Official Title: Impact of Transjugular Intrahepatic Portosystemic Shunts on Liver Stiffness

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Impact of Transjugular Intrahepatic Portosystemic Shunts on Liver Stiffness

Regulatory Sponsor: *Kimberly Forde, MD, MHS (PI)*

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Table of Contents

List of Abbreviations

ESLD – end stage liver disease
TIPS – transjugular portosystemic shunt
PSG – portosystemic gradient
ARFI - acoustic radiation force impulse

Study Summary

Title	**Impact of Transjugular Intrahepatic Portosystemic Shunts on Liver Stiffness**
Short Title	TIPS and Stiffness
Protocol Number	TBD
Phase	N/A
Methodology	Pilot study examining changes in liver stiffness measured by ultrasound before and after TIPS creation
Study Duration	12 months
Study Center(s)	Hospital of the University of Pennsylvania
Objectives	*Primary*: Liver stiffness as measured by ultrasound acoustic radiation force impulse (ARFI) before and after creation of TIPS *Secondary:* Change in portosystemic gradient Clinical success as measured by difference in frequency of repeat paracentesis post-TIPS or freedom from recurrence of variceal bleeding Rate of hepatic encephalopathy *Exploratory:* Serum biomarkers of liver stiffness
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	≥18yo, undergoing TIPS creation for symptomatic portal hypertension Exclusions: BMI >35 and/or cirrhosis due to non-alcoholic steatohepatitis, urgent or emergent TIPS for bleeding, revision of prior TIPS shunt, excessive alcohol use within the last 90 days
Design	Single arm pilot study
Duration of participation	30 days from TIPS creation
Statistical Methodology	Reduction in PSG below 12mm Hg will be associated with a 50% decrease in stiffness as measured by ultrasound
Principal Investigator	Kimberly Forde, MD (Medicine, Hepatology)
Co-Investigators	Marina Serper, MD (Medicine, Hepatology) David Kaplan, MD (Medicine, Hepatology) Rebecca Wells, MD (Medicine, Hepatology) Gregory Nadolski, MD (Interventional Radiology) Anil Chauhan, MD (Radiology)
Key Personnel	Kristi Lelionis CRC (Radiology Research Coordinator, UPenn) Biostatistician (TBD, UPenn)

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

End stage liver disease (ESLD), also known as cirrhosis or end-stage fibrosis, commonly presents with symptomatic portal hypertension. Two manifestations of symptomatic portal hypertension, ascites and variceal bleeding, can be treated by transjugular portosystemic shunt, or TIPS, creation. TIPS involves the percutaneous placement of a stent graft between the portal and hepatic veins to reduce the difference in blood pressure between the portal vein and the heart, also known as the portosystemic gradient, or PSG. Reduction of the PSG has been shown to decrease incidence of bleeding and reduce ascites. (1-3)

Portal hypertension also causes liver stiffening, by ~5 fold or more, which increases myofibroblast differentiation and causes further fibrosis.(4) This increased liver stiffness is believed to play a role in the development of primary liver cancer called hepatocellular carcinoma (HCC) by creating a microenvironment that facilitates cancer development. HCC occurs overwhelmingly (>90%) in the cirrhotic liver (end-stage fibrosis), which is stiff. Thus, we hypothesize that rapidly reducing liver stiffness with TIPS could not only decrease liver stiffness but also limit hepatic fibrosis, and perhaps lower the incidence of HCC.

About 1-2 weeks prior to and after TIPS placement, ultrasound is routinely performed to assess portal vein patency and obtain a baseline assessment of TIPS flow velocity.(5) During ultrasound, a non-invasive measurement of liver stiffness can be obtained using a technique called ultrasound acoustic radiation force impulse (ARFI).(6) Acoustic radiation force is a phenomenon associated with the propagation of sound waves in a media that attenuates the movement of the sound wave by absorption or scatter. Attenuation depends on the frequency of the sound wave, but typically is dominated by absorption. With increasing frequency, the harmonic vibration of tissue in response to a sound wave becomes out of phase with the acoustic wave, and energy is deposited into the tissue. This energy generates a force that causes displacement of the tissue. This displacement (typically a few micrometers) can be used to derive additional information about the tissue beyond what is normally provided in an ultrasound image. The magnitude, location, spatial extent, and duration of acoustic radiation force can be controlled to interrogate the mechanical properties of the tissue. In the liver, the speed at which shear waves propagate in tissue can be used to quantify the shear modulus of the liver tissue allowing non-invasive characterization the liver's stiffness and fibrosis without the need for liver biopsy.

