Advancing **L**iver **T**herapeutic **A**pproaches (ALTA). The **ALTA** Consortium Study Group in the use of TIPS for the management of Portal Hypertension

Short Name: ALTA TIPS

Version 1.2
Amendment 1
Amendment 2

Sponsor Name: W. L. Gore & Associates, Inc., Northwestern University

PROTOCOL SUMMARY

Study Title	**A**dvancing **L**iver **T**herapeutic **A**pproaches (ALTA). The **ALTA** Consortium Study Group in the use of TIPS for the management of Portal Hypertension
Amendment	Version 1.2
Sponsor	W. L. Gore & Associates, Inc., Northwestern University
Study Design	Multi-center, prospective registry of patient characteristics and clinical outcomes of patients undergoing Transjugular Intraheptic Portosystemic Shunt (TIPS) placement.
Study Objective	To assess contemporary patterns of use of TIPS stents and associated patient related outcomes. To utilize knowledge gained to serve as a foundation for future prospective randomized controlled trials.
Study Endpoint(s)	1. Patient survival / liver transplantation 2. TIPS related complications: stenosis/need for revision 3. Worsening or new onset hepatic encephalopathy 4. Recurrent portal hypertensive complications (e.g. ascites, variceal bleeding) 5. Cardiovascular outcomes (new onset heart failure) 6. Renal outcomes
Subject Population	All patients undergoing TIPS placement.
Number of Sites	Lead site: Northwestern University. Additional 11 tertiary academic sites throughout the U.S. (Columbia University, Scripps Clinic, Stanford University, Mayo Clinic Rochester, University of California San Francisco, University of Chicago, University of Florida, University of Wisconsin Madison, Weil Cornell, University of Texas Baylor-Dallas, University of Arizona-College of Medicine Phoenix Banner Health) Expected 1,000 patient cases over 3 years.
Expected Time to Complete Enrollment	Three years of enrollment and up to 5 years of clinical follow-up.
Schedule of Events	• Month 0: TIPS placement (medical history, baseline quality of life assessments) • Months 1, 3, 6, 12, 24, 36, 48, 60: Follow up assessments (survival, transplantation status, TIPS ultrasound, quality of life assessments, impact on cardiovascular/renal function)
Clinical Sites / Sub-PIs	Northwestern University – Dr. Lisa VanWagner University of California San Francisco – Dr. Jennifer Lai Scripps Health – Dr. Catherine Frenette University of Wisconsin Madison – Dr. Erin Spengler University of Florida – Dr. Giuseppe Morelli University of Arizona – Dr. Michael Fallon Stanford University – Dr. Aparna Goel Columbia University – Dr. Elizabeth Verna

	University of Chicago – Dr. Sonali Paul Mayo Clinic Rochester – Dr. Doug Simonetto Weill Cornell – Dr. Brett Fortune Baylor Scott & White Liver Consultants of Texas – Dr. Sumeet Asrani

Amendment 1 – Summary of Changes:
Removal of references to study “sponsor” and replaced with “lead site".

Amendment 2 – Summary of Changes:
Removal of the Hepatic Encephalopathy Staging Algorithm (HESA) and addition of the Clinical Hepatic Encephalopathy Staging Scale (CHESS).

LIST OF ABBREVIATIONS

TIPS – Transjugular Intrahepatic Portosystemic Shunt

HE – Hepatic Encephalopathy

eGFR - estimated glomerular filtration rate

MELD – Model for Endstage Liver Disease

MELD-Na – Model for Endstage Liver Disease incorporating serum sodium

1. Introduction

Portal hypertension is the primary physiologic complication in patients with cirrhosis or other forms of chronic liver disease. Advanced fibrosis or cirrhosis of the liver or chronic portal vein thrombosis can lead to elevated pressures in the portal venous system. This will manifest as abdominal ascites, hepatic hydrothorax, hepatorenal syndrome, portal hypertensive gastropathy and gastro-esophageal varices with or without bleeding. These complications are markers of decompensation and associated with significant morbidity and mortality. Approximately 50% of patients will die from liver related disease at 1 year after development of ascites. These complications often prompt referral for liver transplantation however many patients are not suitable candidate for liver transplant either due to advanced age, comorbidities such as recent malignancy or comorbid psychosocial issues such as ongoing alcohol use.

