A randomized open-label trial of deprescribing proton pump inhibitors to reduce the risk of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt creation

Protocol Identifying Number: Pro00108517

Principal Investigator: James Ronald, MD PhD

Funded by: Duke Radiology Putman Seed Fund

Draft Number: v.1.0

March 29, 2021

Table of Contents

List of Abbreviations……

Statement of Compliance……..

Protocol Summary……..

Schematic of Study Design……

1 Key Roles……

2 Introduction: Background Information and Scientific Rationale……..…….

2.1 Background Information……..……..

2.2 Rationale……..……

2.3 Potential Risks and Benefits……..……...

2.3.1 Known Potential Risks……..……

2.3.2 Known Potential Benefits……..……

3 Objectives and Purpose…….…….

4 Study Design and Endpoints…….…….

4.1 Description of the Study Design……..

4.2 Study Endpoints…….

4.2.1 Primary Endpoint……..

4.2.2 Secondary Endpoints……..……..

4.2.3 Exploratory Endpoints…..……

5 Study Enrollment and Withdrawal…….

5.1 Participant Inclusion Criteria…….

5.2 Participant Exclusion Criteria……

5.3 Strategies for Recruitment and Retention……..

5.4 Participant Withdrawal or Termination……

5.4.1 Reasons for Withdrawal or Termination…….

5.4.2 Handling of Participant Withdrawals or Termination……

5.5 Premature Termination or Suspension of Study……

6 Study Agent……..

7 Study Procedures and Schedule……...

7.1 Study Procedures/Evaluations…….

7.1.1 Study Specific Procedures……...

7.1.2 Standard of Care Study Procedures..……

7.2 Laboratory Procedures/Evaluations…….

7.2.1 Clinical Laboratory Evaluations……...

7.2.2 Other Assays or Procedures……

7.2.3 Specimen Preparation, Handling, and Storage…….

7.2.4 Specimen Shipment……..

7.3 Study Schedule……...

7.4 Justification for Sensitive Procedures……..

7.5 Concomitant Medications, Treatments, and Procedures…….

7.5.1 Precautionary Medications, Treatments, and Procedures……..

7.6 Prohibited Medications, Treatments, and Procedures……..

7.7 Prophylactic Medications, Treatments, and Procedures……..

7.8 Rescue Medications, Treatments, and Procedures……..

7.9 Participant Access to Study Intervention at Study Closure……..

8 Assessment of Safety……..

8.1 Specification of Safety Parameters……..

8.1.1 Definition of Adverse Events (AE)……...

8.1.2 Definition of Serious Adverse Events (SAE)…….

8.1.3 Definition of Unanticipated Problems (UP)……

8.2 Classification of an Adverse Event……..

8.2.1 Severity of Event……

8.2.2 Relationship to Study Intervention…….
8.2.3 Expectedness…….
8.3 Time Period and Frequency for Event Assessment and Follow-Up……...
8.4 Reporting Procedures……
8.4.1 Adverse Event Reporting…….
8.4.2 Serious Adverse Event Reporting……...
8.4.3 Unanticipated Problem Reporting……...
8.4.4 Events of Special Interest…….
8.4.5 Reporting of Pregnancy……
8.5 Study Halting Rules……
8.6 Safety Oversight……..
9 Clinical Monitoring……
10 Statistical Considerations……
10.1 Statistical and Analytical Plans…….
10.2 Statistical Hypotheses……
10.3 Analysis Datasets……
10.4 Description of Statistical Methods……
10.4.1 General Approach……..
10.4.2 Analysis of the Primary Endpoint……..…….
10.4.3 Analysis of the Secondary and Exploratory Endpoints……..…….
10.4.4 Safety Analyses……..
10.4.5 Adherence and Retention Analyses……
10.4.6 Baseline Descriptive Statistics…….
10.4.7 Planned Interim Analyses…….
10.4.8 Additional Sub-Group Analyses……..
10.4.9 Multiple Comparison/Multiplicity……..

10.4.10 Tabulation of Individual Response Data……..

10.4.11 Exploratory Analyses……...

10.5 Sample Size…….

10.6 Measures to Minimize Bias……

10.6.1 Enrollment/ Randomization/ Masking Procedures……

10.6.2 Evaluation of Success of Blinding.....

10.6.3 Breaking the Study Blind/Participant Code……

11 Source Documents and Access to Source Data/Documents……

12 Quality Assurance and Quality Control…….

13 Ethics/Protection of Human Subjects……

13.1 Ethical Standard……..

13.2 Institutional Review Board…….

13.3 Informed Consent Process……

13.3.1 Consent/Assent and Other Documents Provided to Participants….....

13.3.2 Consent Procedures and Documentation……..

13.4 Participant and Data Confidentiality…….

13.4.1 Research Use of Stored Human Samples, Specimens or Data…….

13.5 Future Use of Stored Specimens…….

14 Data Handling and Record Keeping…….

14.1 Data Collection and Management Responsibilities……...

14.2 Study Records Retention……...

14.3 Protocol Deviations…….

14.4 Publication and Data Sharing Policy……

15 Study Administration……

15.1 Study Leadership……

16 Conflict of Interest Policy……

17 Literature References……………………………………………………………………………

List of Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CRC	Clinical Research Coordinator
CLDQ	Chronic Liver Disease Questionnaire
CRF	Case Report Form
GERD	Gastroesophageal Reflux Disease
GI	Gastrointestinal
HE	Hepatic Encephalopathy
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IR	Interventional Radiology
IRB	Institutional Review Board
ITT	Intention-to-Treat
MHE	Minimal Hepatic Encephalopathy
PACE	Protected Analytics Computing Environment
PHES	Psychometric Hepatic Encephalopathy Score
PI	Principal Investigator
PPI	Proton Pump Inhibitor
QOL	Quality of Life
QOLRAD	Quality of Life in Reflux and Dyspepsia
SAE	Serious Adverse Event
TIPS	Transjugular Intrahepatic Portosystemic Shunt
UP	Unanticipated Problem

Statement of Compliance

The trial will be conducted in accordance with the International Conference on Harmonization (ICH), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the Putman Seed Fund Terms of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator (PI):

Print/Type Name

Signed:

Date:

Protocol Summary

Title: A randomized open-label trial of deprescribing proton pump inhibitors to reduce the risk of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt creation.

Precis: A total of 40 patients taking proton pump inhibitors (PPIs) who undergo transjugular intrahepatic portosystemic shunt (TIPS) creation as part of routine clinical care will be randomized in 1:1 fashion to either continue or discontinue their PPIs to determine whether these commonly used gastric acid suppressing agents increase risk of post-TIPS hepatic encephalopathy (HE). Patients will be assessed for symptoms of minimal HE (MHE), using the established psychometric hepatic encephalopathy score (PHES) battery of tests. MHE assessment will be conducted at two timepoints: at baseline prior to randomization and TIPS creation and approximately 4 weeks after randomization and TIPS creation. Stool samples will also be collected at both timepoints to allow characterization of the gastrointestinal (GI) tract microbiome using 16S rRNA sequencing. The pre to post-TIPS change in PHES scores will be compared between patients randomized to continue versus discontinue their PPIs. Quality of life (QOL) will also be assessed. Changes in the GI tract microbiome will be analyzed to determine whether this represents a potential biological mechanism linking PPI use with post-TIPS HE.

Objectives: The primary objective is to determine whether discontinuation of PPIs reduces the risk of post-TIPS HE. Additional secondary objectives will include a comparison of cirrhosis-specific and gastroesophageal reflux disease-specific QOL in the PPI continuation and discontinuation groups. An exploratory objective is to determine whether PPI induced changes in the GI tract microbiome represent a potential biological mechanism mediating PPI-induced risk of post-TIPS HE.

Endpoints: Change in PHES pre to post-TIPS by intention-to-treat (ITT) (primary endpoint). Per-protocol change in PHES; change in Chronic Liver Disease Questionnaire (CLDQ) and Quality of Life in Reflux and Dyspepsia (QOLRAD) scores pre to post-TIPS (secondary endpoints). Mediation analysis of GI tract bacterial taxon abundances as a potential link between PPI use and post-TIPS HE (exploratory endpoint).

