CART-CL.

We will obtain basic demographic data (including phone number), co-morbidities, PCI procedural details as well as the date of initial clopidogrel fill with and the number of days of pills supplied from CART-CL. We have obtained CART-CL data as part of our pilot intervention to improve clopidogrel adherence, demonstrating technical feasibility. Next, we will obtain data on subsequent clopidogrel refills from the CDW, including the date of refill, the number of pills supplied and the prescription number. The pharmacy data in the CDW is refreshed on a daily basis and will be linked to the CART data (Figure 7). The data will be compiled and analyzed in Denver and/or Nashville and will be in a secured database that will be saved on a VA secured server maintained behind the VA firewall. Access to the database and study data will be limited to research staff. Only personnel who are qualified, trained, and IRB-approved in appropriate behavior for the privacy of each patient will be viewing the data. Then, we will be able to use these data to trigger the IVR calls based on when a clopidogrel prescription is due to be refilled and to notify the PACT team about patients who have not refilled clopidogrel. This is consistent with our processes in the pilot intervention to improve clopidogrel adherence as well as in our other prior IVR studies.

Figure 7: Overview of Data Sources and Use



We will work with site champions to identify and interview key clinicians/personnel involved in the delivery of the intervention and the interviews will be designed to understand barriers to and facilitators of intervention implementation. In addition, we will interview patients to obtain feedback regarding the IVR calls as well as other aspects of the intervention.

We will collect data on costs in two main categories: direct medical costs and intervention costs. To calculate medical costs for each patient we will collect Decision Support System (DSS) data for all patients for the one year following the receipt of the stent. We will collect DSS data for outpatient care in primary care, cardiology, pharmacy, and geriatric clinics; and for emergency department use, hospitalization, and medications. For hospitalizations we will report costs for all cause hospitalizations as well as hospitalizations for cardiovascular-related conditions. Similarly for medications, we will estimate costs for all medications and for cardiovascular-related medications.

Risks are minimal. There are no physical discomforts to the participant and this may possibly support the participants' effort for medication compliance. The CART-CL system is part of the standard of care in the VA system at this time and has had no adverse experiences and there are no known risks to utilizing the IVR system. Electronic data files will be encrypted/password-protected on computers maintained in a secure environment per VA security regulations. The study may include risks that are unknown at this time.

Monitoring for unanticipated events will be the responsibility of the Site Study Team members and we will support each site with monthly conference calls to review study procedures, implementation processes, and any issues that may affect the study integrity across and within sites. Any data breech issues should be brought to the attention of the group during the next monthly call after they become aware. All SAEs and UAPs will be reported to the VA CIRB according to the established guidelines. Due to the nature of the study population, certain events are considered expected and will not be reported to the CIRB, such as bleeding, myocardial infarction, stroke, stent thrombosis, repeat PCI procedure, hospitalizations associated with PCI, hospitalizations associated with coronary artery disease (including unstable angina, acute myocardial infarction, multi-vessel coronary artery disease). We will consider death of a participant as an SAE and will report to the VA CIRB within the established guidelines. All SAEs/UAPs will be reported by a local site team member at a site where SAE/UAP took place. We will keep all administrative documents in a shared study folder, accessible by all study team members. SAEs and UAPs will be documented and stored in a shared study folder.

E. Potential Scientific Problems:

Potential issues include:

- failure of the CART-CL system to generate the alerts
- failure of the IVR system to generate the calls to the patients
- inability of the study personnel to contact the patient
- sites refusal to participate in the study
- One potential limitation of the proposed sampling design is that the patients and pharmacists chosen for analysis in this study cannot be considered representative of all sites across the VA. However, the qualitative component of this study seeks a depth of information that can be acquired only by collecting rich data from a limited sample of individuals. Further, the patients and providers reflect many aspects that are common to all VA sites.
- Although we hope the randomized step-wedge design of the trial will lead to treatment groups that are balanced on observed covariates at baseline, we recognize that some imbalances may nevertheless occur and multivariable models maybe necessary to account for these imbalances.
- There are concerns that clopidogrel may become generic, however, the timing of when clopidogrel will become generic is not currently known. We acknowledge that it will be more difficult to monitor adherence if clopidogrel becomes generic and patients fill the medication at non-VA pharmacies. However, a majority of patients still obtain generic cardiovascular

medications (e.g., simvastatin or metoprolol) at VA pharmacies and we expect that this will be the case for clopidogrel. For patients who fill their clopidogrel at non-VA pharmacies, we will ask the patients to see if they would like to receive clopidogrel refill reminder calls and program the IVR calls based on information provided by the patients on date clopidogrel was filled and the number of days supplied.