1.2 Investigational Agent

TIPS creations at the University of Pennsylvania are performed using Viatorr stent grafts, which are FDA approved devices for TIPS creation. ARFI at the University of Pennsylvania is available for clinical use on Phillips Epiq Ultrasound systems using ElastPQ ultrasound shear wave elastography. Both devices are considered standard of care for their respective purposes. Both devices will be used in accordance with their approved indication and manufacture's instructions for use.

1.3 Preclinical Data

Preliminary data from laboratories in PSOC@Penn, an NCI-funded Physical Sciences in Oncology Center to study HCC, show that the liver undergoes significant compression stiffening, particularly with fibrosis and cirrhosis. Portal hypertension causes liver stiffening, by ~5 fold, which increases myofibroblast differentiation and further fibrosis.{Perepelyuk:2016hx} Tissues including liver stiffen and acquire more extracellular matrix with fibrosis. In our pre-clinical data, the relationship between matrix content and stiffness was found to be non-linear. A key feature of this model is that, while it assumes overall liver

incompressibility, it takes into account both tissue blood flow and solid phase compressibility. These findings suggest that both fibrosis and portal hypertension contribute to overall liver stiffness.

1.4 Clinical Data to Date

The present pilot study would serve as the initial data demonstrating that reductions in portosystemic gradient by TIPS will reduce liver stiffness as measured non-invasively by ARFI.

2 Study Objectives

Primary Objectives:
To evaluate the relationship between portosystemic gradient (severity of portal hypertension) and liver stiffness as measured by ultrasound acoustic radiation force impulse (ARFI) before and after creation of TIPS

Secondary:

- Correlate change in portosystemic gradient with change in liver stiffness
- Correlate baseline portosystemic gradient with baseline liver stiffness
- Clinical success as measured by difference in frequency of repeat paracentesis post-TIPS or freedom from recurrence of variceal bleeding
- Rate of hepatic encephalopathy

Exploratory:

- Correlation of serum biomarkers of liver stiffness with baseline ARFI measurements of liver stiffness

3 Study Design

3.1 General Design

An open label, single arm trial investigating changes in liver stiffness as measured by ultrasound acoustic radiation force impulse (ARFI) before and after creation of TIPS. TIPS creation with Viatorr stent graft will be in accordance with its FDA-approved indication for symptomatic portal hypertension and per the manufacturer's instructions for use. Liver stiffness will be measured on pre-TIPS and post-TIPS ultrasounds using Phillips Epiq Ultrasound systems equipped with ElastPQ ultrasound shear wave elastography. Both ultrasounds will be performed at times which are standard of care before and after TIPS creation.

Trial Design

Screening and Consent: Patients referred to Interventional Radiology for primary creation of TIPS for treatment of symptomatic portal hypertension will be screened for enrollment. Following recruitment of those meeting inclusion criteria, patients will be scheduled for liver ultrasound with shear wave elastography prior to the procedure (between 2 to 21 days prior to TIPS creation). In cases where ascites is present, which can interfere with the accuracy of elastography measurements, ultrasound will be scheduled on same day as an elective outpatient paracentesis or up to 2 days following paracentesis, which would be performed as part of routine clinical care to alleviate the patients symptoms of massive ascites and remove excess abdominal fluid prior to TIPS creation in order to allow TIPS procedure to be performed safely.

By consenting to participate in this trial, patients will allow the researchers at the University of Pennsylvania health system to review parameters from their electronic medical record related to symptomatic portal hypertension including:

Etiology of cirrhosis
Medical therapy for portal hypertension or its symptoms including dosage and duration of therapy
Lab parameters: Platelet Count, Creatinine, Total Bilirubin, Sodium, INR, Albumin
Childs-Pugh Score
Model of end stage liver disease (MELD) score and Sodium MELD score
History of frequency and severity hepatic encephalopathy as defined by West Haven criteria
Frequency and volume of paracentesis
Frequency and severity of variceal bleeding

TIPS Creation: TIPS creation will be performed per current practice guidelines with the following modifications.(7) After initial access to the blood stream, 1 tablespoon (15mL) of blood will be obtained for analysis of direct measures of fibrinogenesis or fibrinolysis such as hyaluronic acid and tissue inhibitor of metalloproteinase-1.(8) At TIPS creation, pre- and post-TIPS PSG and absolute values of portal and right atrial blood pressures will be recorded. Following TIPS creation, patients will be admitted to the Hospital of the University of Pennsylvania for monitoring and pain control.

