# Evaluation of the National Randomized Proton Pump Inhibitor De-Prescribing (RaPPID) Program

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# 1 PROTOCOL SUMMARY

## 1.1 SYNOPSIS

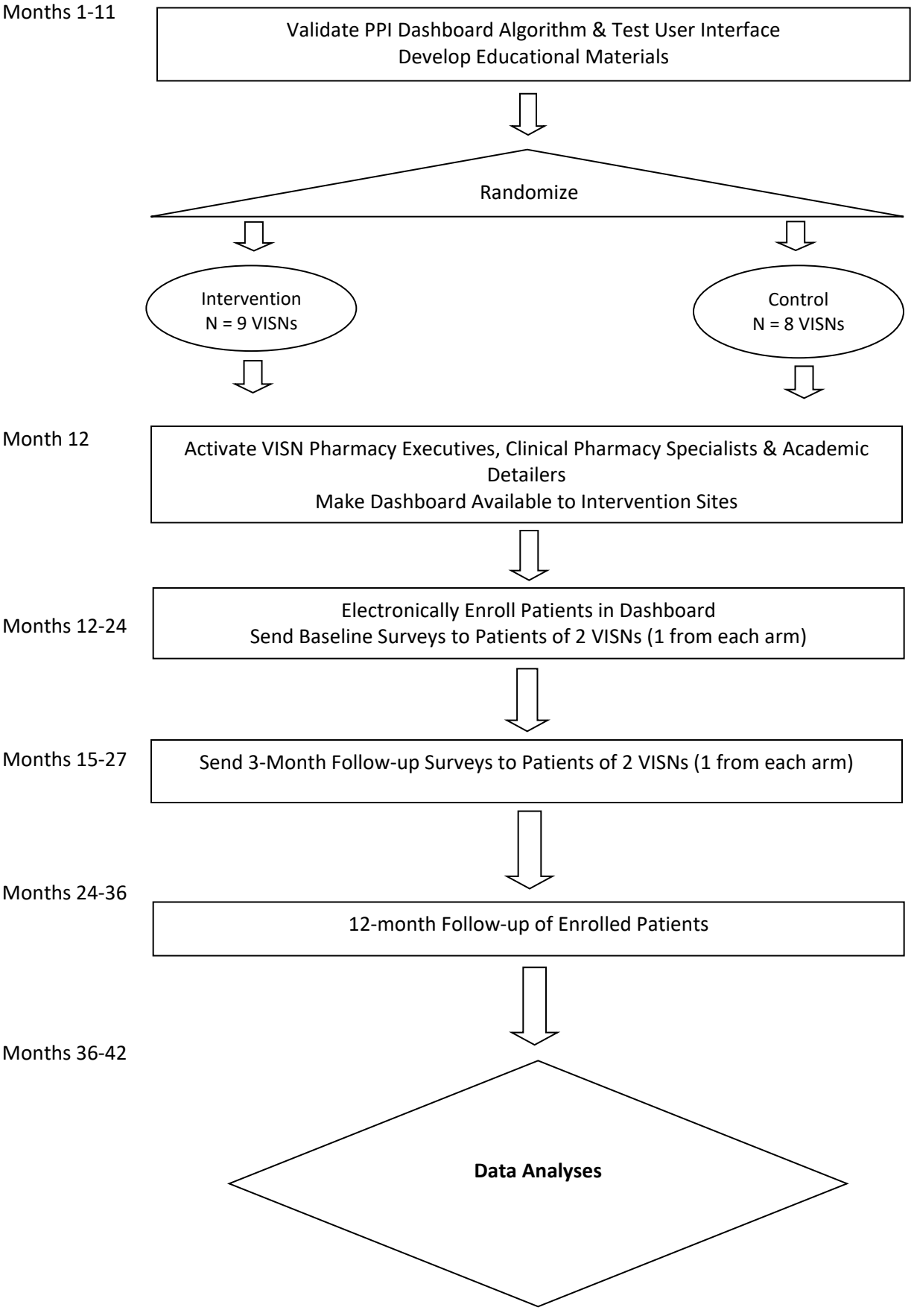
**Background**
Proton pump inhibitors (PPIs) are among the most commonly prescribed medications in the Veterans Health Administration (VHA), accounting for over 11 million 30-day prescriptions and nearly $50 million in medication costs annually. Though effective for treatment of acid-related disorders such as gastroesophageal reflux disease (GERD), PPIs have been associated with a number of possible harms in observational studies (e.g., enteric infections such as Clostridium difficile colitis, pneumonia, chronic kidney disease, fractures, dementia, and a recent VA study reported increased mortality in Veterans receiving PPIs). Unfortunately, PPIs continue to be used without an appropriate indication or for longer and at higher doses than necessary. Accordingly, in September 2019, VHA Pharmacy Benefits Management Services (PBM) deployed the Randomized PPI De-Prescribing (RaPPID) Program – a national, multi-level PPI de-prescribing initiative targeting patients for whom chronic PPI therapy may not be necessary. This program, modeled after a successful initiative in one Veterans Integrated Service Network (VISN), comprises 3 key components: (1) activation of clinical pharmacy specialists; (2) provider education and targeted notifications and academic detailing; and, (3) patient education.

**Objectives**
We sought to evaluate RaPPID through a cluster-randomized trial of PPI de-prescribing involving 17 VISNs to (1) identifying barriers and facilitators to implementation of RaPPID; and (2) understanding whether the program is effective at improving appropriate use of PPIs and whether there are any unintended consequences, (3) assessing how successfully the program components are delivered, a critical question in understanding why the program did or did not work as intended; and, (4) estimating the costs and possible savings associated with the program and with PPI de-prescribing in general.

**Methods**
We evaluated RaPPID in the context of a nationwide, stratified cluster-randomized controlled trial that incorporated assessments of both effectiveness and implementation (hybrid type II; cluster = VISN). Initially, the dashboard algorithm was validated and evaluated, the dashboard was user-tested and refined (months 1-11), the program was deployed nationally in a cluster-randomized fashion (months 12-24), and subjects were followed for 12 months (months 24-36). In months 18-30, we conducted a process evaluation. Data sources included VA Corporate Data Warehouse (CDW), patient surveys, and interviews with VISN Pharmacy Executives, PBM Academic Detailers, pharmacists, and primary care providers.

**Impact**
This approach allowed us to simultaneously understand barriers and facilitators to implementation of a program focused on stopping use of a specific treatment (de-implementation), share data with VA PBM so they could refine the program to maximize fidelity and consistency of implementation, measure important clinical outcomes, and improve the health of Veterans at scale. The study also provided broader lessons about how to effectively undertake other such nation-wide interventions.