- We have identified key aspects of the intervention that are essential and will not change, but realize that for successful implementation and long term maintenance, we will need to have flexibility in aspects of the intervention

F. Data Analysis Plan:

Qualitative analyses: The synthesis stage of data analysis involves triangulating the findings from interviews, surveys, and demographic and other information, making refinements in the explanatory models, exploring comparisons across different methods and samples, revisiting the literature to compare findings to other investigations, and answering questions about facilitators and barriers to intervention participation.

Consistent with qualitative methodology, analysis is planned as a continuous process beginning with initial interviews and continuing throughout and beyond the data generation period (30). The words participants use, their beliefs and needs, and desired strategies for intervention will be described. Data will be coded following a process of initial review, with labeling of data by content, process, or impressions of the person coding. Following initial coding, the data will be examined for categories, domains, or themes. Codes will be analyzed into categories and broad classifications of cultural meaning called domains. Transcriptions of data will be analyzed for themes and patterns (31). After this initial coding is completed, codes will be organized into categories that reflect symbolic domains of meaning, relational patterns within domains, and finally overarching themes (32-33). Relationships within domains are usually structured according to "organizing principles," such as inclusion, symbol, sequence, function, part-whole, or others (34). Using this analysis, an analytic summary of each interview will be written. In the summaries and resulting publications, the research team will use research participants' own words and narratives to preserve the tone and emotion of their experiences and increase the theoretical depth of the final description (35). Narratives, as a specific kind of speech act, will be indexed in the coding process, and a narrative analysis will ensue (36-39). These narratives will be analyzed for substantive and conceptual meaning.

Using the coded and analyzed data, working conceptual models or explanatory models (EMs) of clinicians' and patients' experiences with the intervention will be developed (40-41). Comparisons across interviews to explore differences between clinicians and patients will add detail and depth to the understanding of the effectiveness of the intervention. The qualitative data software package ATLAS.ti will be used to analyze the data (42).

Quantitative analyses: The primary analysis will use patient level data and generalized linear mixed models. These models can accommodate the different types of outcomes, correlation due to clustering of patients within sites, and different numbers of patients across sites and time periods (43). Models will include terms for site (random, to account for correlation of patients within sites and to identify site-level variables), roll-out period (fixed, to avoid confounding of intervention with time trends), stratum (fixed, to account for baseline clopidogrel adherence quartile), and intervention variable (fixed, INT/UC, the effect of interest). The availability of non-intervention usual care control sites provides additional information for estimating the intervention effect, and also will allow us to examine possible dependence of the intervention effect on baseline clopidogrel adherence. These latter analyses for interaction between intervention and baseline adherence will be considered exploratory. Primary yes/no outcomes (clopidogrel fill, bleeding, stroke, MI, mortality) will be analyzed with mixed logistic regression models with these methods. The clopidogrel adherence outcome is a numeric percentage and will be analyzed

with similar models for normal outcomes, using transformations as needed to achieve approximate normality.

Available data for analysis will include clopidogrel fill and adherence data at each site during the 6 month period preceding the first roll-out, and during each of the four subsequent 6 month roll-out periods of the study, and outcomes (mortality, bleeding, stroke, and MI) during the 12 months following the index PCI procedure. Data will be examined graphically and descriptively for general patterns, outliers, or other problems. Descriptive tables will show general patterns and trends in site and average patient characteristics and outcomes, separately for sites under usual care (UC) and those under intervention (INT), and by time periods.

The economic analysis will weigh the benefits of the intervention in terms of patient survival and quality of life against the cost implications of providing the interventions. We will do this through a cost effectiveness analysis (CEA). The CEA will take the perspective of the VA and the time horizon will be the 12 month period following stent placement. For the intervention compared to usual care we will calculate incremental cost effectiveness ratio (ICER) and related statistics. The ICER is estimated as $ICER = (C_1 - C_0)/(QALY_1 - QALY_0)$ where C_1 and C_0 are average cost over 1 year for patients in the INT and UC groups, respectively, and $QALY_1$ and $QALY_0$ are mean quality adjusted years of survival over that year for the respective groups. Below we describe data sources and methods for deriving these estimates.