1.1. Historical Treatments:

Management of portal hypertensive complications has historically focused at controlling the specific complication. This has included diuretics for ascites or volume overload states and endoscopic band ligation of large or bleeding gastro-esophageal varices. Transjugular Intrahepatic Portosystemic Shunt (TIPS), an artificial shunt placed within the liver, is a method to control the complications of liver advanced liver disease by directly reducing the portal blood pressure. This has been demonstrated to be a critical tool in the management of ascites that is refractory to diuretic therapy or when gastro-esophageal variceal bleeding continues despite ongoing band ligation. TIPS has been shown to be highly effective at controlling these complications and has even demonstrated improved transplant free survival compared to standard medical management. Contemporary covered TIPS stents have also resulted in lower rates of stent occlusion and more recent controlled expansion stents have allowed operators to control the degree of portal pressure reduction at the time of placement. Complications have however been associated with TIPS placement. Patients with significant hepatic decompensation can develop worsening liver function resulting in rapid deterioration and death. Hepatic encephalopathy (HE) has been the major comorbidity associated with TIPS and has historically occurred at rates as high as 40-50%. Hepatic encephalopathy can have detrimental consequences on a patient's quality of life and in some cases requires constraint or complete occlusion of the TIPS. Despite these complications, the overall use of TIPS has increased, and the indications have expanded. For example, elective TIPS can be used in patients with portal hypertension to permit safe abdominal surgery. It has also been used in conjunction with portal vein thrombectomy in efforts to restore portal vein flow and permit liver transplantation. Data on the use of contemporary covered stents with controlled expansion has been limited however and patterns of use vary among centers.

1.2. Study Device Description:

All TIPS stents including VIATORR CX, regular VIATORR and bare metal stents placed during a TIPS procedure.

2. Study Objectives

2.1. Primary Objective(s)

The primary objective of the ALTA TIPS is to evaluate the current practice pattern of TIPS stents, the impact on patient outcomes and characterize the peri-procedural complications as well as the long-terms complications such as hepatic encephalopathy among all patients receiving a TIPS in a multi-center prospective registry.

2.2. Secondary Objective(s)

The secondary objectives of ALTA TIPS are:

- To assess patient overall survival and rates of liver transplantation
- To evaluate immediate TIPS related complications
- To quantify the rates of hepatic encephalopathy, characterize the severity and identify predictive risk factors
- To evaluate rates of recurrent portal hypertensive complications and need for revision of TIPS
- To evaluate the impact of TIPS on change in quality of life responses
- To assess the rates of cardiovascular outcomes after TIPS
- To assess the rates renal dysfunction or renal recovery after TIPS
- To assess differences in TIPS approaches on clinical outcomes in order to establish best practices for TIPS placement

3. Study Design

3.1. Study Design Schema

Month 0 – TIPS insertion and registry enrollment

Months 1, 3, 6, 12, 24 (minimal follow up)

Months 36, 48, 60 (maximal follow up)

3.2. Description of Study Design:

This study is a prospective, multicenter, non-randomized single-arm study to evaluate the clinical outcomes and complications of TIPS stent use for the treatment of portal hypertension in patients all patients receiving TIPS.

A maximum of 12 Clinical Sites (referred to as “Sites” in the remainder of this document) in the U.S. will participate in this study. Approximately 1000 patients will be enrolled in this study without a limit of number of subjects enrolled per Site. The anticipated accrual rate is approximately 33 subjects per month for a total accrual period of approximately 0 – 36 months and followed for at least 24 months after enrollment.

Patients may be enrolled into the study provided all inclusion and no exclusion criteria are met as specified in Section 4. Subjects will be evaluated at the time of TIPS placement and at routine standard of care follow-up visits at months 1, 3, 6, 12, 24 and up through months 36, 48, 60 if applicable. Total estimated duration of the study is 36 months of enrollment followed by 24 months of clinical follow up.

3.3. Study Endpoint(s)

3.3.1. Primary Endpoint(s)

Death or liver transplantation

Cause of death defined as:

- direct procedural complication of TIPS placement (as determined by site PI)
- death from decompensation of underlying liver disease exacerbated by TIPS (as determined by site PI)
- death from other cause unrelated to TIPS or underlying liver disease (as determined by site PI)
- liver transplant, expected (listed or anticipated listing prior to TIPS)
- liver transplant, unexpected (not previously listed or anticipated listing prior to TIPS)

3.3.2. Secondary Endpoint(s)

- Incidence and grade of hepatic encephalopathy 0-7 days after TIPS
- Incidence and grade of hepatic encephalopathy at all follow up visits
- Number of hospital admissions for hepatic encephalopathy
- Change in quality of life assessment after TIPS
- Number of paracentesis after TIPS
- Number of thoracentesis after TIPS
- Change in renal function as measured by serum creatinine and estimated glomerular filtration rate (eGFR)
- Change in platelet count after TIPS at follow up visits
- Change in traditional MELD and MELD-Na scores
- Change in protocol serial comprehensive echocardiogram parameters (e.g., markers of cardiac mechanics including myocardial strain, chamber size, left ventricular systolic function, diastolic function, right ventricular systolic pressure and right atrial pressure) at 0, 3, 6, 12 months
- Rate of TIPS revision requiring dilation of initial TIPS stent diameter
- Rate of TIPS revision to address stent occlusion
- Rate of TIPS constraint or complete occlusion

4. Study Population

4.1. Description of Population:

Patients who are over the age of 18 who undergo a TIPS for any reason are eligible for screening for participation in the study.