Population: 40 male and female Duke University Hospital patients over the age of 18 taking PPIs and undergoing TIPS placement as part of routine clinical care

Phase: 2

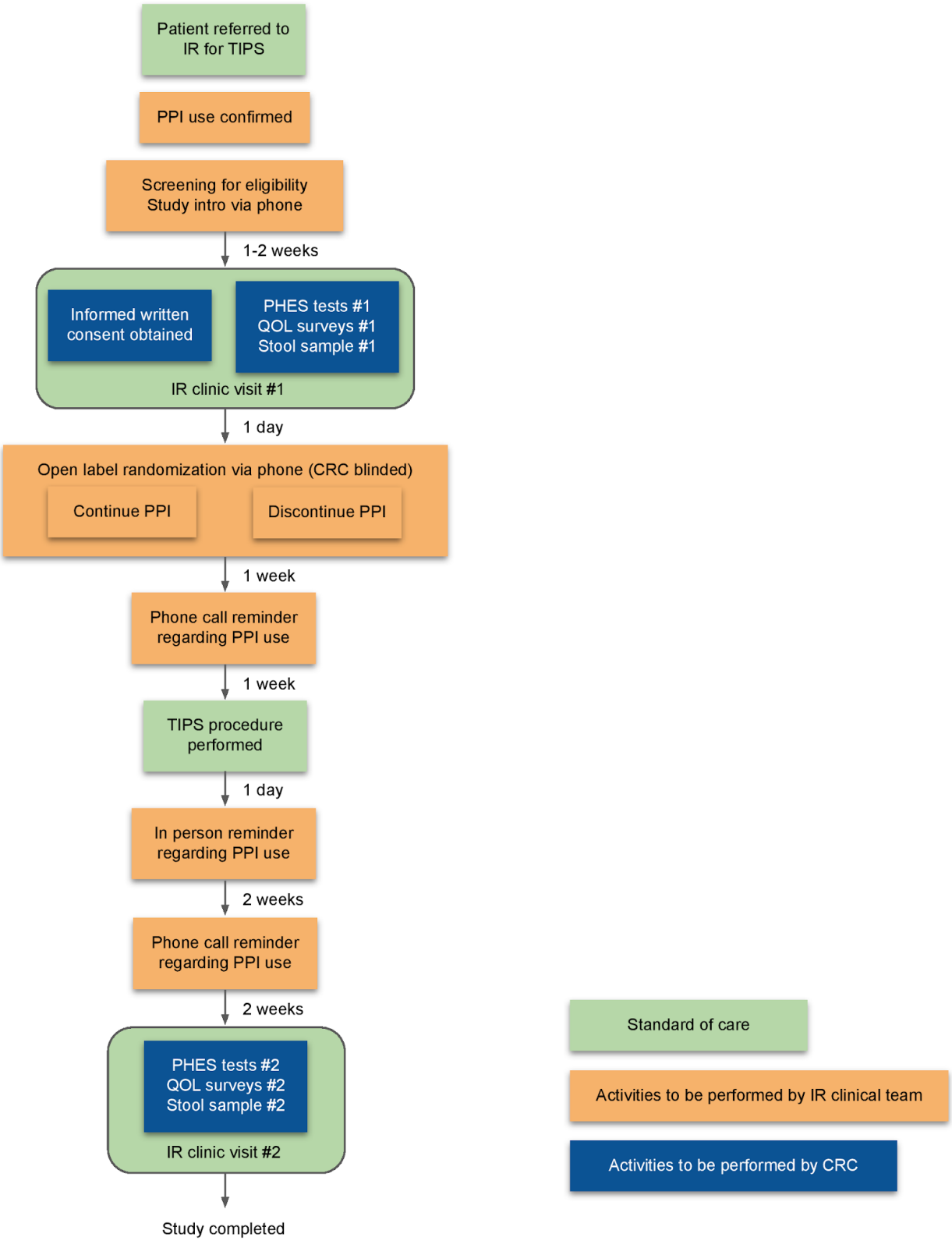
Number of Sites Enrolling Participants: 1

Description of Study Intervention: Patients will be randomized to receive instructions to stop their existing PPI therapy (experimental/discontinuation/deprescribing arm) or to receive no specific instructions regarding PPI therapy (control/continuation arm)

Study Duration: Approximately 24 months

Participant Duration: Approximately 6-8 weeks

Schematic of Study Design



1 Key Roles

Principal Investigator:

James Ronald, M.D. Ph.D.

Duke University Medical Center

2301 Erwin Road

Durham, NC 27710

Email: james.ronald@duke.edu

Phone: 919-684-7299

Lead Clinical Research Coordinator:

Latonia Strader, C.R.C.

Duke University Medical Center

2301 Erwin Road

Durham, NC 27710

Email: latonia.strader@duke.edu

Phone: 919-684-7810

2 Introduction: Background Information and Scientific Rationale

2.1 Background Information

Transjugular intrahepatic portosystemic shunt (TIPS) creation is an important minimally invasive procedure for treatment of complications resulting from cirrhosis and portal hypertension (1). Despite the beneficial effects of TIPS on ascites, gastrointestinal (GI) variceal bleeding risk, and in certain settings survival (2, 3), development of hepatic encephalopathy (HE) after TIPS can limit use of this procedure. HE is the most common complication of TIPS, occurring in 30% to 60% of patients (4). Medical therapy for HE, though effective, can be expensive (5) and cause unpleasant side effects (6). Thus, in patients who experience post-TIPS HE, the reduction in quality of life (QOL) can negate other beneficial effects of TIPS (7, 8). Furthermore, the cost of HE related care is substantial, estimated at $5,370-$50,120 per patient per year (9). Therefore, additional strategies to reduce the risk of post-TIPS HE are needed.

Recent retrospective studies have shown an association between proton pump inhibitor (PPI) use and HE in cirrhotic patients (10-20). Meta-analyses have supported a small but significantly increased risk of HE among cirrhotic patients taking PPIs, with pooled odds ratios ranging from 1.50 to 2.58 (21-24). Among these studies, two focused exclusively on TIPS patients and described a more robust effect size in this high risk population with a greater than 3 fold increased risk of post-TIPS HE among PPI users (19, 20). In an independent, unpublished dataset of 86 TIPS patients, we have further replicated the dose dependent association between PPI use and post-TIPS HE (Figure 1).

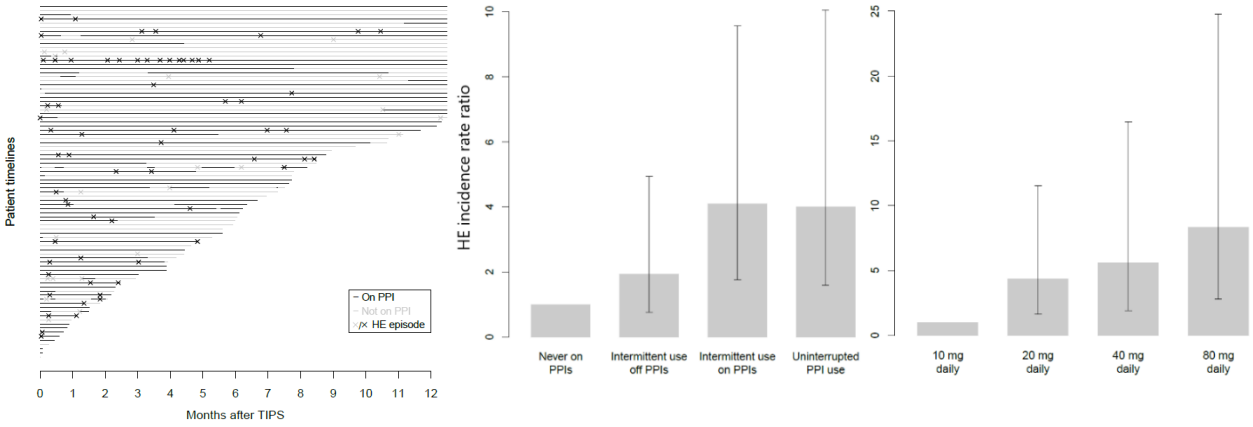


Figure 1: Patient timelines after TIPS showing intervals of PPI use and episodes of HE (left panel). Incidence rate ratios showing statistically significantly increased rates of post-TIPS HE with PPI use (middle panel) and with increasing PPI dosages (right panel).