## 1.2 SCHEMA


Months 1-11
Validate PPI Dashboard Algorithm & Test User Interface
Develop Educational Materials
Randomize
Intervention
N = 9 VISNs
Control
N = 8 VISNs
Month 12
Activate VISN Pharmacy Executives, Clinical Pharmacy Specialists & Academic Detailers
Make Dashboard Available to Intervention Sites
Months 12-24
Electronically Enroll Patients in Dashboard
Send Baseline Surveys to Patients of 2 VISNs (1 from each arm)
Months 15-27
Send 3-Month Follow-up Surveys to Patients of 2 VISNs (1 from each arm)
Months 24-36
12-month Follow-up of Enrolled Patients
Months 36-42
Data Analyses

# 2 INTRODUCTION

## 2.1 STUDY RATIONALE

Focusing VHA resources more efficiently through de-implementation of low-value care is one of VHA's top 5 strategic priorities. But, to date, large-scale, programmatic initiatives to reduce the use of low-value care had been uncommon (24). This partnered evaluation gave VHA the opportunity to reduce the use of a low-value service, thereby improving the health of Veterans, while also making several key scientific contributions. First, it provided real-time insights into barriers and facilitators of a large-scale de-implementation effort from the perspective of Veterans, providers, and systems. The knowledge gained was "fed back" to our partners in PBM to further enhance future efforts to de-prescribe in other clinical contexts (such as de-prescribing of anti-hypertensives and diabetes medications in older adults) (25). Notably, this was among the largest de-prescribing initiatives ever conducted. Additionally, this is a topic of high priority for our partners at PBM, the VHA GI Program Office, and the Chief Research and Development Officer (CRADO). A second major contribution of the study was the ability to make generalizable conclusions about the risk-benefit ratio of PPI de-prescribing, as well as the true risks posed by PPIs, by virtue of the study's large (VHA-wide) scale, cluster-randomized design, and duration. Prior randomized trials of PPI deprescribing have been relatively small and short in duration, limiting their ability to detect serious but uncommon harms of de-prescribing, such as upper GI bleeding or increased healthcare utilization. Additionally, we planned to rigorously assess the impact of reduced PPI use on selected adverse effects. Whether PPIs truly cause the harms with which they have been associated remains a major unresolved scientific question. Thus, the proposed work aligned well with VHA's broader goal of becoming a Learning Health System and leveraging electronic health record (EHR) data to conduct an evaluation of the planned implementation of a high-priority national clinical program.

## 2.2 BACKGROUND

**Proton pump inhibitors (PPIs) are among the most commonly used medications in the United States.** While these medications are highly effective for acid peptic disorders, observational studies suggest that they can cause harm. Prior studies have reported harms associated with PPI use, including vitamin B12 deficiency, hypomagnesemia, fractures, enteric infections (e.g., C. difficile colitis), pneumonia, and myocardial infarctions (1,2). More recent studies have reported additional associations with chronic kidney disease, dementia, stroke, and death (3,9–11).

**Despite data on possible harms, PPIs are overused.** Given the possible harms associated with PPIs, identification of patients unlikely to benefit from long-term daily use is a top priority. The Choosing Wisely® Campaign stated that more than half of those who take PPIs may not need them, and that if gastroesophageal reflux disease (GERD) symptoms resolve after a few weeks, patients should stop their PPIs. Despite such recommendations, preliminary data suggest that >33% of Veterans who use PPIs do not have a clear indication or have well-controlled, uncomplicated GERD. Given that ~15% of Veterans take PPIs chronically, large numbers of Veterans may be incurring harm with little or no benefit.

**Efforts to de-prescribe PPIs have shown efficacy but have failed to be widely adopted.** The data on PPI overuse and harms have generated interest in de-prescribing – "the process of withdrawal of an inappropriate medication, supervised by a healthcare professional with the goal of managing polypharmacy and improving outcomes." (12) De-prescription of PPIs has been evaluated in small trials of patients with GERD. For example, a prospective study conducted at the VA Ann Arbor Healthcare System (VAAAHS) in 2001 evaluated de-prescription in 71 patients with well-controlled GERD. 58% of these 71 patients were successfully de-prescribed at 1 year, but most (73%) required H2-receptor antagonists (H2RAs) or prokinetics for control of symptoms. De-prescription did not reduce quality of life or worsen disease severity (13). In another study of 117 VA patients with well-controlled GERD on twice-daily PPI, 80% were symptom-free 6 months after stepping-down to once-daily dosing (14). Finally, in one VISN, a pharmacy-led program that leveraged clinical pharmacy specialist (CPS) providers, academic detailing, and patient education showed a

reduction in PPI use in an uncontrolled analysis (33% relative reduction in PPI use compared to the average VISN, per PBM), and this reduction has been sustained over several years such that that VISN has the lowest PPI use nationally.

**Stopping PPIs in the wrong patients can cause harm.** By blocking the production of gastric acid, PPIs are highly effective at preventing and treating peptic ulcer disease (PUD) and its complications (e.g., upper gastrointestinal (GI) bleeding and subsequent need for hospitalization, transfusion, endoscopic therapy, surgery). As a corollary, stopping PPIs in patients who are at increased risk for PUD can promote upper GI bleeding, the most common cause of GI hospitalization in the United States. The widespread use of antiplatelet agents for cardiovascular prevention and the growing use of direct anticoagulants means that many Veterans are now at increased risk for upper GI bleeding. Moreover, bleeding is not the only potential unintended consequence of stopping PPIs. A 2017 Cochrane review of randomized trials of PPI de-prescription included 6 studies of de-prescription in patients with PPI-responsive GERD (15). Those randomized to de-prescription followed by on-demand therapy showed a 58% reduction in PPI pill use (3.79 vs 6.57 pills per week), but they also experienced an increase in poor symptom control (RR=1.71; 95% CI: 1.31-2.21). These data suggest that any PPI de-prescribing program must: (1) ensure appropriate de-prescribing – that patients who are taking PPIs for GERD are offered a trial off PPI therapy while those who are at increased risk for GI bleeding are NOT inadvertently taken off their PPIs; and, (2) assess for potential unintended consequences including worsening in upper GI symptoms or quality of life (assessed through patient-reported outcomes (PROs)) and an increase in upper GI bleeding events. Further refinement and validation of an existing electronic algorithm to identify candidates for appropriate de-prescribing was a core deliverable from this study.

**Due to concern about PPI overuse and harms, PBM deployed a national program to appropriately de-prescribe PPIs in 2019-2020.** In light of the data on overuse and PPI harms, PBM deployed a national de-prescribing program in 2019 – the Randomized PPI De-Prescribing (RaPPID) Program. RaPPID was modeled after the successful experience of a VISN program, with modifications to ensure that de-prescribing is appropriate and efficient (using the electronic algorithm developed by our team) and that randomization and deployment was feasible at the national level. Specifically, the program leveraged PBM infrastructure at multiple levels of the health system, including their national network of clinical pharmacy specialist (CPS) providers, an electronic dashboard system, PBM's academic detailing capabilities, and patient education. We worked closely with the Director of Center for Medication Safety at PBM to coordinate the evaluation of RaPPID. PBM's planned de-prescribing program offered a rare opportunity to study the effectiveness of PPI de-prescribing and the barriers and facilitators of a large-scale de-implementation effort.

### 2.2.1 PRELIMINARY WORK

**PPIs are among the most commonly used medications in VHA.** Working with PBM, we examined the prevalence of PPI use in Veterans as well as associated costs. Based on these data, PPIs were used regularly (> 270 days per year) in 15.4% of Veterans. While the cost of these drugs was low on a per-pill basis, their widespread use incurred significant cost – approximately $50,000,000 per year in direct drug costs alone. At least one-third of Veterans using PPIs had no clear indication or had only uncomplicated GERD. Together, these Veterans (using PPI for no indication or for uncomplicated GERD without risk factors for upper GI bleeding) were the focus of RaPPID.

**PPIs have the potential to cause long-term, debilitating harms.** Multiple PD/PIs Drs. Yang and Laine have published multiple pivotal studies investigating the adverse effects of PPIs (16–20). Although these epidemiological studies cannot definitively address whether these adverse effects are truly caused by PPIs, there are biologically plausible mechanisms linking these potent acid suppressants to a number of physiological changes that could mediate the reported adverse effects. Therefore, PPI therapy in patients without an appropriate indication is a low-value, potentially harmful practice that is not recommended.