Post-TIPS Creation Follow-up: Post-TIPS creation follow-up will occur according to standard clinical practice with the addition to ARFI at the time of initial post-TIPS ultrasound. Post-TIPS labs including complete blood count, coagulation studies, and comprehensive metabolic panel will be performed between 5 and 21 days following TIPS creation. Clinical visit for assessment of clinical success and complications including hepatic encephalopathy will be performed between 5 and 21 days following TIPS creation (typically scheduled for 1 week following procedure). Likewise, post-TIPS ultrasound including ARFI will be performed in the same time range (5 to 21 days post TIPS creation). Data collected at Post-TIPS Creation Follow-Up will include:

Lab parameters: Platelet Count, Creatinine, Total Bilirubin, Sodium, INR, Albumin
Childs-Pugh Score
Model of end stage liver disease (MELD) score and Sodium MELD score
Occurrence and severity of hepatic encephalopathy as defined by West Haven criteria
Need for and volume of paracentesis since TIPS creation
Incidence of variceal bleeding since TIPS creation

Long-term Follow-up: Additional follow-up will occur as part of routine clinical care. Patient data up to 12 months following TIPS insertion will be obtained from the electronic medical record or by direct patient contact via phone. Data collected in long-term follow-up will include

Lab parameters: Platelet Count, Creatinine, Total Bilirubin, Sodium, INR, Albumin
Childs-Pugh Score
Model of end stage liver disease (MELD) score and Sodium MELD score
Occurrence and severity of hepatic encephalopathy as defined by West Haven criteria
Need for and volume of paracentesis since TIPS creation
Incidence of variceal bleeding since TIPS creation
Date of TIPS revision or TIPS flow reduction if performed

3.2 Primary Study Endpoints

The primary study endpoint will be **decrease in liver stiffness** following TIPS creation as measured by ARFI using mean propagation velocity values in meters per second. Mean normal values and mean values indicating severe fibrosis range about 0.8-1.7 m/s and about 1-3.4 m/s respectively. We hypothesize TIPS creation will reduce the liver stiffness by $\geq$ 50%. Change in liver stiffness will be correlated to change in PSG.

3.3 Secondary Study Endpoints

1. Baseline PSG (mm Hg) correlation to baseline liver stiffness by ultrasound ARFI (m/s)

2. Clinical success as measured by difference in frequency of repeat paracentesis post-TIPS or freedom from recurrence of variceal bleeding at 12 months
3. Correlation of serum biomarkers of liver stiffness (hyaluronic acid and tissue inhibitor of metalloproteinase-1) with baseline ARFI measurements of liver stiffness

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Symptomatic portal hypertension secondary to cirrhosis undergoing elective outpatient TIPS
2. Age ≥18, Age <80
3. Capable of giving informed consent

4.2 Exclusion Criteria

1. Coagulopathy defined as international normalized ration (INR) >2 which cannot be corrected with fresh frozen plasma
2. Platelet count <50,000/microliter, which cannot be corrected with platelet transfusion
3. BMI >35 and/or cirrhosis due to non-alcoholic steatohepatitis (due to inaccurate elastography measurements in patients with fatty liver)
4. Urgent or emergent TIPS for bleeding
5. Portal vein thrombosis with in the main, 1st, or 2nd order branches of the portal vein
6. Hepatic vein thrombosis (ie no Budd Chiari syndrome)
7. Excessive alcohol use defined as more than 2 oz in 24 hours on any individual day within the last 30 days
8. Inability to provide informed consent
9. Pregnant or nursing women
10. Enrollment in concurrent therapeutic trial for symptomatic portal hypertension

4.3 Subject Recruitment and Screening

Currently, approximately 20-30 elective outpatient TIPS are created per year by the Interventional Radiology practice at Hospital of the University of Pennsylvania. These patients are referred from the Departments of Medicine Division of Gastroenterology.