Biological mechanisms to account for the association between PPI use and HE remain unknown, but a potential pathway involves alterations in the GI tract microbiome. Randomized placebo controlled studies have demonstrated that PPI use leads to distinct changes in the microbiome (25). These changes, characterized by colonization of the lower GI tract by oral flora not destroyed in a more alkaline stomach, appear to be reversible upon discontinuation of PPIs (25, 26). Separate observational studies have characterized the differences in GI flora

between cirrhotic patients with HE versus those without HE (27). In patients with HE, reduced levels of Lachnospiraceae, Ruminococcaceae, and Clostridiales and increased Enterobacteriaceae and Streptococcaeae closely mirror the changes caused by PPI use (25, 27). Thus, given the concordant changes in the lower GI tract microbiome seen with PPI use and in patients with HE, these bacterial taxa could play a role in mediating HE. However, other mechanisms, such as a simple effect of pH, are also plausible. Lactulose, long established as an effective treatment for HE, is a colonic acidifying agent (28). In a reduced pH environment in the colon, ammonia is protonated to the less well absorbed ammonium ion, which is thus excreted (28). By raising luminal pH, PPIs may counteract this process.

PPIs are among the most commonly used medications, but a Cochrane review has reported that 25% to 70% of patients may be prescribed a PPI inappropriately (29). Among TIPS patients, 60% to 75% take PPIs (19, 20). While short courses of PPIs are indicated for ulcer disease (30, 31) and possibly for prevention of esophageal variceal band ligation ulcers (32), PPIs do not appear in practice guidelines for prevention and management of portal hypertensive bleeding in cirrhotic patients (33). Thus, discontinuation of inessential PPI therapy in cirrhotic patients undergoing TIPS creation may be a simple and cost effective intervention to reduce the risk of post-TIPS HE.

Since the link between PPI use and HE is based solely on retrospective, observational data and because biological mechanisms remain unexplored, this protocol proposes a prospective, randomized study design to more definitively support or refute a role for PPI use as a risk factor for HE. Such a study design would more clearly determine whether discontinuation of PPI therapy can reduce the risk of post-TIPS HE and may also provide mechanistic insights into the interplay between upper GI tract pH, the GI tract microbiome, and HE.

2.2 Rationale

Rationale for a randomized trial

The rationale for this proposed prospective, randomized deprescribing trial is that currently available retrospective data implicating PPI use in post-TIPS HE are inadequate to justify discontinuation of PPIs. This is based on three considerations. First and foremost, retrospective data are unable to support causal conclusions. Therefore, the observation that TIPS patients taking PPIs experience higher rates of post-TIPS does not imply that discontinuation of PPIs would reduce rates of HE in these patients. Second, a Cochrane review of randomized PPI deprescribing trials described increased rates of gastroesophageal reflux disease (GERD) symptoms in patients who stopped their PPIs (29). Therefore, even if PPI use is causally linked to increased risk of post-TIPS HE, the harmful effects from worsening GERD in patients discontinuing PPIs may outweigh the beneficial reduction in post-TIPS HE. Third, retrospective observational studies provide few insights into biological mechanisms. Therefore, even if discontinuation of PPIs was known to be beneficial, this narrow strategy would fail to advance the understanding of physiologic connections between upper GI tract pH, the GI tract microbiome, and HE.

Rationale for microbiome analysis

In addition to better establishing causality and better assessing the potential benefits and risks of deprescribing PPIs to prevent HE, the proposed prospective, randomized study design will allow further analyses to dissect the role of the GI tract microbiome in HE. The proposed study seeks to further evaluate the role of the GI tract microbiome via statistical mediation analysis as illustrated in Figure 2 (34). Scenario A depicts a direct effect of PPIs on HE. Scenario B depicts simple mediation. The microbiome is considered a mediator if (1) PPIs are causally related to HE (i.e. $c \neq 0$ in scenario A), (2) PPIs are causally related to microbiome change (i.e. $a \neq 0$ in scenario B), and (3) the microbiome significantly predicts HE after controlling for PPI use (i.e. $b \neq 0$ in scenario B). Complete mediation is said to occur if $c' = 0$ (i.e. the impact of PPI use on HE is driven entirely through changes in the microbiome), whereas partial mediation is said to occur if $c' \neq 0$ (i.e. PPIs affect the risk of HE both through the microbiome but also through other unexplained mechanisms, such as a direct effect of pH). Formal statistical methods for quantifying such relationships in mediation analysis have been described (34).

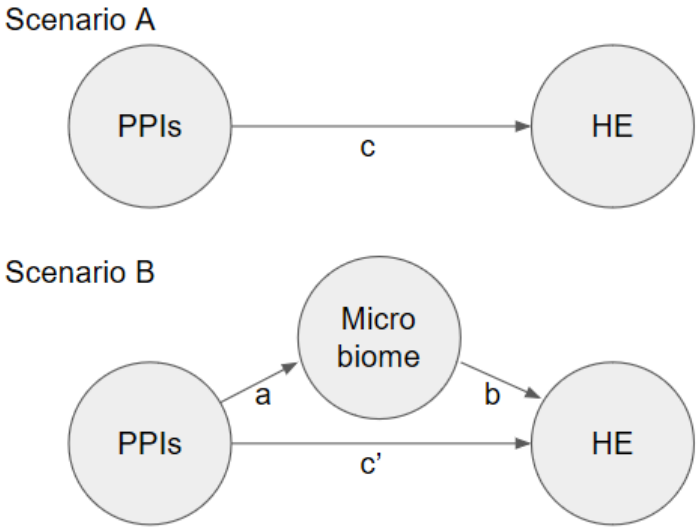


Figure 2: Arrows demonstrate directionality of hypothesized causal chains linking PPI use, the microbiome, and post-TIPS HE.

Rationale for a deprescribing trial

This protocol proposes a randomized deprescribing study design, whereby patients who are already taking PPIs are randomized continue or discontinue their PPI. Because currently available retrospective data suggest PPIs may increase risk of HE, it would be potentially unethical to administer PPIs to patients not already on these agents. In contrast, a deprescribing trial, where patients are randomized to continue or discontinue a potentially ineffective or harmful medication, can be considered in such circumstances (35). Such deprescribing trials are well accepted in the field of geriatrics to combat polypharmacy and reduce pill burden, and PPIs have been the focus of multiple deprescribing trials (29).

Rationale for studying TIPS patients

This study focuses on deprescribing PPIs in the subset of cirrhotic patients undergoing TIPS creation. While a PPI deprescribing trial could be considered in cirrhotic patients in general or in other patient subsets, HE represents an acute clinical problem in TIPS patients and prevention and management of HE in this group remains a challenge (36). Retrospective studies have shown greater than 3 fold higher rates of HE associated with PPI use among TIPS patients (19, 20), compared with 1.50 to 2.58 fold higher rates among cirrhotic patients in general (21-24).

Therefore, TIPS patients may be more likely to enjoy benefits related to reduction in HE that outweigh the risks of worsening GERD symptoms.

2.3 Potential Risks and Benefits

2.3.1 Known Potential Risks

Adverse reactions to abrupt discontinuation of PPIs have been characterized in a deprescribing trial conducted in 164 patients age 65 and older with a history of acute grade I-III esophagitis (37):

- GERD: heartburn (54.8% in discontinuation arm vs 8.3% in PPI continuation arm), acid regurgitation (41.9% vs 12.5%)
- Esophagitis documented by endoscopy: 69.6% vs 20.4%
- Other rare adverse events (AEs) occurring in both arms: glossitis, headache, diarrhea, cardiac arrhythmia, urticaria, abdominal pain, impotence, dysuria, leukopenia, pruritus, dizziness

Patients with gastric or duodenal ulcers, grade IV esophagitis (deep ulcer or esophagitis with complications) were excluded from this study. No ulcers, complications from esophagitis, or cases of grade IV esophagitis were reported in the discontinuation arm.

2.3.2 Known Potential Benefits

Potential benefits of PPI discontinuation include reduction in post-TIPS HE symptoms and decreased pill burden.