To estimate the cost of the intervention we will use micro-cost techniques. The cost of developing and tailoring the email and IVR systems will be derived from logs of the time, salaries and benefits of personnel devoted to those tasks. The costs of inpatient pharmacists will be derived from direct observations. We will randomly selected times and study sites to conduct brief interviews with inpatient pharmacists to assess typical time related to delivering the intervention. Estimates of PACT team-member time will be assessed similarly.

To estimate mean QALYs for the intervention and usual care groups requires data on survival time over the 12 months post stent for every patient, and a measure of the quality of life for each patient over those 12 months. Data on survival will come from CDW vital statistics file.

Although we hope the randomized step-wedge design of the trial will lead to treatment groups that are balanced on observed covariates at baseline, we recognize that some imbalances may nevertheless occur and multivariable models maybe necessary to account for these imbalances. To assess differences in costs we will use analytic models that account for the skewed nature of cost data, and we will pay special attention to the possible biases caused by heteroscedastic error terms across INT and UC groups (44-45). Because QoL data are bounded by 0 and 1, we use beta models to estimate differences in QALYs by treatment group (46). We will use bootstrapping to estimate the uncertainty of the ICER. If the INT group is found to have better outcomes but at higher mean costs than UC, we will produce cost effectiveness acceptability curves to depict the probability that the intervention would be cost effective at various levels of willingness to pay for an additional QALY (47).

G. Summarize Knowledge to be Gained:

This study will refine the current state of knowledge on improving medication adherence in multiple ways. First, it combines multiple interventions that have been separately shown to be effective in improving medication adherence and addresses causes of clopidogrel non-adherence identified by patients. Second, the intervention focuses on a novel setting (i.e., patients discharged following PCI and transitioning to outpatient care) in contrast to prior adherence interventions that have focused only on patients with stable chronic diseases (e.g., hypertension). Third, the targeted medication in this study has demonstrated short-term benefits and where non-adherence can have immediate adverse outcomes (e.g., stent thrombosis with discontinuation of clopidogrel). Fourth, the study utilizes existing

resources (i.e., cardiac data systems integrated with the VA electronic health record, VA pharmacists and patient-aligned care teams) to implement the intervention, improving the feasibility of broader implementation. Finally, this study is being conducted as a type I hybrid implementation study and therefore includes extensive study of the implementation process, which will yield both contributions to implementation science and facilitate wider dissemination if the intervention is found to be effective.

H. References:

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Appendix 1: Draft questions for the email survey:

1. Do you take care of patients who receive stent(s) and are taking clopidogrel therapy? O Yes O No (Can stop questionnaire)
2. What is your current position? O Resident/Fellow physician O Other type of physician O Inpatient Pharmacist O Nurse O Outpatient Pharmacist O Physician Assistant O Cardiologist O Nurse Practitioner O Hospitalist
3. Who is primarily responsible for prescribing clopidogrel at your facility at hospital discharge? (check all that apply) O Resident/Fellow physician O Other type of physician O Inpatient Pharmacist O Nurse O Outpatient Pharmacist O Physician Assistant O Cardiologist O Nurse Practitioner O Hospitalist
4. How often do you estimate that pharmacists bring the patient's discharge medications to the bedside at your facility? O All of the time (100%) O Infrequently (10-39%) O Most of the time (70-99%) O Almost never (1-9%) O Some of the time (40-69%) O Never (0%)
5. If not all of the time, why is this not the usual practice in your opinion? *(Free text comment)*
6. Do you think it is feasible to have clopidogrel brought to the patient's bedside prior to hospital discharge? O Yes O No If yes, who would be in the best position to do this? If no, what are the barriers that make this not feasible?
7. Who is primarily responsible for prescribing clopidogrel at your facility in the outpatient setting? (check all that apply) O Resident/Fellow physician O Other type of physician O Inpatient Pharmacist O Nurse O Outpatient Pharmacist O Physician Assistant O Cardiologist O Nurse Practitioner