During the initial contact with the patient, potential candidates will be screened by research coordinator, PI, or co-PI for adequacy for the clinical trial. If the applicant meets inclusion criteria without any exclusion criteria, the patient will be approached by research coordinator to discuss enrollment. All patients who are identified as potential candidates for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The potential subject will be given an opportunity to read the consent form thoroughly and ask and be provided answers to any questions that they may have regarding the study. The subject will be asked to sign the consent form only if they have indicated that they are willing to do so without reservation. The informed consent will be obtained before the subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate and the investigator or investigator-designated research professional obtaining consent. The subjects will be informed that their participation is entirely voluntary, that if they chose not participate their care will not be affected and that they may withdraw consent at any time.

Patients who experience a major complication from TIPS creation (eg hemobilia, ischemic liver failure) that likely affects the success of the TIPS to treat portal hypertension will be withdrawn at the discretion of the PI and study team and replaced with additional subjects.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

• PI Decision: Subjects may be withdrawn at any time during the study if the PI believes it is in the subject's best interest. In this event, the reasons for withdrawal will be documented. Patients who experience a major complication from TIPS creation (eg hemobilia, ischemic liver failure) that likely affects the success of the TIPS to treat portal hypertension will be withdrawn at the discretion of the PI and study team and replaced with additional subjects.
• Subject Participation: Refusal to continue with treatment, follow-up, comply with the protocol or withdrawal of consent. In this event, the reasons for withdrawal will be documented.

Patients withdrawing from the study will be entitled to pursue all treatment options available for the treatment of end-stage liver disease without prejudice from the providing physicians.

Once the subject has discontinued treatment, the primary reason for discontinuing treatment must be clearly documented in the subject's records and on the eCRF. The investigator will assess each subject for response at the time of withdrawal.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

All data collected prior to subject withdraw will be retained in eCRFs and included for analysis.

Even though subjects may be withdrawn prematurely from the study, attempts will be made to collect data on clinical success, TIPS complications and patency data for TIPS on such subjects throughout the protocol defined follow-up period for that subject. Such data is important to the integrity of the final study analysis of secondary end-points. If a subject withdraws consent to participate in the study, attempts will be made to obtain permission to record at least TIPS patency, complication, and clinical success data up to the protocol-described end of subject follow-up period. Methods that may be used to obtain primary patency data will include phone calls to the subject, phone calls to next-of-kin if possible, and certified letters to the subject or next-of-kin. If permission to collect or the specific patency data cannot be obtained after 4 phone calls and 4 letters to the subject and/or next-of-kin, the patient will be regarded as lost to follow up.

5 Study Interventions

5.1 Descriptions

<u>TIPS Creation</u>
TIPS creation will be in accordance with its FDA-approved indication under moderate sedation or general anesthesia with local anesthesia using Viatorr stent graft. In brief, using real time ultrasound guidance, access to the internal or external jugular vein will be achieved using a 21G needle and a guidewire advanced into the superior vena cava under fluoroscopic guidance. Using this access, a 10F vascular sheath will be placed and 15mL of blood obtained for analysis of hyaluronic acid and tissue inhibitor of metalloproteinase-1 (biomarkers of liver fibrosis). A catheter will be used to select a hepatic vein. Next, entry to the portal vein will be achieved using a portal access needle. Upon confirming portal entry with contrast injection, a guidewire will be advanced into the portal vein and the needle exchanged for flush marker catheter. PSG will be measured and portogram performed. After angioplasty of the parenchymal tract, an appropriate length Viatorr stent graft will be inserted to create TIPS. Repeat portogram and measurement of PSG will be performed using a flush catheter. The catheter and sheath will be removed and hemostasis achieved with manual compression.

Ultrasound with ARFI
Pre-TIPS hepatic ultrasound will be performed between 2 and 21 days prior to TIPS creation using gray scale, color Doppler, and spectral Doppler imaging to evaluate hepatic vein and portal vein patency, direction and velocity of flow respectively. ARFI will be performed in the right hepatic lobe. Three measurements of stiffness (m/s) will be performed and the mean value recorded.