**Most patients using PPIs are concerned about adverse effects.** In 2017, co-investigator Jacob Kurlander surveyed 755 patients using PPIs for GERD in an online survey sample (manuscript under review at JAMA-IM). Of these 755 patients, 54% reported awareness of one or more PPI-related adverse effects, most commonly chronic kidney disease (17%), and 78% reported at least some concern about PPI adverse effects. Only 24% reported that a physician had discussed PPI risks and benefits with them, and only 9% had been encouraged to stop by a physician. Independent predictors of a prior attempt to stop included: (1) physician recommendation (OR 3.26, 95% CI: 1.82-5.83); and (2) concern about PPI-related adverse effects (OR 12.0, 95% CI: 6.51-22.2). Notably, patients at high risk of upper GI bleeding, who require long-term PPIs for gastroprotection, were just as likely to have stopped their PPI as others (OR 0.97, 95% CI: 0.66-1.44). This study underscores the prevalence of public concern about PPI-related harms and the potential dangers of self-directed attempts at PPI discontinuation, which could be harmful in the wrong patients.

**Providers are also concerned about PPI-related adverse effects but inappropriately recommend withdrawing PPIs from high-risk patients.** We surveyed a representative sample of internists in the United States (N=487, response rate 53%) to evaluate how physicians were changing their PPI prescribing practices due to concern about adverse effects (21). Of the sample, 63% reported sometimes or often taking steps to reduce their patients' exposure to PPIs by reducing the dose, switching to an H2RA, or stopping the PPI altogether. Providers were also asked to report how likely they would be to recommend PPI de-prescription in a patient with bone loss (a potential PPI adverse effect) in vignettes of patients at low, intermediate, and high risk for upper GI bleeding. Surprisingly, providers were *more likely* to stop PPI in the high-risk vignette (62%) than in the intermediate-risk vignette (47%) or the low-risk vignette (32%). These findings show the importance of having an algorithm that can identify patients who are at high risk for GI bleeding to guide appropriate de-prescribing of PPIs.

**An electronic algorithm can reliably identify candidates for PPI de-prescription in a pilot study.** Dr. Yang, and co-investigator, Brian Sauer, have previously used CDW data to identify candidates for PPI de-prescribing. For example, Drs. Yang and Sauer developed an electronic algorithm to identify Veterans who had been prescribed PPIs in 2012. They identified ~3,000,000 Veterans who had at least one PPI prescription in the prior year, 33% of whom did not have an appropriate indication. In other work, Dr. Yang undertook pilot development and validation of an algorithm to identify appropriate candidates for PPI de-prescribing (i.e., *chronic* PPI users with uncomplicated GERD or without clear indication – the target population for RaPPID) at the Philadelphia VA Medical Center. A CDW-based algorithm was developed to identify candidates for de-prescribing, and validation was performed through manual record review of 100 patients randomly selected from over 9,000 PPI users. The sensitivity of the CDW algorithm for identifying appropriate de-prescribing candidates was 100% (95% CI: 90%-100%), and the specificity was 97% (95% CI: 89%-100%). While these results were impressive, they were obtained at a single center. Additional refinement and validation were performed during our planning period. Given the large number of Veterans using PPIs, it was imperative that the algorithm used to identify de-prescribing candidates in RaPPID have high specificity to prevent alert fatigue and obsolescence among providers.

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 KNOWN POTENTIAL RISKS

There were no physical risks from participation. The study's chief risk is the psychosocial/financial/legal risk of potential loss of confidentiality. We stored electronic files that contain personal identifiers. The investigative team used their considerable experience in maintaining the confidentiality of large datasets and adhered to all VHA established procedures in place to ensure data confidentiality.

### 2.3.2 KNOWN POTENTIAL BENEFITS

No direct benefits to the subjects themselves were anticipated, as they were not being treated. However, this study's findings directly enhanced all Veterans' care by gaining insights about how to appropriately de-prescribe PPIs and how to

effectively undertake other such interventions to "unlearn" entrenched clinical practices in the future. Thus, the benefit to future VA patients was likely to be substantial.

### 2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

**Risk Minimization**

The risks to subjects were minimal and were addressed by following strict privacy and confidentiality procedures regarding how data are collected, stored, and used throughout the course of this project. There were no physical risks to participation in this study. There was potential risk of psychological, financial, or legal harm due to exposure of personally identifying information (PII) or protected health information (PHI). However, the risk of a breach of confidentiality was low. Throughout the study, VHA, IRB, and HIPAA guidelines were followed to ensure the privacy and integrity of the information collected. Any breach would have been immediately reported to the PD/PIs and the appropriate IRBs. To minimize the risk of a breach of confidentiality, we performed the following steps. First, as soon as the cohort was defined by the data manager, each patient in the cohort was assigned a unique study ID unrelated to any identifying information. We then created a limited access electronic tracking file that mapped the study participant's identifying information to the study ID.

**Importance of Knowledge to be Gained**

VHA has long been a leader in measuring and delivering high-quality care. In recent years, however, it has become increasingly apparent that efforts to promote quality have inadvertently led to the use of not only high-value, but also low-value care. To date, however, large-scale, programmatic initiatives to reduce the use of low-value care have been uncommon. This partnered evaluation gave VHA the opportunity to simultaneously address the use of a low-value clinical service and to understand multi-level barriers to de-implementation of a commonly prescribed medication. Additionally, by randomizing the program, VHA ensured that efforts to de-prescribe PPIs do not cause unintended harms (such as upper GI bleeding) and assess the effect of reduced PPI use on selected adverse effects (such as enteric infections, fractures, pneumonia, and hypomagnesemia). Notably, this was the largest de-prescribing initiative ever conducted. Studying its effects in real time yielded valuable generalizable knowledge about how systems can effectively de-implement low-value care. Moreover, the randomized evaluation yielded clinical knowledge about the balance of benefit and harm for PPIs, knowledge that was unlikely to be acquired in any other evaluation.

## 3 PRIMARY OBJECTIVES AND ENDPOINTS

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
|---|---|---|
| **Primary** | | |
| Proportion of days PPIs are prescribed at or above the baseline daily dosing-frequency, over the 12 months following the index visit. | We hypothesize (H1) that the proportion of days will be lower in intervention group than in the control group (i.e., that the outcome will be superior in the intervention vs control group). This outcome is analogous to the medication possession ratio. | This is the appropriate measure of success of de-prescribing because it captures a variety of results in a single endpoint, including discontinuation without resumption, discontinuation with intermittent or on-demand use, and resumption of daily PPI at or above baseline dosing frequency. |

# 4 STUDY DESIGN

## 4.1 OVERALL DESIGN

**Study Design:** We evaluated RaPPID in the context of a nationwide, stratified cluster-randomized controlled trial that incorporated assessments of both effectiveness and implementation (hybrid type II) (28). RaPPID was a multi-level de-prescribing program modeled after a similar initiative developed and deployed in one VISN in 2015. After validating and testing the deprescribing algorithm and dashboard, developing educational materials and randomization (months 1-11), the program was deployed nationally in a cluster-randomized fashion (months 12-24). During the randomization and subsequent follow-up period (months 24-36), we assessed the program's impact on a variety of clinical outcomes.

**Study Population and Sample:** De-prescribing of PPIs has potential clinical and economic benefits (by reducing unnecessary daily use of a medication with possible long-term harms). However, de-prescribing may also be harmful due to worsening upper GI symptoms and increased risk of upper GI bleeding. To maximize potential benefit and minimize potential harm, RaPPID focused on "chronic PPI users" (defined as daily PPI for ≥ 90 days during the 120-day period prior to PCP visit) with uncomplicated GERD, OR with no clear indication for PPI. Those who had acceptable indications for chronic PPI therapy (e.g., NSAID use, anti-thrombotic use, PUD, Barrett's esophagus, erosive esophagitis, eosinophilic esophagitis) were excluded. Identification of candidates for appropriate de-prescription was facilitated by a high-specificity electronic algorithm, as discussed in Section 2.2, Background.