3 Objectives and Purpose

Primary objective: To determine whether discontinuation of PPIs in patients undergoing TIPS creation reduces the risk of post-TIPS HE, as assessed by psychometric hepatic encephalopathy score (PHES) tests of minimal hepatic encephalopathy (MHE).

Secondary objectives: To determine whether discontinuation of PPIs impacts chronic liver disease or GERD related QOL, as assessed by the Chronic Liver Disease Questionnaire (CLDQ) and Quality of Life in Reflux and Dyspepsia (QOLRAD) surveys.

Exploratory objectives: To perform mediation analysis to determine whether the relationship between PPI use and post-TIPS HE is driven by changes in the GI tract microbiome, characterized through 16S rRNA sequencing of stool samples.

4 Study Design and Endpoints

4.1 Description of the Study Design

The proposed study is a single center randomized, open-label, deprescribing trial of PPI users undergoing TIPS creation. The study will involve two arms: the experimental/PPI discontinuation arm will be instructed to stop taking their PPIs prior to TIPS creation and the control/PPI continuation arm will receive no special instructions regarding their preexisting PPI medication. Patients will be assessed for MHE using the PHES test battery and for QOL using the CLDQ and QOLRAD surveys prior to randomization, and approximately 6-8 weeks later after TIPS creation. Stool samples will be collected at both time points. After the second and final assessment approximately 4 weeks after TIPS creation patients will have completed the study.

4.2 Study Endpoints

4.2.1 Primary Endpoint

The primary endpoint of this study will be an intention-to-treat (ITT) analysis of the change in PHES pre versus post-TIPS, compared between the PPI continuation and discontinuation arms.

4.2.2 Secondary Endpoints

Secondary endpoints of the study will include a per-protocol analysis of the change in PHES pre versus post-TIPS in the PPI continuation versus discontinuation arm; an ITT analysis of the change in CLDQ and QOLRAD scores pre versus post-TIPS in the PPI continuation versus discontinuation arms; episodes of overt HE, defined as a West-Haven score greater than or equal to 2 (e.g. gross disorientation, drowsiness, asterixis, and inappropriate behavior), on-demand use of histamine H2 blockers or PPIs due to GERD symptoms, and AEs.

4.2.3 Exploratory Endpoints

As an exploratory endpoint, the GI tract microbiome will be characterized by 16S rRNA sequencing of stool samples at both time points. The change in bacterial taxon abundances pre versus post-TIPS will be estimated in each patient. Statistical mediation analysis will be used to explore whether PPI use impacts the risk of HE through changes in the GI tract microbiome (Figure 2).

5 Study Enrollment and Withdrawal

5.1 Participant Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Undergoing TIPS creation as part of routine clinical care
- On PPIs therapy (at least 20 mg omeprazole equivalent daily)
- Provision of signed and dated informed consent form by participant or legal representative
- Stated willingness to comply with all study procedures and availability for the duration of the study
- Male or female, age greater or equal to 18

Women and members of minority groups and their subpopulations will be offered the opportunity to participate in the study in accordance with the NIH Policy on Inclusion of Women and Minorities as Participants in Research Involving Human Subjects. The following PPI doses are considered equivalent: omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, esomeprazole 20 mg, and dexlansoprazole 30 mg (38, 39).

5.2 Participant Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Grade IV esophagitis or gastric or duodenal ulcer
- Recent endoscopic esophageal variceal band ligation necessitating PPI therapy for prevention of banding ulcer
- Zollinger-Ellison syndrome
- Active Helicobacter pylori infection
- Pregnancy

5.3 Strategies for Recruitment and Retention

Potential patients will be identified by the Interventional Radiology (IR) clinical team at the time of referral for TIPS creation. At the time of referral for TIPS, patients will be screened for eligibility and exclusion criteria. Potential study candidates will be contacted by the IR team and the study will be described to the patient by the treating IR physician. Patients who are potentially interested in participating will then have the opportunity to undergo a formal written informed consent discussion at the time of the pre-TIPS IR clinic visit. No compensation will be provided for study participation.

5.4 Participant Withdrawal or Termination

5.4.1 Reasons for Withdrawal or Termination

An investigator may terminate participation in the study if:

- Any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.4.2 Handling of Participant Withdrawals or Termination

Patients who withdraw consent prior to randomization will not have undergone any study related intervention. Therefore, replacement of these participants will be permitted. Any patients who undergo randomization and withdraw prior to completion of the study will be analyzed according to the principle of ITT.

5.5 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the IRB.

6 Study Agent

Patients will be randomized to receive instructions to stop their existing PPI therapy (experimental/discontinuation/deprescribing arm) or to receive no specific instructions regarding PPI therapy (control/continuation arm). Therefore, considerations related to storage, handling, formulation, and labeling of study agent are not applicable.

7 Study Procedures and Schedule

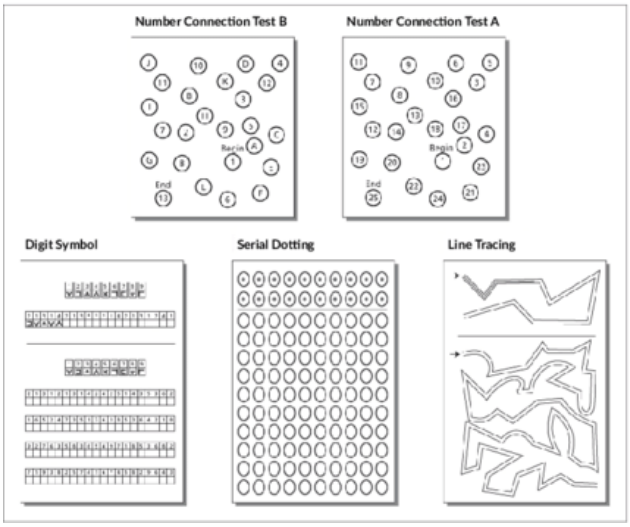
7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

The following will study specific procedures will occur:

- Prior to randomization, all patients will undergo assessment of MHE, using the established PHES battery of pencil-and-paper tests (Figure 3), QOL assessments using the CLDQ and QOLRAD surveys, and will be provided with return-by-mail at home stool collection kits
- Patients will be randomized to either receive instructions to immediately discontinue their PPI, or to receive no specific instructions regarding their PPI
- Patients in the PPI discontinuation arm will receive intermittent phone call reminders encouraging them to refrain from PPI use, to attempt lifestyle interventions to counteract GERD symptoms (e.g. smoking cessation, avoiding late evening meals, and head-of-the-bed elevation) (40), and to use on-demand over-the-counter histamine H2 blocker therapy for intolerable GERD symptoms
- Approximately 4 weeks following TIPS creation, all patients will undergo reassessment of MHE and QOL and will be provided with return-by-mail at home stool collection kits
- At the completion of the study, all patients will be invited to resume or discontinue PPI therapy at their discretion and upon discussion with their primary care, gastroenterology, and IR physicians

Psychometric Hepatic Encephalopathy Score



Test	Description
Number connection test A (NCT-A)	Randomly dispersed numbers are to be connected with each other in serial order as quickly as possible.
Number connection test A (NCT-B)	Randomly dispersed numbers and letters are to be connected in alternating series (1-A-2-B...) as quickly as possible.
Digit-symbol	Digits from 1 to 9 are assigned respective symbols. Under each digit the corresponding symbol is to be written within a given time.
Serial dotting	Draw a dot inside each circle as quickly as possible.
Line tracing	A given line is to be traced as quickly as possible.

Figure 3: PHES tests from (41).

7.1.2 Standard of Care Study Procedures

The following occur as standard of care for all patients undergoing TIPS creation:

- After receiving a referral TIPS creation, the treating IR physician reviews the patient's electronic medical records including history, medications, allergies, physical examination and imaging findings, and laboratory tests to evaluate the patient's candidacy for the procedure
- All patients referred for TIPS creation undergo a pre procedure consultation with the treating IR physician
- All TIPS procedures are performed under general anesthesia. Portal vein access is achieved using intracardiac echocardiography/intravascular ultrasound guidance. Controlled expansion covered Viatorr covered stent grafts are deployed and dilated to achieve a target reduction in the portosystemic pressure gradient of 50% or <12 mm Hg for varices and <8 mm Hg for ascites (1). Patients are admitted to the hospital following TIPS creation for post procedure observation.
- Patients undergo routine follow up with the IR clinical team approximately 4 weeks after TIPS creation.