Post-TIPS ultrasound will be performed between 5 and 21 days following TIPS creation using gray scale, color Doppler, and spectral Doppler imaging to evaluate TIPS, hepatic vein and portal vein patency, direction and velocity of flow respectively. ARFI will be performed in the right hepatic lobe. Three measurements of stiffness (m/s) will be performed and the mean value recorded.

For patients with symptomatic ascites, ultrasound will be coordinated with subject's elective paracentesis or up to two days following paracentesis to minimize interference with ARFI measurements from the presence of ascites. These paracenteses are considered standard clinical care to alleviate symptoms of massive ascites and remove excess abdominal fluid prior to TIPS creation to permit TIPS to be created safely.

5.2 Treatment Regimen

TIPS will be created using standard clinical techniques. All patients' pre-TIPS and post-TIPS care will occur as part of standard of care with the exception of the addition of elastography at the time of ultrasound before and after TIPS creation. Patients will not be charged for the cost of the addition of ARFI to ultrasounds. Data related to cirrhosis, TIPS creation, follow-up TIPS performance and complications will be extracted from the electronic medical record at the University of Pennsylvania. Patients will be followed 12 months following TIPS creation.

5.3 Method for Assigning Subjects to Treatment Groups

The study is a non-randomized open label single arm pilot trial to provide preliminary clinical data on the change in liver stiffness in patients with symptomatic portal hypertension following TIPS creation. All procedures will be performed at times of routine clinical service. TIPS will be created using standard clinical techniques. All patient's pre-TIPS and post-TIPS care will occur as part of standard of care with the exception of the addition of elastography at the time of ultrasound before and after TIPS creation.

Monthly, the coordinators will provide documentation of the number of patients screened who chose not to enroll in the study. Otherwise, when a screened patient is recruited to the study, the coordinator will register the patient into the study database (RedCAP) and generate a study identification number, which will be recorded on the eCRF.

5.4 Preparation and Administration of Study Interventions

All procedures and imaging will be performed using FDA-approved devices/equipment for their intended FDA-approved indication using standard clinical practice as outlined in manufacturer's instructions for use. Thus, no special preparation or administration of these interventions is necessary.

Women who are able to become pregnant will be tested for pregnancy by urine pregnancy test. The results of this test must be negative at the time of enrollment. At the time of enrollment, documentation of pregnancy status will be recorded on eCRF as one of the following: (a) reproductive age UPT negative, (b) unable to become by nature means and approximate date of menopause, or (c) unable to become pregnant by surgical means and approximate date of surgery. For patients of reproductive age, UPT will be retested on date of TIPS creation.

5.5 Subject Compliance Monitoring

N/A

5.6 Prior and Concomitant Therapy

Patients may continue medical therapy for symptomatic portal hypertension. Enrollment in concurrent therapeutic clinical trial to treat portal hypertension is not allowed.

5.7 Blinding of Study Intervention

This protocol does not utilize blinding. Subjects and investigators will know the treatment being administered.

6 Study Procedures

6.1 Visit 1: Date of Enrollment and Clinical evaluation by Interventional Radiology

Initial consult for TIPS creations. Patient will be evaluated for enrollment in the clinical trial at the time of IR consult visit after consenting to undergo TIPS creation and confirmation that patient meets all inclusion and no exclusion criteria. After enrollment, the patient will be entered into eCRF (RedCap) and assigned a subject number. At this time, baseline clinical data including etiology of cirrhosis, medical therapy for portal hypertension or its symptoms including dosage and duration of therapy, Lab parameters (Platelet Count, Creatinine, Total Bilirubin, Sodium, INR, Albumin), Childs-Pugh Score, Model of end stage liver disease (MELD) score and Sodium MELD scores, history of hepatic encephalopathy including frequency and severity of hepatic encephalopathy as defined by West Haven criteria, frequency and volume of paracentesis, and frequency and severity of variceal bleeding will be recorded from the electronic medical record.