### 4.1.1 PROCEDURES

**Overview of RaPPID:** RaPPID was a multi-level program modeled after a successful de-prescribing initiative in one VISN. The program had 3 main components: (1) activation of VISN Pharmacy Executives (VPEs) and their subsequent activation of Clinical Pharmacy Specialist (CPS) providers at VA Healthcare Systems within their VISNs; (2) provider education with targeted academic detailing and notifications; and, (3) patient education. CPS providers are pharmacists with training and expertise in medication stewardship, quality improvement, and medication-use evaluation. Many CPS providers have a broad scope of practice that allows them to prescribe and de-prescribe medications, deliver provider and patient education, and provide professional-to-professional academic detailing, and they often work with other clinical providers and patients to improve appropriate medication use (29). PBM has successfully used CPS providers in several national medication safety initiatives. In RaPPID, PBM leveraged this national network of experienced CPS providers to undertake this initiative focused on safely de-prescribing PPIs. Specifically, PBM asked VPEs randomized to the intervention to identify local CPS providers to champion the program at their respective facilities. CPS providers were then be "activated" with a variety of standardized tools (see below). It is important to note that while PBM had extensive experience in conducting medication evaluations, RaPPID was novel in several ways: (1) it was randomized – PBM had experience conducting randomization in the context of research studies using similar tools, (2) it involved one of the most commonly prescribed medications in VHA – prior evaluations had been significantly smaller in scale; and, (3) it involved appropriate de-prescribing – prior de-prescribing efforts had focused on acute medication safety issues, where de-prescribing recommendations were less nuanced and less apt to cause harm (such as upper GI bleeding due to inappropriate de-prescribing of PPIs).

**Activation of CPS Providers:** CPS providers were "activated" with a variety of standardized tools, including: (1) the PPI Dashboard; (2) educational materials to help CPS providers promote RaPPID to PCPs and clinical staff at their facilities; and, (3) educational materials for patients who were de-prescribed, to provide guidance and support for managing bothersome symptoms in the period immediately after de-prescribing. The PPI Dashboard served several important purposes. It allowed the CPS providers to efficiently identify PPI de-prescribing candidates up to 4 weeks ahead of a scheduled primary care visit. It also allowed CPS providers to track patients who had been de-prescribed and monitor adoption of de-prescribing by individual providers. Data on adoption allowed the CPS providers to deliver academic

detailing (using local and regional academic detailing resources managed by PBM) to providers who appeared to be slow to adopt de-prescribing recommendations.

**RaPPID De-Prescribing Regimen:** The RaPPID de-prescribing regimen varied according to whether the Veteran was receiving once-daily or twice-daily PPI therapy. For patients on twice-daily PPI, the dosing frequency was reduced to once-daily and maintained at that dose (i.e., 50% dose reduction). For patients on once-daily PPI, the dose was to first be tapered to once-daily PPI every other day for 2 weeks, followed by discontinuation. All patients were to be prescribed H2RAs to be taken as needed for intermittent upper GI symptoms. Written educational information regarding de-prescription was to be provided to patients by the primary care team. The recommended de-prescribing regimen and appropriate management of recurrent symptoms was a key component of provider and patient education and (as needed) academic detailing.

**Deployment of RaPPID:** CPS providers used a variety of methods to initiate contact with PCPs at healthcare systems within VISNs randomized to RaPPID, including direct contact at primary care staff meetings and electronic contact via email. PCPs were to be educated and trained on: (1) the scientific justification for RaPPID; (2) VHA's national commitment to the program; (3) the protocol for de-prescribing; and, (4) resources for Veterans who are de-prescribed (educational materials, consultation with CPS providers). CPS providers adapted (as needed) standardized educational materials to their local sites and worked with primary care leadership at their sites to devise efficient methods for disseminating these materials (e.g., during team meetings). Additionally, the VHA National Program Office for Gastroenterology notified VHA GI Section Chiefs and providers of the effort as part of national field calls and email listserv updates. Once RaPPID was deployed, CPS providers used the Dashboard to identify and track candidates for de-prescribing and notified PCPs of candidates using locally adapted approaches (e.g., note in CPRS, email).

### 4.1.2 PROVIDER EDUCATIONAL MATERIAL EXCERPT

The text and table below were part of the educational materials for Pharmacy and Primary Care providers.

It is recommended that patients meeting inclusion-exclusion criteria should be deprescribed using one of the methods below. Some patients with GERD are expected to have recurrence of frequent bothersome symptoms intermittently in the coming months or years. Studies have suggested such patients can be well-managed by intermittent courses of once-daily PPI for up to 4 weeks. On-demand PPI therapy (in which the patient takes PPIs as they determine is needed based on symptoms and response) is also shown to be well accepted by patients with GERD. Only a minority of GERD patients should require daily maintenance PPI therapy to provide acceptable symptom relief.

| **Patients Taking PPIs** | |
|---|---|
| **Once Daily** | **Twice Daily** |
| ▪ Taper to every other day for 2 weeks and then discontinue<br>▪ Prescribe H2-receptor antagonists (e.g., famotidine, ranitidine) to take as needed for intermittent recurrent symptoms | ▪ Taper to once daily PPI, taken 30-60 minutes before a meal |
| Patients should be cautioned that they may have rebound symptoms for a few weeks after discontinuation. | |

### 4.2 JUSTIFICATION FOR INTERVENTION

Proton pump inhibitors (PPIs) are among the most commonly prescribed medications in the Veterans Health Administration (VHA), accounting for over 11 million 30-day prescriptions and nearly $50 million in medication costs annually. Though effective for treatment of acid-related disorders such as gastroesophageal reflux disease (GERD), PPIs have been associated with possible harms in observational studies (e.g., enteric infections such as Clostridium difficile colitis, pneumonia, chronic kidney disease, fractures, dementia) (1,2), and a 2017 VA study reported increased mortality in Veterans receiving PPIs (3). Unfortunately, PPIs continue to be used without an appropriate indication or for longer and at higher doses than necessary (4,5). Accordingly, in 2019, VHA Pharmacy Benefits Management Services (PBM) deployed the Randomized PPI De-Prescribing (RaPPID) Program – a national, multi-level PPI de-prescribing initiative targeting patients for whom chronic PPI therapy may not be necessary. This program, modeled after a successful initiative in one VISN, was comprised of 3 key components: (1) activation of clinical pharmacy specialists; (2) provider education and targeted notifications and academic detailing; and (3) patient education.

RaPPID was among the largest concerted efforts at de-prescribing ever undertaken in VHA. Prospective evaluation of the program therefore presented a unique opportunity not only to enhance the program itself, but also to gain insights into how to reduce the use of low-value services more broadly, a key VHA priority for the coming decade. Indeed, estimates suggest that 10% of all healthcare spending in the U.S. pays for unnecessary care (6). But reducing the use of low-value care is challenging for many reasons. Programs to reduce low-value care often employ multiple interacting components, deployed in active healthcare delivery contexts, and they require patients, providers, and systems to "unlearn" well-established behaviors and expectations about healthcare delivery (7,8). These challenges are compounded when efforts are scaled to the level of an entire health system.

### 4.3 END-OF-STUDY DEFINITION

The end of the study is defined as completion of the 12-month follow-up period of the last enrolled subject.