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

Routine clinical laboratory evaluation prior to TIPS procedure includes assessment of a complete metabolic panel, complete blood count, and coagulation studies (prothrombin time/international normalized ratio). These laboratory evaluations are performed as part of standard of care for patients undergoing TIPS creation. No study specific clinical laboratory assessments are proposed.

7.2.2 Other Assays or Procedures

Microbiome analyses from stool samples will be performed by Duke University core facilities according to established protocols. DNA extraction will be performed using the Qiagen PowerSoilPro DNA Kit. Polymerase chain reaction amplification of the V4 variable region of the 16S rRNA gene will be performed following the Earth Microbiome Project protocol (http://www.earthmicrobiome.org/). DNA sequencing will be performed by the Duke Sequencing and Genomic Technologies shared resource on an Illumina MiSeq instrument. Sequence data will be analyzed by the Genomic Analysis & Bioinformatics Core.

7.2.3 Specimen Preparation, Handling, and Storage

Patients will be provided with commercially available at home stool DNA Genotek OMNIgene-GUT collection kits (https://www.dnagenotek.com/US/products/collection-microbiome/omnigene-gut-kit/OMR-200.100.html). Patient friendly instructions for use of this kit are available from the manufacturer and will be further explained to study participants by the CRC. Briefly, at home after stooling, patients use a small spatula provided in the kit to obtain a stool sample which is placed in a stabilizing collection tube. The tube is then placed in a bio-specimen bag. Fecal samples collected with the OMNIgene-GUT kit can be stored at room temperature for up to 60 days.

7.2.3 Specimen Shipment

Patients will be supplied with a prepaid 2-way mailers shipping box with peelable adhesive strip for sample return. Custom labels are created for traceability.

7.3 Study Schedule

7.3.1 Screening

Patients referred to IR for TIPS creation are screened for procedure candidacy by the treating IR physician. At this time screening for study eligibility will also be performed. Patients deemed eligible for the study will be contacted by the IR clinical team to confirm ongoing PPI use and to introduce them to the study prior to the routine pre-TIPS IR clinic visit. Patients potentially interested in study participation will then be referred to the study team CRC. The CRC will then formally screen the patient for eligibility based on a review of the electronic medical record. In accordance with IRB and HIPAA regulations, no PHI will be recorded during this screening evaluation.

7.3.2 Enrollment/Baseline

At the time of the routine pre-TIPS IR clinic visit, patients who remain potentially interested in participating in the study will meet with the study team CRC and informed written consent will be obtained from subjects who elect to participate. Baseline MHE assessment via the PHES tests and QOL surveys will then be administered and home stool collection kits will be provided.

7.3.3 Follow-Up

After enrollment and baseline assessments, open-label randomization will be performed. Patients randomized to the PPI discontinuation arm will be contacted via telephone and instructed to discontinue their PPI. These patients will receive a reminder telephone call approximately 1 week later. All patients will then undergo the TIPS procedure per routine standard of care. While inpatient after the TIPS procedure and 2 weeks later by telephone, patients in the PPI discontinuation arm will again be reminded to abstain from PPI use. Adverse events occurring within 30 days of TIPS creation will be recorded, in accordance with Society of Interventional Radiology guidelines (42).

7.3.4 Final Study Visit

The final study visit will occur at the routine 4 week post-TIPS follow up IR clinic visit. Final assessments of MHE and QOL will occur and the final home stool collection kits will be provided.

7.3.5 Early Termination Visit

Not applicable.

7.3.6 Unscheduled Visit

Unscheduled visits related to complications from the TIPS procedure may occur as needed, per routine standard of care.

7.3.7 Schedule of Events Table

Procedures	Referral for TIPS (~Day -14)	Pre-TIPS IR clinic visit (Day 0)	Post-clinic phone call (Day 1)	PPI reminder phone call (~Day 7)	TIPS performed (~Day 14)	In person PPI reminder (Day 15)	PPI reminder phone call (~Day 28)	Post-TIPS IR clinic visit (~Day 42)
Screening by IR clinical team	X							
Informed written consent		X						
MHE assessment		X						X
QOL assessment		X						X
Stool sample		X						X

collection kit provided								
Randomization			X					
Reminder to refrain from PPI use				X		X	X	
TIPS procedure					X			

7.4 Justification for Sensitive Procedures

Not applicable.

7.5 Concomitant Medications, Treatments, and Procedures

All concomitant standard of care medications for post-TIPS HE (e.g. lactulose, rifaximin) deemed necessary by gastroenterology and IR physicians will be permitted. Use of such medications will be documented on case report forms (CRFs).

For GERD symptoms related to discontinuation of PPIs, patients will be encouraged to undertake lifestyle interventions (e.g. smoking cessation, avoiding late evening meals, and head-of-the-bed elevation) (40). If lifestyle interventions are inadequate to control GERD symptoms, patients may use on-demand over-the-counter histamine H2 blocker therapy. On-demand use of PPIs will be discouraged but permitted for refractory, intolerable GERD symptoms. Use of on-demand pharmacological agents will be recorded on the CRFs.

7.5.1 Precautionary Medications, Treatments, and Procedures

Not applicable.

7.6 Prohibited Medications, Treatments, and Procedures

Not applicable.

7.7 Prophylactic Medications, Treatments, and Procedures

Not applicable.

7.8 Rescue Medications, Treatments, and Procedures

Not applicable.

7.9 Participant Access to Study Intervention at Study Closure

After completion of the study patients will be informed that they may resume or discontinue their PPI based on their own preferences and in consultation with their primary care, gastroenterology, and IR physicians.

8 Assessment of Safety

8.1 Specification of Safety Parameters

Safety parameters included as secondary endpoints include episodes of overt HE and drug related AEs (see Section 4.2).

8.1.1 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.1.2 Definition of Serious Adverse Events (SAE)

An AE or suspected adverse reaction is considered “serious” if, in the view of the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, prolongation of hospitalization, or a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Important medical events that may not result in death, be life-threatening, or result in prolongation of hospitalization may be considered serious when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent on of the outcomes listed in this definition. Examples of such medical events include development of grade IV esophagitis, gastric or duodenal ulcers, or West-Haven grade 4 HE (e.g. comatose, unresponsive to pain, decorticate or decerebrate posturing).

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated problems involving risks to participants or others include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related study documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant populations being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; and
- Suggest that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

8.2 Classification of an Adverse Event (AE)

8.2.1 Severity of Event

Adverse events will be graded according to the following guidelines to describe severity:

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Intervention

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgement. The degree of certainty about causality will be graded using the categories below:

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event occurs in a plausible time relationship to the study intervention and cannot be explained by concurrent disease or other medications.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event occurs within a reasonable time after the study intervention, is unlikely to be attributed to concurrent disease or other medications.
- Possibly Related – There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after the study intervention). However, other factors may have contributed to the event (e.g. the participant's clinical condition or other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related" as appropriate.
- Unlikely to be Related – A clinical event whose temporal relationship to the study intervention makes a causal relationship improbable (e.g. the event did not occur within a reasonable time after the study intervention) and in which other medications or underlying disease provides plausible explanations (e.g. the participant's clinical condition or other concomitant treatments).
- Not Related – The AE is completely independent of study intervention, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 Expectedness

The PI James Ronald, MD PhD will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during the study or during routine clinical monitoring following completion of the study. All AEs not meeting the

criteria for SAEs will be captured on the CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to the study intervention (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Events will be followed for outcome information until resolution or stabilization.

8.4 Reporting Procedures

8.4.1 Adverse Event Reporting

For any problem or AE requiring prompt reporting to the IRB but not meeting criteria for a SAE, within ten business days of the investigator becoming aware of the event, study personnel will send to the IRB a Safety Event submission in the eIRB.