4.2. Inclusion Criteria:

The patient is / has:

1. Age ≥18 at the time of informed consent signature.
1. Capable of complying with Protocol requirements, including follow-up.
2. An Informed Consent Form signed by Subject or legal representative.

4.3. Exclusion Criteria

The patient is / has:

1. Prisoner
2. Pregnant female at the time of informed consent signature.
3. Undergoing TIPS placement as part of an investigational study outside usual clinical care

5. Study Procedures/Evaluations

5.1. Schedule of Events

	Screening/ TIPS (Month 0)	**Month 1 (Routine Clinical Visit)**	**Month 3 (Phone Call if no Visit)**	**Months 6, 12**	**Months 24, 36, 48, 60 (Routine Clinical Visits)[x]**
Informed Consent	X				
Demographics and Medical History	X				
Physical Exam	X	X	±	X	X
TIPS procedural assessment	X				
Update Medical History		X	X	X	X
Quality of Life Assessments*	X	X	X	X	X
Hepatic Encephalopathy Assessments*	X	X	±	X	X
Duplex Ultrasound	X	X		X	X
Standard of care comprehensive echocardiography[#]	X	X	X	X	
Outcome Assessment		X	X	X	X

*study-related interventions

[#]All echocardiogram images will be transferred to the coordinating center (Northwestern University) for future standardized analysis as part of the impact of TIPS on cardiac function ancillary study

[x]Visit to be marked as “not complete” if no visit occurred; a telephone call will be made by the study team to review questionnaires and confirm outcomes.

5.2. Informed Consent Process

All patients must provide informed consent prior to any study related procedures being performed. The case history (*i.e.*, source documents/Subject chart) for each Subject shall document that such informed consent was obtained. The site-specific IRB approved consent form will be signed and personally dated by the Subject and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the Subject records. A copy of the informed consent document will be given to the Subject for their records.

5.3. Pre-Screening / Screening

All patients being referred for TIPS will be screened for enrollment. Patients may be approached for before the scheduled TIPS procedure, at the time of TIPS or within 14 days after TIPS placement.

5.4. Enrollment

Patients will be considered enrolled after signing informed consent and provided inclusion/exclusion criteria at met. If consent is signed (either by the patient or surrogate) after the TIPS procedures (such as in the event of emergent TIPS) then the patient will be considered enrolled at the time of TIPS. Patients may not be enrolled however if 14 days have passed from time of TIPS before informed consent.

5.5. Procedure

There are no investigational procedures or interventions as part of this study.

5.6. Repeat Interventions

The treating physicians may decide a repeat TIPS or intervention is required as part of routine medical care. This is not considered investigational however this information will be captured are part of the registry.

5.7. Follow-Up:

Routine follow up visits with the treating physician are considered standard of care after TIPS placement.

Month 1 (Day 14-45 post-TIPS) – As per standard of care, the treating physician will see the patient within one month after TIPS placement, obtain routine laboratory assessments (complete blood counts, complete metabolic panel and INR/Prothrombin Time) as well as obtain a liver ultrasound with doppler assessment to evaluate patency of the TIPS stent and a transthoracic echocardiogram to assess cardiac function. As part of the study, patients will be asked to complete quality of life assessments and be assessed for hepatic encephalopathy with grading.

Month 3$\pm$1 month – A routine clinical visit may or may not occur depending on the treating physicians' preference. If it occurs, data similar to Month 1 will be collected as applicable. If no visit occurs, then the study coordinators will contact the patient by phone to complete quality of life assessments and schedule standard of care comprehensive echocardiography.

Months 6, 12, 24, 36, 48, 60 - A routine clinical visit may or may not occur depending on the treating physicians' preference. If it occurs, data similar to Month 1 will be collected as applicable. If no visit occurs, then the study coordinators will contact the patient by phone to complete quality of life assessments and schedule standard of care comprehensive echocardiography (Months 3, 6, 12)

If a subject undergoes repeat TIPS or further intervention to the porto-venous system, then this information will be captured in an ad-hoc procedure visit. Only details from the procedure note will be collected for study related purposes. The subject will continue following I the original study schedule based on the index TIPS date.