O Hospitalist O Primary care physician
8. Does your site have a program (e.g. pharmacist follow-up) to facilitate or ensure adherence to clopidogrel in the outpatient setting? O Yes O No If yes, please describe the program. *(Free text comment)*
9. What happens if patients delay or do not refill their clopidogrel as an outpatient? Please describe. *(Free text comment)*
10. Do you think it would be helpful to notify a provider when a patient has not refilled their clopidogrel? O Yes O No If yes, who would be the best person to notify? *(Free text comment)*
11. In your opinion, is it feasible for providers to contact the patient to assess and ensure patients refill their clopidogrel? O Yes O No If no, what are the potential barriers? *(Free text comment)* If yes, who would be the best person to do that at your facility?
12. Do you think an automated telephone call reminding patients to refill their clopidogrel would be helpful? O Yes O No If no, what would be other alternatives to remind patients to refill their clopidogrel? *(Free text comment)*
13. Would you be willing to lead implementation of a multi-faceted intervention to improve clopidogrel adherence at your site? O Yes O No

If no, who would you recommend?

Appendix 2: Key informant interviews for baseline assessment of clopidogrel adherence programs

1. Introduce self:

Hello, my name is [name of interviewer]. I am working on the Hybrid Effectiveness-Implementation Clopidogrel Study. [Name of person who set up interviews] contacted you [when: e.g., a few weeks ago] to set up this interview appointment.

2. Introduce the project:

- The Hybrid Effectiveness-Implementation Clopidogrel Study is a study to test an intervention to improve clopidogrel adherence among patients who undergo percutaneous coronary intervention (PCI).
- We are evaluating a multi-faceted intervention comprising of automated alerts that will remind pharmacists to come to the bedside of PCI patients to educate them and ensure they are discharged with clopidogrel, and interactive voice response (IVR) follow-up telephone calls with patients to refill clopidogrel. The goals of the study are to test the effectiveness of the intervention in improving clopidogrel adherence and reducing adverse outcomes, and to understand how to best implement the intervention in VA facilities.
- The intervention consists of 4 components:
  - A reminder from CART-CL will be sent to the inpatient pharmacist prior to discharge that a patient has received a stent;
  - The pharmacist will educate the patients on the importance of and adherence to clopidogrel following PCI, as well as bring clopidogrel to the patient's bedside prior to hospital discharge;
  - Interactive voice response (IVR) calls will be made to patients prior to the time of clopidogrel refill to remind patients and to facilitate refills during follow-up; and
  - A Patient Aligned Care Team (PACT) member will contact patients who delay filling clopidogrel.

3. Explain the purpose of the interview

I/we are interviewing a number of people at your site who can help us understand the medication and hospital discharge process for PCI patients, and how this project might best fit in with what is going on now. We wanted to talk with you before the Hybrid Effectiveness-Implementation Clopidogrel Study is implemented so we can understand what is going on now to improve clopidogrel adherence, how you currently work with primary care, and hear your opinions about how the study should work here.

4. Describe how we will assure confidentiality, obtain consent, and answer any questions.

I want to let you know what will happen to the information you provide. I am recording this conversation so that we do not miss anything that you have to say. People working on this study will be the only ones who will use the interview recordings and the recordings will be stored on the secure VA site behind VA firewall. We will take steps to ensure the information you provide remains confidential. Individuals will not be named in any notes, report or summary.