8.4.2 Serious Adverse Event Reporting

The study clinician will complete a SAE Form within the following timelines:

- Immediately (within 24 hours) upon learning of an unanticipated study-related death, study personnel will notify the IRB via e-mail or fax by providing a brief summary of the event. Then, within 1 week (five business days), study personnel will send to the IRB a Safety Event submission in the eIRB.
- For a reportable SAE, study personnel will notify the IRB within five business days of the investigator becoming aware of the event. Study personnel will send a Safety Event submission in the eIRB.

All SAEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the IRB and should be provided as soon as possible.

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the criteria for UPs require the creation and completion of an UP report form. The PI will report UPs to the IRB. The UP report will include the following information:

Protocol identifying information: protocol title and number, PI's name, and the IRB project number;

- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB within 1 week (5 business days) of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within ten business days of the investigator becoming aware of the problem.

8.4.4 Events of Special Interest

Not applicable.

8.4.5 Reporting of Pregnancy

Not applicable.

8.5 Study Halting Rules

The study intervention will be halted when three SAEs determined to be "definitely related" or "probably related" to PPI discontinuation are identified.

8.6 Safety Oversight

Safety oversight will be under the direction of the PI who has appropriate expertise in TIPS procedures and in post procedure care. Safety oversight will occur continuously throughout the study.

9 Clinical Monitoring

Study audits may be performed to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s). Audits may be performed at any time at the discretion of the Duke University Health System IRB.

10 Statistical Considerations

10.1 Statistical and Analytic Plans

A separate statistical analysis plan will not be created. See below for detailed description of the statistical analysis plan.

10.2 Statistical Hypotheses

Primary endpoint: The null hypothesis is that there is no difference between PPI continuation and discontinuation groups in the change in PHES pre versus post-TIPS. The alternative hypothesis is that there is a difference in the change in PHES pre versus post-TIPS in the PPI continuation and discontinuation groups:

$$H_0: \mu_{+PPI} = \mu_{-PPI} \text{ versus } H_1: \mu_{+PPI} \neq \mu_{-PPI}$$

Here μ_{+PPI} represents the mean difference in PHES among patients in the PPI continuation arm, and μ_{-PPI} represents the mean difference in PHES among patients in the PPI discontinuation arm.

Secondary endpoints:

- Per-protocol evaluation of PPI deprescribing on post-TIPS HE: The null hypothesis is that there is no difference in the change in PHES among patients who adhered with PPI discontinuation instructions versus those who continued to use PPIs.
- ITT analysis of the change in CLDQ and QOLRAD scores: The null hypothesis is that there is no difference in the pre to post-TIPS change in CLDQ/QOLRAD scores among patients in the PPI discontinuation arm compared to patients in the PPI continuation arm.
- Episodes of overt HE: The null hypothesis is that there is no difference in the number of patients experiencing an episode of overt HE, defined as a West-Haven score greater than or equal to 2, in the PPI discontinuation arm compared to patients in the PPI continuation arm.
- On-demand requirement for acid suppression therapy: Descriptive statistics will be presented on the number of patients in the PPI discontinuation arm reporting on-demand use of histamine H2 blockers or PPIs.
- Adverse events: The null hypothesis is that there is no difference in the number of patients experiencing an AE in the PPI discontinuation arm compared to patients in the PPI continuation arm.

Exploratory endpoints:

For analyses exploring the role of the microbiome in mediating PPI induced post-TIPS HE, the null hypothesis is that $b = 0$ and that $c = c'$ (no mediation, see Figure 2). The alternative hypothesis is that $b \neq 0$ and $c' < c$ (partial or complete mediation) (34).

10.3 Analysis Datasets

Analysis datasets will include all randomized patients (ITT analysis dataset) and patients who discontinued PPI therapy (defined as those who used on-demand histamine H2 blockers or PPIs less than twice weekly) versus those who continued PPIs therapy (defined as a daily dose of a least 20 mg omeprazole equivalent) (per-protocol analysis dataset).

10.4 Description of Statistical Methods

10.4.1 General Approach

- For descriptive statistics, such as patient demographics, means and ranges will be reported for continuous variables, whereas counts and percentages will be reported for categorical variables.
- For inferential tests, differences in sample means will be assessed by two-sided unpaired T-tests, whereas differences in proportions will be assessed by two-sided Fisher's exact tests.
- For statistical mediation analysis, the non-parametric bootstrap method of Preacher and Hayes will be utilized (34).
- For all inferential tests, a two-sided p-value less than 0.05 will be considered significant.

10.4.2 Analysis of the Primary Endpoint

For the primary outcome, statistical analysis will be conducted via a two-sided unpaired T-test of the hypothesis H_0: $\mu_{+PPI} = \mu_{-PPI}$ versus H_1: $\mu_{+PPI} \neq \mu_{-PPI}$. The estimate of μ_{+PPI}, the mean difference in pre versus post-TIPS PHES in the PPI continuation arm, is derived from the sample mean:

$$\overline{x}_{+PPI} = 1/n \sum (x_{post\text{-}TIPS,i} - x_{pre\text{-}TIPS,i})$$

Here $x_{post\text{-}TIPS,i}$ and $x_{pre\text{-}TIPS,i}$ are the PHES test scores 4 weeks after TIPS and 2 weeks before TIPS for i^{th} subject in the PPI continuation arm. The estimate of μ_{-PPI} is obtained in an identical fashion from patients in the PPI discontinuation arm. For the primary outcome analysis will be conducted according to the principle of ITT.

10.4.3 Analysis of the Secondary and Exploratory Endpoints

- Per-protocol evaluation of PPI deprescribing on post-TIPS HE: Statistical analysis will be conducted via a two-sided unpaired T-test of the hypothesis H_0: $\mu_{+PPI} = \mu_{-PPI}$ versus H_1: $\mu_{+PPI} \neq \mu_{-PPI}$. Here μ_{+PPI} and μ_{-PPI} are the pre to post-TIPS change in PHES estimated from the sample means in the per-protocol dataset.
- ITT analysis of the change in CLDQ and QOLRAD scores: Statistical analysis will be conducted via a two-sided unpaired T-test of the hypothesis H_0: $\mu_{+PPI} = \mu_{-PPI}$ versus H_1: $\mu_{+PPI} \neq \mu_{-PPI}$. Here μ_{+PPI} and μ_{-PPI} are the pre to post-TIPS change in QOL scores on the respective surveys, estimated in the ITT dataset.
- Episodes of overt HE: Statistical analysis will be conducted via a two-sided Fisher's exact test of the hypothesis H_0: $p_{+PPI} = p_{-PPI}$ versus H_1: $p_{+PPI} \neq p_{-PPI}$. Here p_{+PPI} is the proportion of patients in the PPI continuation arm experiencing at least one episode of

greater than or equal to West-Haven grade 2 overt HE, and p_{-PPI} is the corresponding proportion in the PPI discontinuation arm.

- On-demand requirement for acid suppression therapy: The proportion of patients in the PPI discontinuation arm needing on-demand histamine H2 blockers and PPIs will be reported.
- Adverse events: Statistical analysis will be conducted via a two-sided Fisher's exact test of the hypothesis H_0: $p_{+PPI} = p_{-PPI}$ versus H_1: $p_{+PPI} \neq p_{-PPI}$. Here p_{+PPI} is the proportion of patients in the PPI continuation arm experiencing at least AE, and p_{-PPI} is the corresponding proportion in the PPI discontinuation arm.
- Exploratory analysis of the role of the GI tract microbiome in mediating PPI induced post-TIPS HE: Analysis will be conducted using statistical mediation analysis (34, 43). Criteria for assessing mediation are based on the following equations:

$$Y = \mu_1 + c\,X + \varepsilon_1$$

$$M_j = \mu_2 + a\,X + \varepsilon_2$$

$$Y = \mu_3 + c'\,X + b\,M_j + \varepsilon_3$$

Here Y is a vector where the i^{th} element represents the pre to post-TIPS change in PHES for the i^{th} patient. M_j is a vector describing the bacterial abundance for the j^{th} taxon with the i^{th} element representing the pre to post-TIPS change for the i^{th} patient. X is an indicator vector where the i^{th} element is 0 if the patient was randomized to the PPI discontinuation arm and 1 otherwise. The μ and ε terms represent intercepts and error terms, respectively. Variable M_j is considered a mediator if the regression coefficients satisfy (1) $c \neq 0$, (2) $a \neq 0$, and (3) $b \neq 0$. The non-parametric bootstrap test of Preacher and Hayes will be utilized to formally test these relationships (34). For microbiome studies, the mediating effects on HE are analyzed using relative abundances of bacterial taxa at the family and genus levels in a causal compositional mediation model (43). Due to the multiplicity of bacterial families and genera, the false discovery rate will be used for multiple testing correction (44).