## 5 STUDY POPULATION

### 5.1 INCLUSION CRITERIA

The target population was chronic proton pump inhibitor (PPI) users who had a scheduled primary care visit.

| **Chronic PPI Users**<br>Defined as: ≥90-day prescription during the 120-day period prior to a scheduled primary care visit | |
|---|---|
| **Patients Who Take PPIs** | |
| **Once Daily**<br>**Meeting any of the following criteria:** | **Twice Daily**<br>**Meeting any of the following criteria:** |
| ▪ No clear indication for PPIs<br>▪ Uncomplicated GERD (i.e., no erosive esophagitis, stricture, dysphagia, or Barrett's esophagus) | ▪ No clear indication for PPIs<br>▪ Any indication (except Zollinger-Ellison) |

**Inclusion of Women, Minorities, and Children**

Racial and ethnic minority patients were represented in the VA National Patient Care Database and other VA datasets. 2017 estimates were that 11% of the VHA population was Black, 6% were Hispanic/Latino, and 4% were of another minority group. At 8%, women constitute a minority of the VHA population. However, this number is increasing, and all women Veterans who met inclusion criteria were included in this study. No children were included in this study.

### 5.2 EXCLUSION CRITERIA

The RaPPID Program avoided de-prescribing PPIs in patients for whom chronic PPI therapy was recommended by guidelines, consensus statements, and/or expert opinion. Stopping PPIs in these patients could have caused harms such as upper GI bleeding. Patients taking PPIs were excluded from the dashboard if they had one or more of the characteristics listed in the table below.

| **Twice-daily PPI Users with Zollinger-Ellison** | |
|---|---|
| **Once-daily PPI Users with any the following characteristics:** | |
| ▪ Eosinophilic esophagitis<br>▪ Esophagitis<br>▪ Barrett's esophagus<br>▪ Peptic ulcer<br>▪ Zollinger-Ellison<br>▪ Idiopathic pulmonary fibrosis | ▪ Pancreatic enzyme replacement<br>▪ Esophageal ulcer<br>▪ Esophageal stenosis/stricture<br>▪ Dysphagia (other than oropharyngeal) |
| **OR** | |
| **NSAID Users**<br>**Meeting any of the following criteria:** | **Low-dose Aspirin Users**<br>**Meeting any of the following criteria:** |
| ▪ age > 65 years of age<br>▪ Take a 2nd NSAID<br>▪ Take daily aspirin<br>▪ Take an anti-thrombotic drug<br>▪ Take an oral steroid | ▪ age ≥ 60 years of age<br>▪ Take NSAIDs regularly<br>▪ Take an anti-thrombotic drug<br>▪ Take a corticosteroid |

## 6 EXPERIMENTAL MANIPULATIONS

### 6.1 EXPERIMENT

| **Experiment: Behavioral** | |
|---|---|
| **Intervention Arm**<br>PPI De-prescribing Program | **Control Arm**<br>Usual Care/No PPI De-prescribing Program |
| ▪ Alerts to clinical pharmacy specialists and primary care providers informing them of individual patients scheduled for upcoming primary care visits who meet criteria for PPI de-prescription<br>▪ Activation of clinical pharmacy specialists<br>▪ Education of primary care providers<br>▪ Patient Education | ▪ Usual Care<br>▪ Did not receive the national de-prescribing program |

The study focused on the effect of the operational intervention, RaPPID, as compared to usual care. See Section 4.1.1 for detailed descriptions of intervention components.

### 6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization of VISNs (regions) was done by the study biostatistician. The investigators and operational partners were informed of the assignments after randomization was finalized.
There was no blinding once randomization was complete.

### 6.3 PARTICIPANT WITHDRAWAL FROM THE STUDY & LOST TO FOLLOW-UP

Not applicable for RCT as all subjects electronically enrolled were analyzed.
For patient reported outcomes, we expected some missing data. Our initial analyses only used observed data, but for missing data for items within scales, we used recommended imputation strategies. For missing 3-month survey assessments, we used logistic regression with missing follow-up as a dependent variable to see if missingness is associated with baseline variables, including facility-level variables. We included baseline variables found to be predictive of missingness in the longitudinal data model, and if missingness was at random, longitudinal mixed-effects provided an unbiased estimate of the study group effect. If the extent of missingness is more than 20%, we conducted a secondary analysis by combining results based on multiply imputed data using sequential regression multivariate imputation method,

## 7 PROCEDURES AND STUDY ASSESSMENTS

### 7.1 PROCEDURES

It was recommended that patients meeting inclusion-exclusion criteria should be deprescribed using one of the methods below. Some patients with GERD were expected to have recurrence of frequent bothersome symptoms intermittently in the coming months or years. Studies have suggested such patients can be well-managed by intermittent courses of once-daily PPI for up to 4 weeks. On-demand PPI therapy (in which the patient takes PPIs as they determine is needed based on symptoms and response) was also shown to be well accepted by patients with GERD. Only a minority of GERD patients should require daily maintenance PPI therapy to provide acceptable symptom relief. The table below was part of the educational materials for Pharmacy and Primary Care providers.

| **Patients Taking PPIs** | |
|---|---|
| **Once Daily** | **Twice Daily** |
| ▪ Taper to every other day for 2 weeks and then discontinue<br>▪ Prescribe H2-receptor antagonists (e.g., famotidine, ranitidine) to take as needed for intermittent recurrent symptoms | ▪ Taper to once daily PPI, taken 30-60 minutes before a meal |
| Patients should be cautioned that they may have rebound symptoms for a few weeks after discontinuation. | |

### 7.2 DATA COLLECTION

Data was collected from several sources, including: (1) VHA Corporate Data Warehouse (CDW); (2) surveys of Veterans; and (3) semi-structured interviews with CPS providers, GI providers, and PCPs as part of the process evaluation. Key measures are shown the table below.

### 7.2.1 VARIABLES & DATA SOURCES

| Variable | Description | Time Frame | Data Source |
|---|---|---|---|
| **Primary Outcome** | | | |
| PPI de-prescribing | Proportion of days PPI prescribed after index visit **(H1)** | 12 mo | CDW |
| **Secondary Outcomes** | | | |
| Utilization of outpatient care | Outpatient visit, ED visit, or upper endoscopy (EGD) for: (1) upper GI symptoms/conditions; (2) any cause | 12 mo | CDW |
| Utilization of inpatient care | Hospital admission for: (1) upper GI symptoms/conditions; (2) any cause | 12 mo | CDW |
| Serious GI complications | Complications of peptic ulcer disease (bleeding, obstruction, perforation) | 12 mo | CDW |
| PPI-related harms | E.g., fractures, enteric infections, pneumonia, kidney disease, dementia | 12 mo | CDW |
| Upper GI symptoms | Upper GI symptoms (RDQ) | 0, 3 mo | Surveys |
| Cost | Healthcare expenditures related to VA and non-VA care | 24 mo | Calculated |
| Reach | Proportion of patients offered de-prescribing | 3 mo | Post Survey |
| Adoption | Reduction in PPI use before / after program deployment | 3, 12 mo | CDW |
| Implementation | Implementation fidelity and consistency at each site (process) | 3, 12 mo | Staff Interviews |

### 7.2.2 STUDY ASSESSMENTS - VETERAN SURVEYS

One potential unintended consequence of PPI de-prescription is worsening upper GI symptoms. Worsening symptoms can substantially affect quality of life and promote use of medications and healthcare resources. Importantly, these medications and healthcare resources need not be sought within VA. For example, medications to alleviate heartburn may be obtained over-the-counter (OTC) or from a non-VA provider. Therefore, we used surveys to assess and track outcomes that could not be measured electronically, including upper GI symptoms, quality of life, and use of non-VA healthcare resources. We developed two surveys with distinct elements: (1) a pre-visit survey, to be completed 1-2 weeks prior to the index primary care visit; and (2) a post-visit survey, to be completed 3 months after the index primary care visit. Surveys were administered to subjects in the VISN with the most Dashboard activity (a high participation VISN) and a comparable control VISN.