6.2 Visit 2: Pre-TIPS Ultrasound

Pre-TIPS hepatic ultrasound will be performed between 2 and 21 days prior to TIPS creation using gray scale, color Doppler, and spectral Doppler imaging to evaluate hepatic vein and portal vein patency, direction and velocity of flow respectively. ARFI will be performed in the right hepatic lobe. Three measurements of stiffness (m/s) will be performed and the mean value recorded in eCRF. Patency of hepatic veins and portal veins as well as spectral Doppler velocity measurements will be recorded in eCRF. For patients with symptomatic ascites, ultrasound will be coordinated with subject's elective paracentesis or up to two days following paracentesis to minimize interference with ARFI measurements from the presence of ascites.

6.3 Visit 3: TIPS Creation

TIPS creation will be in accordance with its FDA-approved indication under moderate sedation or general anesthesia with local anesthesia using Viatorr stent graft (FDA-approved for TIPS). In brief, using real time ultrasound guidance, access to the internal or external jugular vein will be achieved using a 21G needle and a guidewire advanced into the superior vena cava under fluoroscopic guidance. Using this access, a 10F vascular sheath will be placed and 15mL of blood obtained for analysis of hyaluronic acid and tissue inhibitor of metalloproteinase-1 (biomarkers of liver fibrosis). A catheter will be used to select a hepatic vein. Next, entry to the portal vein will be achieved using a portal access needle. Upon confirming portal entry with contrast injection, a guidewire will be advanced into the portal vein and the needle exchanged for flush marker catheter. PSG will be measured and portogram performed. After angioplasty of the parenchymal tract, an appropriate length Viatorr stent graft will be inserted to create TIPS. Repeat portogram and measurement of PSG will be performed using a flush catheter. The catheter and sheath

will be removed and hemostasis achieved with manual compression. After TIPS creation, patients will be admitted to the Hospital of the University of Pennsylvania for monitoring and pain control.

At the time of TIPS creation, absolute mean right atrial and portal vein pressures before and after TIPS creation as well as PSG at both time points will be recorded.

6.4 Visit 4: Post-TIPS Ultrasound and Clinical Follow-up Visit

Follow-up clinic evaluation in interventional radiology will be performed by the treating physician or a member of the study team between 5 and 21 days following TIPS creation. During this same time period (5 to 21 days post-TIPS creation), routine post-TIPS laboratory studies will be performed including CBC, CMP, and coagulation factors. Ammonia levels will be ordered as clinically indicated for patients with history of encephalopathy or development of encephalopathy following TIPS.

Post-TIPS ultrasound will be performed between 5 and 21 days following TIPS creation using gray scale, color Doppler, and spectral Doppler imaging to evaluate TIPS, hepatic vein and portal vein patency, direction and velocity of flow respectively. ARFI will be performed in the right hepatic lobe. Three measurements of stiffness (m/s) will be performed and the mean value recorded.

For patients with symptomatic ascites, ultrasound will be coordinated with subject's elective paracentesis or up to two days following paracentesis to minimize interference with ARFI measurements from the presence of ascites.

At the time of this visit the following data will be collected:
Lab parameters: Platelet Count, Creatinine, Total Bilirubin, Sodium, INR, Albumin
Childs-Pugh Score
Model of end stage liver disease (MELD) score and Sodium MELD score
Occurrence and severity of hepatic encephalopathy as defined by West Haven criteria
Need for and volume of paracentesis since TIPS creation
Incidence of variceal bleeding since TIPS creation
Patency of TIPS, hepatic veins and portal veins
Spectral Doppler velocity measurements of TIPS, hepatic veins and portal veins
Mean liver stiffness score from ARFI

6.5 Visit 5, etc: On-going Clinical Follow-up

Subsequent follow-up by interventional radiology or hepatology for TIPS complications or dysfunction and management of portal hypertension/cirrhosis will occur per routine clinical practice. Data related to the function and outcomes of TIPS will be extracted from the electronic medical record or by direct patient contact via the phone. Patients data will be recorded for up to 12 months following TIPS creation. Data collected in long-term follow-up will include

- Lab parameters: Platelet Count, Creatinine, Total Bilirubin, Sodium, INR, Albumin
- Childs-Pugh Score
- Model of end stage liver disease (MELD) score and Sodium MELD score
- Occurrence and severity of hepatic encephalopathy as defined by West Haven criteria
- Need for and volume of paracentesis since TIPS creation
- Incidence of variceal bleeding since TIPS creation
- TIPS, hepatic vein and portal vein flow and velocity measurements from repeat ultrasounds if performed
- Date of TIPS revision or TIPS flow reduction if performed

7 Statistical Plan

7.1 Study Objectives, Sample Size Determination and Power Calculation

Objectives
This trial is designed to be the initial pilot trial evaluating the changes in liver stiffness following TIPS creation. The knowledge gained from this investigation will serve as the basis for clinical trials comparing the effect of decreasing liver stiffness on progression of cirrhosis and hepatocellular carcinoma.