10.4.4 Safety Analyses

Analyses of AEs will be performed as described above in Section 10.4.3.

10.4.5 Adherence and Retention Analyses

Analysis of on-demand acid suppression pharmacotherapy will be performed as described above in Section 10.4.3. No retention analyses are planned.

10.4.6 Baseline Descriptive Statistics

Baseline characteristics of the PPI continuation and discontinuation arms will be compared, including demographics, comorbidities, prior HE and anti-HE therapy, and TIPS procedure characteristics, using means and ranges for continuous variables and counts and percentages for categorical variables. Inferential tests to assess differences in baseline characteristics of the

groups will be performed using T-tests for continuous variables and Fisher's exact tests for categorical variables.

10.4.7 Planned Interim Analyses

10.4.7.1 Safety Review

As described above in Section 8.5 Study Halting Rules, if three SAEs related to PPI discontinuation are identified the study will be halted.

10.4.7.2 Efficacy Review

Not applicable.

10.4.8 Additional Sub-Group Analysis

Not applicable.

10.4.9 Multiple Comparison/Multiplicity

As described above in Section 10.4.3 the false discovery rate criteria of Benjamini and Hochberg (44) will be used for multiple testing correction in GI tract microbiome mediation analyses.

10.4.10 Tabulation of Individual Response Data

Not applicable.

10.4.11 Exploratory Analyses

Exploratory analyses related to the GI tract microbiome are described above in Section 10.4.3. These analyses are considered exploratory for the following reasons:

- To formally conclude mediation in the most rigorous sense, two additional criteria must be met in addition to those described above: (1) there can be no measurement error in the mediator variable M_j (2) Y cannot cause M_j. In this study measurement error is present in M_j, the change in abundance of the j^{th} bacterial taxon pre to post-TIPS. In addition, the pre to post-TIPS change in PHES could potentially cause changes in the GI tract microbiome, for example in patients prescribed rifaximin therapy due to overt post-TIPS HE.
- In mediation analysis, sample sizes of 50 patients are typically required to detect large effects, and medium size effects may require 100 patients (45). Therefore, the present study may lack power to detect medium size or small mediation effects.
- Because microbiome mediation analysis utilizes relative abundances of bacterial taxa at the family and genus levels (43) a multiple testing correction is required as described above. The necessity for multiple testing correction further reduces statistical power.

10.5 Sample Size

The target sample size is estimated to provide statistical power for the primary outcome, the pre to post-TIPS change in PHES compared between the PPI continuation and discontinuation groups. Compared to pre-TIPS, patients perform approximately 18%, 51%, 26%, and 48% worse post-TIPS on the number connection A/B, digit symbol, and block design tests, respectively (46). Assuming a similar degree of PHES worsening pre- versus post-TIPS among the PPI continuation arm, but that cessation of PPIs would improve HE such that test performance is unchanged in the discontinuation arm, the estimated power with 20 patients in each arm (40 patients total) would be 71% to 96%. The proposed sample size and study duration are commensurate with previous studies. For example, previous clinical trials of lactulose and rifaximin for minimal HE randomized 61 patients for 12 weeks (47) and 42 patients for 8 weeks (48). Approximately 30 patients undergo elective TIPS creation per year at Duke University Hospital, with approximately 60-75% of those taking PPIs. Thus, approximately 20 patients per year are expected to be eligible for the study.

10.6 Measures to Minimize Bias

10.6.1 Enrollment/Randomization/Masking Procedures

Randomization codes will be generated and maintained by the PI. Randomization of subjects between the PPI continuation and discontinuation groups will be performed in a 1:1 fashion. The patient and treating IR physician will not be blinded (open-label design). The CRC performing MHE assessments via PHES tests and QOL assessments via the CLDQ and QOLRAD surveys will be blinded to patient assignment.

10.6.2 Evaluation of Success of Blinding

Not applicable.

10.6.3 Breaking the Study Blind/Participant Code

Not applicable.

11 Source Documents and Access to Source Data/Documents

Source data will include CRFs and the electronic medical record. CRFs will include Duke medical record number, a study subject identifier, PHES test results, QOL survey results, and patients' reported use of on-demand histamine H2 blockers and PPIs. Raw source data and post-processed data from stool microbiome sequencing will be maintained in the Duke Protected Analytics Computing Environment (PACE).

12 Quality Assurance and Quality Control

Quality control procedures will be implemented beginning with the data entry into CRFs. Any missing data or data anomalies will be reviewed by the PI and will be communicated to study members for clarification/resolution. The study team will provide direct access to all trial related source data/documents and reports for the purpose of monitoring and auditing by the IRB.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The written informed consent form is submitted with this protocol to the IRB.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators and their staff. Therefore, the study protocol, documentation, data, and all other information generated will be

held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval from the PI and IRB.

Representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study.

The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, stored in locked file cabinets in the locked IR office suite and on a secured password protected computer in the PI's locked office.

13.4.1 Research Use of Stored Human Samples, Specimens or Data

- Electronic data will be stored in PACE
- Bacterial DNA isolated from stool samples will be stored in a -80C freezer in the locked IR laboratory of Dr. Charles Kim.

13.5 Future Use of Stored Specimens

Future use of stored specimens will be require a separate application to the IRB for approval.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the study team and PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, the original entry will be crossed out with a single line, and initialed and dated. Erasing, overwriting, or correction fluid will not be permitted on original documents.

Clinical data will be entered into the PI's password protected computer in a locked office in the IR suite in Duke University Hospital. No data will be stored, transmitted, or shared with non-study personnel, on non-secured or non-Duke University Health System computers.

14.2 Study Records Retention

Study documents will be retained for a minimum of 6 years following completion of the study in accordance with IRB regulations.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study team. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the study team to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation. Protocol deviations will be sent to the local IRB per their guidelines.

14.4 Publication and Data Sharing

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. In addition, in accordance of with Food and Drug Administration Amendments Act of 2007 which mandates that a "responsible party" (i.e., the PI) register and report results of certain "applicable clinical trials" (including trials of drugs and biologics: controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation), the trial will be registered with ClinicalTrials.gov and results reported.

15 Study Administration

15.1 Study Leadership

The PI will govern the conduct of the study. The study will be subject to Duke University Health System IRB oversight.

16 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.

17 Literature References

1. Boyer TD, Haskal ZJ. The role of transjugular intrahepatic portosystemic shunt in the management of portal hypertension. Hepatology 2005; 41:386-400.
2. Bureau C, Thabut D, Oberti F, et al. Transjugular Intrahepatic Portosystemic Shunts With Covered Stents Increase Transplant-Free Survival of Patients With Cirrhosis and Recurrent Ascites. Gastroenterology 2017; 152:157-163.
3. Lv Y, Yang Z, Liu L, et al. Early TIPS with covered stents versus standard treatment for acute variceal bleeding in patients with advanced cirrhosis: a randomised controlled trial. Lancet Gastroenterol Hepatol 2019; 4:587-598.