**Pre-Visit/Baseline Survey**

The pre-visit survey included several established scales and individual survey items. Upper GI symptoms were assessed using the Reflux Disease Questionnaire (RDQ), a validated PRO scale. Quality of life was assessed using the Short Form-12 (SF-12). We also included single items to assess baseline trust in PCP, concern about PPI-related harms, and receptiveness to de-prescribing of PPIs, all taken from an existing survey instrument.

**Post-Visit Survey**

For the 3-month follow-up survey, we again assessed symptoms and quality of life using the RDQ and SF-12, respectively. As a measure of "reach" for our process evaluation, we developed a single item to assess whether the patient recalls a discussion with the PCP about PPI de-prescription. Furthermore, we developed items to assess use of non-VA medications for symptom control (PPIs, H2RAs, antacids) and the use of non-VA healthcare. We also asked Veterans to report the source of payment for these services (e.g., out of pocket, private insurance).

# 8 STATISTICAL ANALYSES

We **hypothesized** that RaPPID will reduce the use of PPIs without a clinically meaningful increase in upper GI symptoms or upper GI complications such as bleeding.

*Primary outcome measure:* The **primary outcome** was the proportion of days PPIs are prescribed at or above the baseline daily dosing-frequency, over the 12 months following the index visit. We **hypothesized (H1)** that the proportion of days would be lower in intervention group than in the control group (i.e., that the outcome would be superior in the intervention vs control group). This outcome is analogous to the medication possession ratio. This was the appropriate measure of success of de-prescribing because it captured a variety of results in a single endpoint, including discontinuation without resumption, discontinuation with intermittent or on-demand use, and resumption of daily PPI at or above baseline dosing frequency. *Secondary outcome measures:* We also measured a variety of secondary outcomes to assess unintended, adverse events related to PPI de-prescribing. We hypothesize that utilization of outpatient care (H2) and the patient reported outcome (PRO) of upper GI symptoms (H3) will be non-inferior in the intervention vs control group.

*Utilization of outpatient and inpatient care:* Using CDW data, we assessed utilization of outpatient care – clinic visits or emergency department visits (using stop codes) for predefined upper GI symptoms/diagnoses (based on ICD-10 codes) or upper endoscopies (based on CPT codes). We also assessed use of inpatient care (i.e., hospital admissions) for predefined upper GI symptoms/diagnoses (based on ICD-10 codes).

*Upper GI symptoms and quality of life:* We assessed upper GI symptoms using the RDQ, a validated PRO instrument (30,31). We also measured generic quality of life using the SF-12 (32).

*Serious GI complications:* We assessed upper GI complications (bleeding, perforation, obstruction) using ICD-10 codes.

*PPI-related harms:* To ensure that we captured all relevant harms, we reviewed published observational studies of PPI harms to identify relevant diagnoses and ICD-9/10 codes.

*Covariates:* Covariates included demographics (age, sex, race/ethnicity), Charlson comorbidity index, indication for PPI use (uncomplicated GERD vs no indication), and baseline PPI dosing frequency (once-daily vs twice-daily). We also collected covariates on a subset of patients (1 intervention VISN and 1 control VISN), using our survey questionnaires, including baseline RDQ symptom score, trust in provider, baseline concern about PPI harms, and receptiveness to de-prescribing of PPIs.

## 8.1 SAMPLE SIZE DETERMINATION

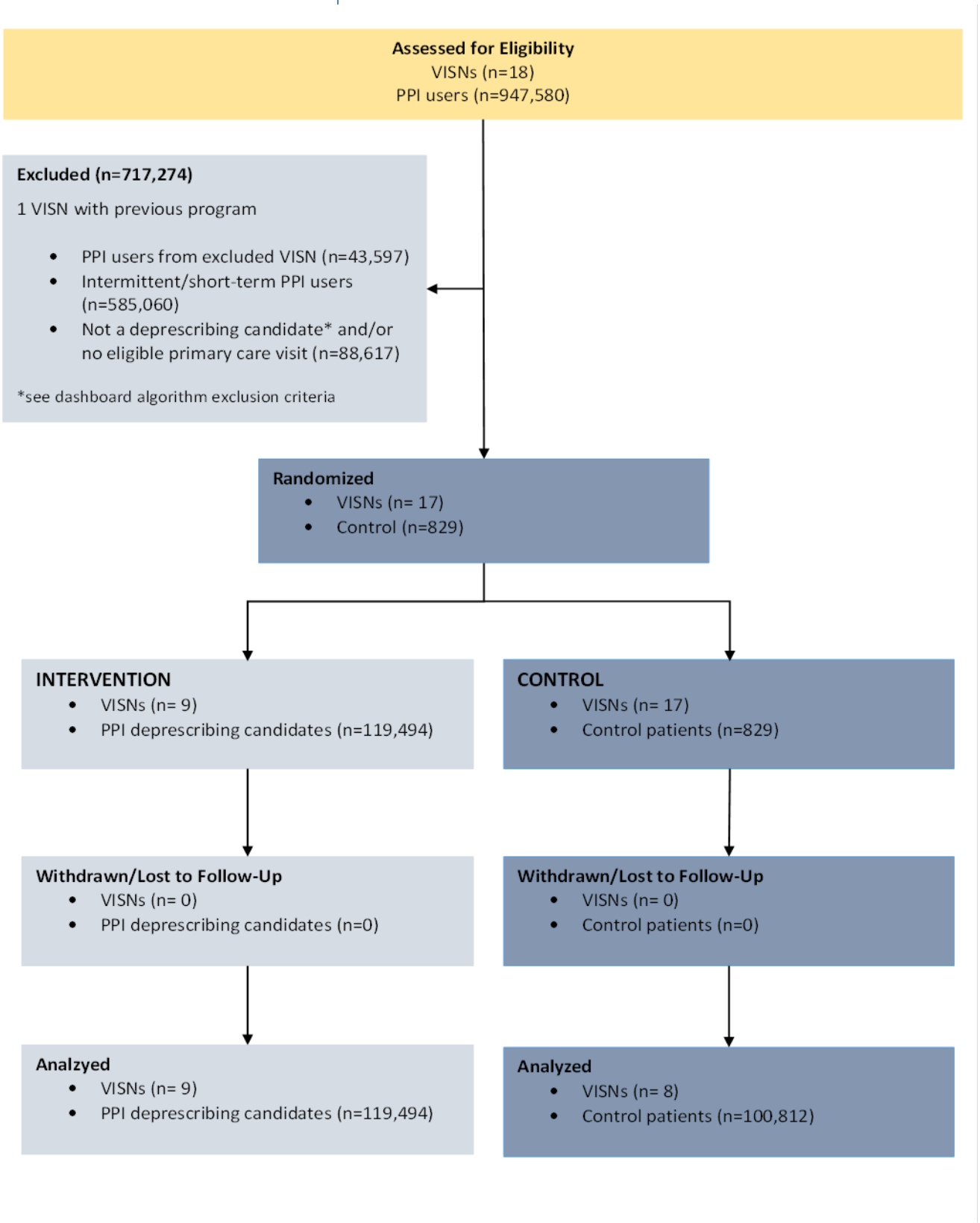
### 8.1.1 PRIMARY OUTCOME

Assuming approximately the same number of eligible subjects in each VISN (with an average of 10,563 candidates per VISN) and an ICC of 0.12, randomizing 17 VISNs will give more than 80% power to detect % days on PPI of 75% vs. 50%, 85% vs. 60%, 80% vs. 55%, or 70% vs. 45%, but to detect a difference between 70% vs. 50%, power is only 61% using 0.05 level 2-sided test.