Primary Objective: To evaluate the relationship between portosystemic gradient (severity of portal hypertension) and liver stiffness as measured by ultrasound acoustic radiation force impulse (ARFI) before and after creation of TIPS

Secondary:
- Correlate change in portosystemic gradient with change in liver stiffness
- Correlate baseline portosystemic gradient with baseline liver stiffness
- Clinical success as measured by difference in frequency of repeat paracentesis post-TIPS or freedom from recurrence of variceal bleeding
- Rate of hepatic encephalopathy

Exploratory:
- Correlation of serum biomarkers of liver stiffness with baseline ARFI measurements of liver stiffness

Sample Size Determination and Power Calculation

Sample size estimation is based on our hypothesis that TIPS creation will result in a $\geq$ 50% reduction in the mean liver stiffness. Mean normal values and mean values indicating severe fibrosis range about 0.8-1.7 m/s and about 1-3.4 m/s respectively. Prior investigations have demonstrated that ARFI can distinguish pathological grade F3 and F4 stage fibrosis. The optimal cut-off value to identify fibrosis stage F3 or higher was 1.54 m/s, with sensitivity and specificity of 97% and 100% respectively.(9). Thus, if we assume the mean pre-TIPS stiffness value will be 3.08 m/s or higher indicating advanced fibrosis and the standard deviation of ARFI will be set to 30%(10), the null hypothesis that the mean value of liver stiffness will not be different after TIPS creation will be tested against a two-sided alternative, the mean value of liver stiffness will decrease by an effect size of 50% or greater. A sample size of 18 patients will provide sufficient power to reject the null hypothesis if the effect size was a little as a 20% reduction in liver stiffness using a paired t-test with a type I error rate of 0.05 and power of 0.80.

We anticipate 10% of subjects enrolled in this study will be removed from analysis due to major complication of TIPS creation interfering with accurate liver stiffness measurement. Thus, 20 patients will be enrolled in the trial. If 30 elective outpatients are scheduled for TIPS creation each year at the Hospital of the University of Pennsylvania, then we expect 18 months will be needed to complete enrollment.

7.2 Statistical Methods

Primary Objective: Mean liver stiffness value by ARFI before and after TIPS creation will be compared using a paired t-test.

Secondary Objectives: When comparing dichotomous variables before and after TIPS creation, a 2-sided $\chi 2$ test will be used. Fisher's exact test will be used for contingency tables with fewer than 10 subjects in each category. When comparing continuous variables, a 2-sided t test will be used, provided that the

distributions are sufficiently close to the normal distribution. Otherwise, a 2-sided Mann-Whitney test will be used.

7.3 Subject Population(s) for Analysis and Duration of Study

Analysis of both primary and secondary end points will be performed on all subjects undergoing successful TIPS creation who complete follow up ultrasound and clinical evaluation. Approximately 20 patients will be enrolled in this trial. Each patient will be followed for 1 year following TIPS creation. However, the primary end point will be recorded during visit 3 within 21 days of TIPS creation. Thus, we expect 18 months will be needed to complete enrollment and complete follow-up of all patients through the primary end-point.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. 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)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following completion of the last survey.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the study team and investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events

should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (eCRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others
  (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.3.1 Investigator reporting: notifying the medical monitor

N/A

8.3.2 Investigator reporting: notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems <u>within 10 working days from the time the investigator becomes aware of the event:</u>

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  <u>Unexpected</u> (An event is “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process
Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Other Reportable events:
For clinical drug trials, the following events are also reportable to the Penn IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

8.3.3 Sponsor Reporting: NIH

Investigators must report serious adverse events (SAE) attributed to study procedures to the NIH within the timelines described below.