4. Fonio P, Discalzi A, Calandri M, et al. Incidence of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt (TIPS) according to its severity and temporal grading classification. Radiol Med 2017; 122:713-721.
5. Khokhar N, Qureshi MO, Ahmad S, et al. Comparison of once a day rifaximin to twice a day dosage in the prevention of recurrence of hepatic encephalopathy in patients with chronic liver disease. J Gastroenterol Hepatol 2015; 30:1420-1422.
6. Liu A, Perumpail RB, Kumari R, Younossi ZM, Wong RJ, Ahmed A. Advances in cirrhosis: Optimizing the management of hepatic encephalopathy. World J Hepatol 2015; 7:2871-2879.
7. Campbell MS, Brensinger CM, Sanyal AJ, et al. Quality of life in refractory ascites: transjugular intrahepatic portal-systemic shunting versus medical therapy. Hepatology 2005; 42:635-640.
8. Orloff MJ, Hye RJ, Wheeler HO, et al. Randomized trials of endoscopic therapy and transjugular intrahepatic portosystemic shunt versus portacaval shunt for emergency and elective treatment of bleeding gastric varices in cirrhosis. Surgery 2015; 157:1028-1045.
9. Neff G, Zachry W, III. Systematic Review of the Economic Burden of Overt Hepatic Encephalopathy and Pharmacoeconomic Impact of Rifaximin. Pharmacoeconomics 2018; 36:809-822.
10. Dam G, Vilstrup H, Watson H, Jepsen P. Proton pump inhibitors as a risk factor for hepatic encephalopathy and spontaneous bacterial peritonitis in patients with cirrhosis with ascites. Hepatology 2016; 64:1265-1272.
11. Lin ZN, Zuo YQ, Hu P. Association of Proton Pump Inhibitor Therapy with Hepatic Encephalopathy in Hepatitis B Virus-related Acute-on-Chronic Liver Failure. Hepat Mon 2014; 14:e16258.
12. Matei D, Pasca S, David A, et al. Proton pump inhibitors increase the risk for hepatic encephalopathy in patients with cirrhosis and ascites. Journal of Hepatology 2017; 1:S136.
13. Nardelli S, Gioia S, Ridola L, Farcomeni A, Merli M, Riggio O. Proton Pump Inhibitors Are Associated With Minimal and Overt Hepatic Encephalopathy and Increased Mortality in Patients With Cirrhosis. Hepatology 2019; 70:640-649.
14. Shanab AA, Smith A, Abbas M, et al. Proton pump inhibitors-a risk factor for hepatic encephalopathy in patients listed for liver transplantation? Hepatology: WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA, 2018; p. 1176A-1176A.
15. Tergast TL, Wranke A, Laser H, et al. Dose-dependent impact of proton pump inhibitors on the clinical course of spontaneous bacterial peritonitis. Liver Int 2018; 38:1602-1613.
16. Tsai CF, Chen MH, Wang YP, et al. Proton Pump Inhibitors Increase Risk for Hepatic Encephalopathy in Patients With Cirrhosis in A Population Study. Gastroenterology 2017; 152:134-141.
17. Zhu J, Qi X, Yu H, et al. Association of proton pump inhibitors with the risk of hepatic encephalopathy during hospitalization for liver cirrhosis. United European Gastroenterol J 2018; 6:1179-1187.
18. Tapper EB, Henderson JB, Parikh ND, Ioannou GN, Lok AS. Incidence of and Risk Factors for Hepatic Encephalopathy in a Population-Based Cohort of Americans With Cirrhosis. Hepatology Communications 2019; 3:1510-1519.
19. Lewis DS, Lee TH, Konanur M, et al. Proton Pump Inhibitor Use Is Associated with an Increased Frequency of New or Worsening Hepatic Encephalopathy after Transjugular Intrahepatic Portosystemic Shunt Creation. J Vasc Interv Radiol 2019; 30:163-169.
20. Sturm L, Bettinger D, Giesler M, et al. Treatment with proton pump inhibitors increases the risk for development of hepatic encephalopathy after implantation of transjugular intrahepatic portosystemic shunt (TIPS). United European Gastroenterol J 2018; 6:1380-1390.
21. Bian J, Wang A, Lin J, et al. Association between proton pump inhibitors and hepatic encephalopathy: A meta-analysis. Medicine (Baltimore) 2017; 96:e6723.

22. Ma YJ, Cao ZX, Li Y, Feng SY. Proton pump inhibitor use increases hepatic encephalopathy risk: A systematic review and meta-analysis. World J Gastroenterol 2019; 25:2675-2682.
23. Shi D, Zhou Z, Dai Y, Pan X, Cao Q. Proton Pump Inhibitor Therapy and Hepatic Encephalopathy Risk in Cirrhotic Patients: A Systematic Review with Meta-analysis. Clin Drug Investig 2019; 39:847-856.
24. Tantai XX, Yang LB, Wei ZC, et al. Association of proton pump inhibitors with risk of hepatic encephalopathy in advanced liver disease: A meta-analysis. World J Gastroenterol 2019; 25:2683-2698.
25. Macke L, Schulz C, Koletzko L, Malfertheiner P. Systematic review: the effects of proton pump inhibitors on the microbiome of the digestive tract—evidence from next-generation sequencing studies. Alimentary Pharmacology & Therapeutics 2020; 51:505-526.
26. Bajaj JS, Acharya C, Fagan A, et al. Proton Pump Inhibitor Initiation and Withdrawal affects Gut Microbiota and Readmission Risk in Cirrhosis. Am J Gastroenterol 2018; 113:1177-1186.
27. Bajaj JS. The role of microbiota in hepatic encephalopathy. Gut Microbes 2014; 5:397-403.
28. Elkington S. Lactulose. Gut 1970; 11:1043.
29. Boghossian TA, Rashid FJ, Thompson W, et al. Deprescribing versus continuation of chronic proton pump inhibitor use in adults. Cochrane Database Syst Rev 2017; 3:Cd011969.
30. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. Gut 2017; 66:6-30.
31. Wolfe MM, Sachs G. Acid suppression: Optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology 2000; 118:S9-S31.
32. Lo EA, Wilby KJ, Ensom MH. Use of proton pump inhibitors in the management of gastroesophageal varices: a systematic review. Ann Pharmacother 2015; 49:207-219.
33. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017; 65:310-335.
34. Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behavior Research Methods, Instruments, & Computers 2004; 36:717-731.
35. Steinman MA, Landefeld CS. Overcoming Inertia to Improve Medication Use and Deprescribing. Jama 2018; 320:1867-1869.
36. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology 2014; 60:715-735.
37. Pilotto A, Leandro G, Franceschi M. Short- and long-term therapy for reflux oesophagitis in the elderly: a multi-centre, placebo-controlled study with pantoprazole. Alimentary Pharmacology & Therapeutics 2003; 17:1399-1406.
38. Kirchheiner J, Glatt S, Fuhr U, et al. Relative potency of proton-pump inhibitors-comparison of effects on intragastric pH. Eur J Clin Pharmacol 2009; 65:19-31.
39. Kukulka M, Eisenberg C, Nudurupati S. Comparator pH study to evaluate the single-dose pharmacodynamics of dual delayed-release dexlansoprazole 60 mg and delayed-release esomeprazole 40 mg. Clin Exp Gastroenterol 2011; 4:213-220.
40. Ness-Jensen E, Hveem K, El-Serag H, Lagergren J. Lifestyle Intervention in Gastroesophageal Reflux Disease. Clin Gastroenterol Hepatol 2016; 14:175-182.e171-173.
41. Karkar R, Kocielnik R, Zhang X, et al. Beacon: Designing a Portable Device for Self-Administering a Measure of Critical Flicker Frequency. Proceedings of the ACM on Interactive, Mobile, Wearable and Ubiquitous Technologies 2018; 2:1-27.
42. Khalilzadeh O, Baerlocher MO, Shyn PB, et al. Proposal of a New Adverse Event Classification by the Society of Interventional Radiology Standards of Practice Committee. J Vasc Interv Radiol 2017; 28:1432-1437.e1433.

43. Sohn M, Li H. Compositional mediation analysis for microbiome studies. The Annals of Applied Statistics 2019; 13:661-681.
44. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society: Series B (Methodological) 1995; 57:289-300.
45. MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. Psychological methods 2002; 7:83-104.
46. Bajaj JS, Heuman DM, Sterling RK, et al. Validation of EncephalApp, Smartphone-Based Stroop Test, for the Diagnosis of Covert Hepatic Encephalopathy. Clinical Gastroenterology and Hepatology 2015; 13:1828-1835.e1821.
47. Prasad S, Dhiman RK, Duseja A, Chawla YK, Sharma A, Agarwal R. Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy. Hepatology 2007; 45:549-559.
48. Bajaj JS, Heuman DM, Wade JB, et al. Rifaximin improves driving simulator performance in a randomized trial of patients with minimal hepatic encephalopathy. Gastroenterology 2011; 140:478-487.e471.