1. Role of interviewee

   1.1. I'd like to begin by asking what your role is within this facility.

   1.2. Probes:

      1.2.1. Do you have responsibilities outside this facility?

      1.2.2. Is there anything else?

2. Current discharge medication process
    2.1. Can you give me a brief overview of how discharge medication is organized here?
    2.2. Probes:
        2.2.1. When do patients receive discharge medications?
    2.3. When and how do you provide education to the patient or their caregivers about medications?
    2.4. When and how is communication with the patients' primary care team handled?
3. Current challenges to discharge medication process
    3.1. What challenges do you (or your facility) see in ensuring that PCI patients are discharged on clopidogrel?
    3.2. What challenges do you (or your facility) see in ensuring that hospital patients in general are discharged on required medications?
    3.3. Probes:
        3.3.1. What are the main things that contribute to these challenges?
        3.3.2. Main Facilitators?
4. Current challenges to clopidogrel adherence in the outpatient setting
    4.1. Do you think patient are taking clopidogrel as prescribed in the outpatient setting?
    4.2. What challenges do you (or your facility) see in ensuring that patients refill and continue to take clopidogrel as prescribed?
    4.3. Probes:
        4.3.1. What are the main things that contribute difficulties with adhering to clopidogrel treatment?
        4.3.2. What do you think are things that can help patients take clopidogrel as prescribed?
5. Receptiveness to Hybrid Effectiveness-Implementation Clopidogrel Study Intervention
    5.1. How receptive do you think clinicians [and others] will be to the intervention? Why?
    5.2. What concerns do you think pharmacists and clinicians might have about this intervention? How do you think we could address these concerns?
    5.3. What other changes would you recommend to make the intervention more effective? Easier to implement?
    5.4. How big of a change do you think the intervention will be compared to the way you're currently managing clopidogrel prescriptions for hospital patients?
6. Clinician views of intervention
    6.1. When you imagine actually implementing an intervention like this, what kinds of things would cause you to be enthusiastic about it?
    6.2. What kinds of things would cause you to be uncomfortable about an intervention like this?
7. The Environment
    7.1. On a scale of 0 to 10, how difficult would it be to implement this program in this facility? Why?
    7.2. On a scale of 0 to 10, how much do you think the program will help patients? Why?
    7.3. What kind of feedback would you want about the program when it is implemented (e.g., # pts eligible, clopidogrel adherence rate, stories from patients)?
    7.4. What can we do to help staff feel prepared and confident about the intervention?

8. Sustainability

   8.1. What else are the most important things that we would need to show for this facility to continue/expand a program like Hybrid Effectiveness-Implementation Clopidogrel Study?

   8.2. What kind of case would need to be made to convince people to continue/expand this program after the evaluation phase is done?

   8.3. Do you have any recommendations or considerations that we haven't discussed?

   8.4. Anything you'd like to suggest as we refine the intervention over the next few months?

9. Close

   That covers all the questions that we wanted to ask. Thank you so much for all the information you have provided.

   9.1. Do you have any final questions for us?

   9.2. Is it ok if we contact you for another interview in the future?

Appendix 3: Interviews to assess barriers and facilitators to intervention implementation of clopidogrel adherence programs

Provider/Intervention Personnel Questions:

1. What is your current role in the Hybrid effectiveness-implementation clopidogrel study?
2. Please tell us about your experience with the Hybrid effectiveness-implementation clopidogrel study to date.
3. What's your impression of how it's going (questions for inpatient pharmacist or other designee for education and bring clopidogrel to the bedside)?
    a. Are you being notified that a PCI procedure has been performed?
    b. If not, why?
    c. How can the notification process be improved?
    d. Do you have time to educate and bring clopidogrel to the patient's bedside?
    e. If not, what are the barriers?
    f. How can the education process or the process of bring clopidogrel to the bedside be improved?
    g. Other suggestions to improving the discharge process for patients receiving a stent?
4. What's your impression of how it's going (questions for outpatient PACT team member or other designee)?
    a. Have you been notified that a patient has not refilled clopidogrel?
    b. If yes, did you contact the patient and what did you do when you contacted the patient?
    c. How do you think the process can be improved?
5. Scale of 0 to 10, how difficult has it been to implement this program at your facility? Why?
6. What should be modified or improved?

Patient Questions:

1. Please tell us about your experience with the Hybrid effectiveness-implementation clopidogrel study to date.
2. What's your impression of the discharge process?
    a. Did you receive any education about clopidogrel prior to discharge? If so, what did you think of the education that you received?
    b. Did you receive the clopidogrel wallet card prior to discharge? If so, what did you think of the wallet card that you received and do you carry it with you?
    c. Did someone bring clopidogrel to the bedside prior to discharge? If so, what did you think of that?
3. Have you received an automated call reminding you to refill your clopidogrel?
    a. If yes, what did you think of the call? Was it helpful in reminding you to refill your medication?
    b. If not, what would make it more helpful to remind you to refill your medication?
    c. Did you use other options on the IVR call such as being connected to the pharmacy refill line or having the pharmacist call you to answer your questions?
    d. If yes, how was the process of interacting with the telephone system?
    e. What other features would you like to see with the telephone system?
4. Scale of 0 to 10, how much is a program like this helping you? Why?