• Relevant follow-up information such as resolution and duration of the SAE attributed to study procedures should be submitted as soon as it becomes available.
• Serious AE reports that are related to study procedures will be transmitted within fifteen (15) calendar days from the date investigators are made aware of the AE.

- Serious AE reports that are unrelated to study procedures will be transmitted within thirty (30) calendar days from the date investigators are made aware of the AE.
- All Non-serious Adverse Events originating from the study will be forwarded in a semi-annual report

8.3.4 Sponsor reporting: Notifying FDA

Medical Device Reporting (MDR): In accordance with FDA regulation (21 CFR 803), the sponsor will report to the FDA when they learn that any of their devices may have caused or contributed to a death or serious injury. Manufacturers must also report to the FDA when they become aware that their device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

8.4 Unblinding Procedures

N/A

8.5 Stopping Rules

The study will be terminated after completed follow up of the last patient enrolled (ie 1 year after this patient has TIPS created).

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting).

8.6.1 Auditing and Inspection

This protocol will be audited and inspected in accordance with DSMP submitted separately.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists,

pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (eCRF) is the primary data collection instrument for the study. eCRFs will be created in the RedCap system to capture the data that the investigator wishes to collect for the purposes of research and for safety monitoring. Data will be entered into this system in a timely manner. Forms used in the source document should reflect the information needed for the completion of the eCRFs in RedCap.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last follow up visit with the last enrolled patient.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The study PI is responsible for ensuring the ongoing quality and integrity of the research study. In addition, this study will be monitored or audited in accordance with Institutional Data and Safety Monitoring Plan. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

Certain studies, as identified by the ORA, will be monitored on an on-going basis by the DOCM. Each study will have an individualized monitoring plan developed by the DSMC and the study team. This plan must be approved by the DOCM Director. Once the ORA determines that a study needs prospective monitoring, the DSMC will work with the PI and study team to develop a monitoring plan that will cover

- All of the Regulatory documentation
- Informed Consents
- Eligibility criteria
- Treatment administration and accountability
- Adverse/Serious Adverse Events and toxicities
- Response assessment
- Subject follow-up
- Data completeness

• Source documentation to Case Report Form (CRF)
• Manufacturing (where applicable)

At the conclusion of the monitoring visit, the monitor will spend time with the PI and/or study team to discuss the findings and to provide guidance on resolving deficiencies. A formal letter will be sent to the PI within about five business days. The PI does not have to respond the monitoring letter unless specifically requested to do so by the monitor. Studies that are high risk protocols are audited approximately six months from their first subject accrual and approximately every six month thereafter for the duration of the study. However, this schedule may be changed at the discretion of the DSMC. High enrolling or quick enrolling studies will be audited more frequently as necessary. Investigators are notified in advance of the selection of their protocol for review and cases are randomly selected. Three subjects or 10% of the total accrual, whichever is higher, are audited. A formal report is provided to the PI within about five business days of the audit. The Committee may alter the frequency of re-monitoring based on the audit findings and degree of deficiencies. If an audit is unacceptable due to major deficiencies, representatives from the DOCM acting on behalf of the DSMC meet with the PI to discuss the findings of the audit and necessary corrective actions. If the deficiencies involve subject safety or serious regulatory violations, DSMC Chair, and DOCM Director will meet to discuss necessary actions concerning study status.

10.3 Study Exceptions and Deviations

In order to harmonize with the IRB, the DSMC has changed its designations from Deviations and Violations to Exceptions and Deviations

Exception

A one time, intentional action or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. If the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, advance documented IRB and DSMC approval is required.

For in-house studies with a Medical Monitor or Safety Monitoring Committee (not DSMB), approval must be obtained from the Medical Monitor or Safety Monitoring Committee prior to submitting your exception request to the DSMC.

Deviation

A one time, unintentional action or process that departs from the IRB and DSMC approved study protocol, involving one incident and identified retrospectively, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints) or compromises the safety and welfare of the subjects, the deviation must be reported to the DSMC within 5 business days and the IRB within 10 business days.

11 Ethical Considerations

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before

commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment B for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

NIH

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the applicable University conflict of interest policies.

12.3 Subject Stipends or Payments

None

13 Publication Plan

The Principal Investigator and Institution shall be free to publish and present the results and data from the Study.

14 References

15 Attachments

eCRF
Monitoring Plan
ICF

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