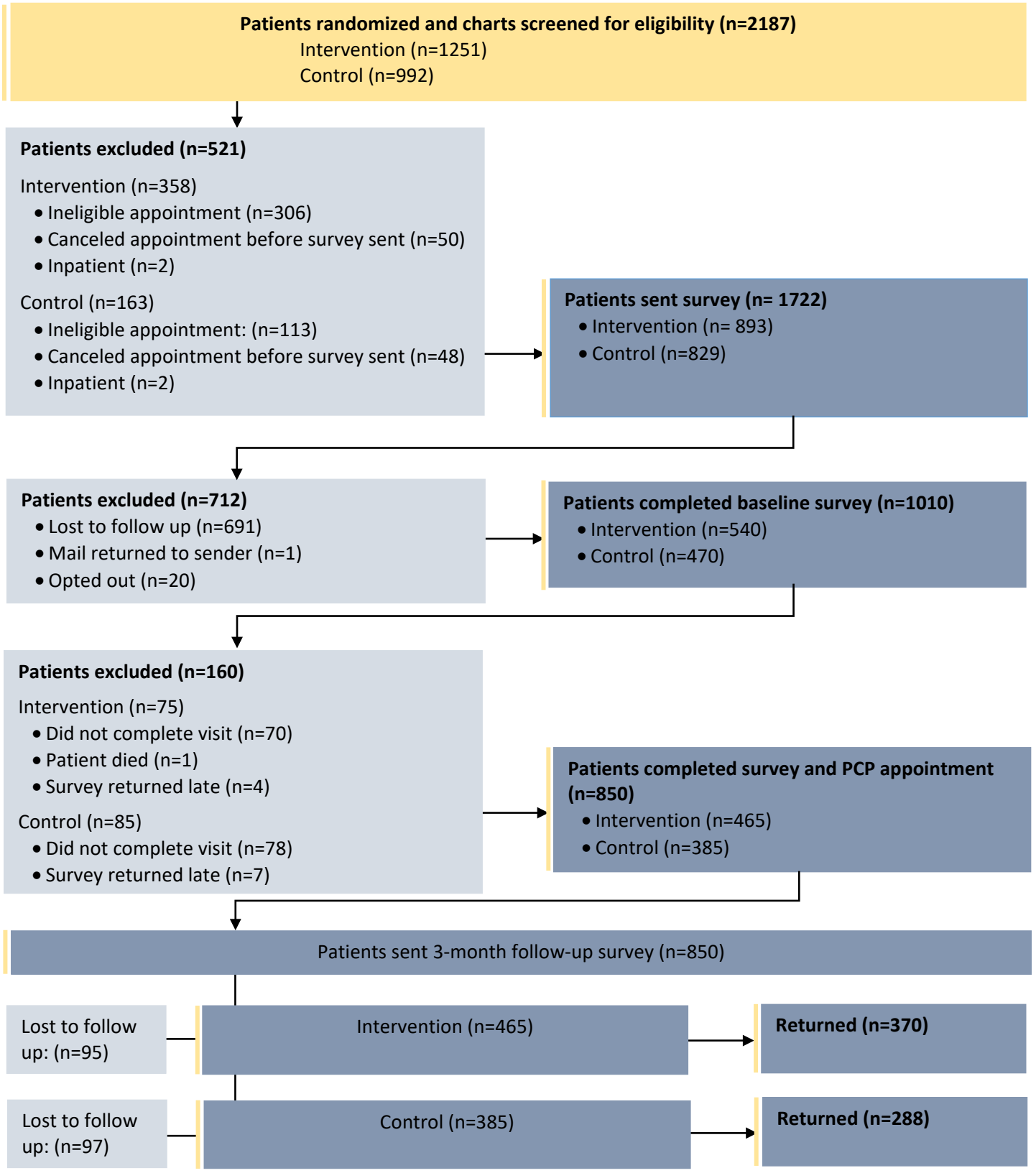
### 8.1.2 VETERAN SURVEYS

Recruitment numbers were based on a power calculation in which patient-reported symptoms, as measured by the Reflux Disease Questionnaire, were treated as a continuous variable rather. Based on previous research, we assumed an RDQ score Standard Deviation (SD)=1.3 for GERD patients for this calculation. To detect the between-group difference of 0.71 vs. 1.13, assuming SD=1.3 with 90% power and alpha=0.01, we need 287 surveys completed per group (574 in total) at 3 months and 820 in total surveys returned at baseline to account for 30% dropout by month 3. We estimated a 50% response rate for the baseline survey and a 70% response rate for the follow-up survey. we mailed 1,722 baseline surveys and approximately 850 follow-up (3 month) surveys.

### 8.1.3 FINAL REPORT UPDATE: RCT CONSORT DIAGRAM



### 8.1.4 FINAL REPORT UPDATE: SURVEYS CONSORT DIAGRAM



## 8.2 POPULATIONS FOR ANALYSES

- Intention-to-Treat (ITT) Analysis Population
- Repeated Measures
    - In addition to intent-to-treat, patient reported outcomes will be measured through surveys over time.

## 8.3 STATISTICAL ANALYSES

Analyses proceeded in 3 phases. In the 1st phase, we examined the distribution of all study variables to assess extreme values, missing data, variances, possible coding errors, skewness, and type of distribution. In the 2nd phase, we evaluated bivariate associations between study arm and outcomes, as well as between each covariate and outcomes, using generalized linear models with generalized estimating equations to account for clustering. This was done to determine unadjusted measures of effect, assess possible confounders, and anticipate any collinearity in subsequent analyses. In the final phase, we fit multivariable models to identify the effects of the intervention.

Primary outcome (H1): To assess the primary outcome (proportion of days PPIs are prescribed), we used an intent-to-treat analysis with a mixed-effects model, with proportion of PPI days over 12 months as the dependent variable. The primary independent variable was study arm. Because randomization was done at the VISN (regional) level, we anticipated that patients seen at the same facility will show a positive intraclass correlation (ICC). The mixed-effects model accounted for such clustering by including VISNs as random intercepts. It also controlled for VISN strata variables used in randomization. We did not account for patient dropout since all data collection is done electronically and does not require further patient participation.

To assess secondary outcomes (utilization of outpatient care and upper GI symptoms patient reported outcomes), we used generalized linear mixed-effects models with logit link (hierarchical logistic regression) to account for VISN-level clustering and randomization strata. The primary independent variable was study arm. For each outcome, an odds ratio (OR) for adverse events in the intervention group relative to the control group was obtained from each logistic regression model, where a significant OR less than 1.0 will favor the intervention group. For analyses of the patient reported outcomes, the outcome of interest was the RDQ score assessed at 3 months. For both outcomes, non-inferiority was assessed by comparing the effect estimate and its 90% CI with a non-inferiority margin.

### 8.3.1 BASELINE DESCRIPTIVE STATISTICS

Intervention and control groups were compared on demographics of age, race, ethnicity, marital status, education, and Charlson Comorbidity Index (CCI).

# 9 SUPPORTING DOCUMENTATION

## 9.1 Regulatory, Ethical, and Study Oversight Considerations

Study documents were and will be retained in accordance with the Records Control Schedule (RCS) 10-1 which provides Veterans Health Administration (VHA) records retention and disposition requirements for VHA Central Office, Program Offices, and field facilities.

## 9.2 PROTOCOL DEVIATIONS

***Final report update: no SAEs were reported throughout the duration of the study.***

Because this was a minimal risk study with the intervention being implemented as part of VHA clinical operations and involving only use of paper and telephone surveys and telephone interviews about PPI de-prescribing experiences, we did not anticipate any serious adverse events (SAEs). Serious adverse events to be monitored included the following: 1) a breach of a participant's confidentiality or privacy that involved potential risk to that participant or others, 2) deviations from VA IRB regulations and policies, and 3) unanticipated problems (UAPs) that involved social or economic harm instead of the physical or psychological harm associated with adverse events. SAEs were prospectively tracked according to the following plan: reports of SAEs and protocol deviations were made by the study team member who discovered the event, the site PI, or site project manager (if applicable) to the primary site (Ann Arbor) project manager. The primary site project manager and PI would report the event to the Ann Arbor VA IRB (Primary Site IRB). Any SAEs and UAPs meeting the definition of serious would be reported within 5 business days of discovery to the Ann Arbor VA IRB. AEs and UAPs that did not meet the definition of serious were to be reported to Ann Arbor project manager as they were discovered, and would be reported to the Ann Arbor VA IRB in summary at the time of continuing review/project closure. Protocol deviations/violations that were likely to substantially adversely affect 1) the rights, safety, or welfare of a participant; 2) a participant's willingness to continue participation; or 3) the integrity of the research data, including VA information security requirements will all be reported within 5 working days of being made aware of the occurrence.

## 9.3 PUBLICATION AND DATA SHARING POLICY

This study will comply with all Department of Veterans Affairs regulations and policies.

## 9.4 CONFLICT OF INTEREST POLICY

***Final report update: no conflicts were reported throughout the duration of the study.***

The independence of this study from any actual or perceived influence was critical. Therefore, any actual conflict of interest of persons who had a role in the design, conduct, analysis, publication, or any aspect of this trial was disclosed and managed. Furthermore, persons who had a perceived conflict of interest was required to have such conflicts managed in a way that was appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the Department of Veterans Affairs has established policies and procedures for all study group members to disclose all conflicts of interest and an established mechanism for the management of all reported dualities of interest.

## 9.5 ABBREVIATIONS AND SPECIAL TERMS

| | |
|---|---|
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| BIA | Budget Impact Analysis |
| CAR | Clinical Analytics and Reporting |
| CBOC | Community Based Outpatient Clinic |
| CCMR | VA Ann Arbor Center for Clinical Management Research |
| CDW | Corporate Data Warehouse |
| CFIR | Consolidated Framework for Implementation Research |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |

| | |
|---|---|
| CKD | Kidney Disease |
| CLIA | Clinical Laboratory Improvement Amendments |
| CMCVAMC | Corporal Michael J. Crescenz VA Medical Center |
| CMP | Clinical Monitoring Plan |
| CMS | Centers for Medicare Services |
| COC | Certificate of Confidentiality |
| Co-I | Co-Investigator |
| COIN | Center of Innovation |
| CONSORT | Consolidated Standards of Reporting Trials |
| CPS | Clinical Pharmacy Specialist |
| CPT | Current Procedural Terminology |
| CRADO | Chief Research and Development Officer |
| CRF | Case Report Form |
| CSR&D | Clinical Science Research & Development |
| DART | Data Access Request Tracker |
| DCC | Data Coordinating Center |
| DHHS | Department of Health and Human Services |
| DSMB | Data Safety Monitoring Board |
| DRE | Disease-Related Event |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Forms |
| ED | Emergency Department |
| EHR | Electronic Medical Records |
| FAC | Field Advisory Committee |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FFR | Federal Financial Report |
| GCP | Good Clinical Practice |
| GEE | Generalized Estimating Equations |
| GERD | Gastroesophageal Reflux Disease |
| GI | Gastroenterology/Gastrointestinal |
| GLM | Generalized Linear Model |
| GLP | Good Laboratory Practices |
| GMP | Good Manufacturing Practices |
| GWAS | Genome-Wide Association Studies |
| H2RA | Histamine-2 Receptor Antagonist |
| HCUP | Healthcare Cost and Utilization Project |
| HIPAA | Health Insurance Portability and Accountability Act |
| HRQOL | Health-Related Quality of Life |
| HSR&D | Health Services Research & Development |
| IB | Investigator's Brochure |
| ICC | Intraclass Correlation Coefficient |
| ICD-9 | International Classification of Diseases, Ninth Revision |
| ICD-10 | International Classification of Diseases, Tenth Revision |
| ICH | International Council on Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| IDE | Investigational Device Exemption |
| IDEAS | Informatics, Decision-Enhancement and Analytic Sciences Center |
| IHPI | Institute for Healthcare Policy and Innovation |
| IIR | Investigator Initiated Research |
| IND | Investigational New Drug Application |

| | |
|---|---|
| IOM | Institute of Medicine |
| IRB | Institutional Review Board |
| ISM | Independent Safety Monitor |
| ITT | Intention-To-Treat |
| LSMEANS | Least-squares Means |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Myocardial Infarction |
| MOP | Manual of Procedures |
| MUE | Medication Use Evaluation |
| NCRC | NCRC – North Campus Research Complex |
| NCT | National Clinical Trial |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| NIH | National Institutes of Health |
| NIH IC | NIH Institute or Center |
| OHRP | Office for Human Research Protections |
| OR | Odds Ratio |
| OTC | Over-the-Counter |
| PBM | Pharmacy Benefits Management Services |
| PCP | Primary Care Provider |
| PD/PI | Project Director/Principal Investigator |
| PI | Principal Investigator |
| PIE | Partnerships for Implementation and Evaluation |
| PP | Per Protocol |
| PPI | Proton Pump Inhibitor |
| PRO | Patient Reported Outcome |
| PUD | Peptic Ulcer Disease |
| QA | Quality Assurance |
| QC | Quality Control |
| QOLRAD | Quality of Life in Reflux and Dyspepsia |
| QUERI | Quality Enhancement Research Initiative |
| QuEST | Qualitative Evaluation for Systematic Translation |
| RAPID | VA Office of Reporting, Analytics, Performance Improvement, and Deployment |
| RAPPID | Randomized Proton Pump Inhibitor De-Prescribing Program |
| RA | Research Assistant |
| RDQ | Reflux Disease Questionnaire |
| RCT | Randomized Controlled Trial |
| RE-AIM | Reach Effectiveness Adoption Implementation Maintenance Framework |
| RR | Relative Risk |
| RRP | Rapid Response Proposal |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SDR | Service Directed Research |
| SF-12 | Short Form Health Survey (12 Items) |
| SMC | Safety Monitoring Committee |
| SOA | Schedule of Activities |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| UP | Unanticipated Problem |
| US | United States |
| TDF | Theoretical Domains Framework |

| | |
|---|---|
| VA | Veterans Affairs |
| VAAAHS | VA Ann Arbor Healthcare System |
| VACHS | VA Connecticut Healthcare System |
| VAMedSAFE | VA Center for Medication Safety |
| VAPSHCS | VA Puget Sound Health Care System |
| VASLC | VA Salt Lake City Healthcare System |
| VERAM | Veterans Education and Research Association of Michigan |
| VHA | Veterans Health Administration |
| VISN | Veterans Integrated Service Network |
| VREC | Veteran Research Engagement Council |

## 9.6 PROTOCOL AMENDMENT HISTORY

| Version | Date | Description of Change | Brief Rationale |
|---|---|---|---|
| 1.0 | 4/26/2019 | Randomization changed from facility level to VISN level | Operational partner decision based on feasibility of implementation of intervention |

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