If a subject dies or receives a liver transplant, then the subject will be considered having met the primary endpoint and study participation will be complete.

5.8. Subject Withdrawal from the Study

A Subject may withdraw from the study at any time and should notify the Investigator in this event. The Investigator may also withdraw the Subject from the study at any time based on his / her medical judgment.

5.9. Subject Lost to Follow-Up

A Subject will be considered lost to follow-up and withdrawn from the study once they have missed two consecutive follow-up visits and three documented attempts have been made by the Investigator or designee to contact the Subject and emergency contact by phone.

5.10. Subject Study Completion

A Subject has completed the study when the primary endpoint of death or liver transplantation occurs, the subject completes Month 60 visit or if the study period of 5 years with a minimum of 2 years of post-TIPS follow up. Any Subject that does not complete these requirements due to voluntary withdrawal, physician withdrawal, or any other reason will be considered a withdrawal.

6. Study Administration

6.1. Monitoring

Onsite site monitoring for this study will not be provided. Uploaded registry data will be reviewed centrally by the coordinating center (Northwestern University) and issues with data validation will be sent to individual sites to address any missing or aberrant data.

6.2. Protocol Deviations

A Protocol deviation is defined as any change, divergence, or departure from the study design or procedures of a research protocol. The Investigator is responsible for promptly recording and reporting Protocol Deviations to the lead site and the reviewing IRB per IRB policy. The lead site will determine the effect of the protocol deviation on the scientific soundness of the study and Subject safety and determine if additional reports or actions are required. Additional action may include Site retraining or Site termination.

The Investigator will not implement any changes to the protocol without first obtaining written agreement documented approval from the IRB sites, except in the event of an immediate hazard(s) to a Subject. The Investigator will report the Protocol Deviation in accordance with the applicable regulations.

6.3. Protocol Amendments

The Investigator will obtain IRB approval on all amendments in a timely manner.

6.4. Access to Source Data/Documents

Source data are defined as all information necessary for the reconstruction and evaluation of the Clinical Investigation.

The Investigator will keep all study records, source data available for inspection by the IRB and regulatory authorities.

6.5. Study Records Retention

The Investigator will maintain complete, accurate and current study records as required by applicable regulatory requirements. Electronic records will be maintained during the study and for a minimum of 10 years after completion of the study.

6.6. Publication Plan

It is the intent of the lead site that the multicenter results of this study will be submitted for publication (in a peer reviewed journal). A publications and presentations committee will be established to review the multicenter results, develop and review all publications and presentations at the completion of the study.

7. Data Collection and Submission

The electronic data capture system (EDC system) for this study will be a REDCap database hosted and maintained by Northwestern University.

7.1. Data Collection Methods

Data will be abstracted from the subjects' medical records and uploaded directly to REDCap. Questionnaire and hepatic encephalopathy assessments will be collected on paper case report forms stored in the subjects' paper chart and uploaded to REDCap.

7.2. Data Clarification and Correction

Data verification and queries will be processed every 14 days. Sites will have 14 days to respond to queries.

7.3. CRF Completion Schedule

Sites will be expected to upload data within 14 days of completion of the clinical visit.

8. Risk Assessment

The Risk Assessment section must be consistent with the Risk-Benefit Analysis section of the Clinical Evaluation Plan, the Instructions for Use (see Hazards and Adverse Events section in IFU) and align with the Informed Consent Form.

Describe possible interactions with concomitant medical treatments, any prohibited and restricted therapies during the study, or, any precautions which should be taken during the study for any therapies, if applicable.

There are no anticipated Adverse Events with participation in this registry study. There are no drug or device interventions that are investigational. The TIPS procedure has been associated with complications that include bleeding, infection, heart failure, hepatic encephalopathy and/or death. All data collected will be abstracted from the subjects' routine medical chart with additional phone call assessments for vital status and hospitalization outcomes.

9. Adverse Events and Safety Monitoring

9.1. Anticipated Adverse Events

Anticipated Adverse Events are complications that are known to be associated with patients undergoing TIPS. See Section 8, Risk Assessment. No assessment of Adverse Events will be performed as this is an observational registry study.

9.1.1. Subject Death

Subject death is considered a primary endpoint in this study.

10. Statistical Analysis

10.1. Study Hypotheses

This prospective, registry study will characterize the current patient population receiving TIPS, the primary and secondary indications, the role of TIPS either as a bridge to transplant or as definitive therapy, procedural complication rates, rates of hepatic encephalopathy after TIPS, and the degree of change of quality of life survey responses.

10.2. Sample Size Assumptions

Based on prior retrospective data, a sample size of approximately 1000 patients will be required in order to draw meaningful conclusions regarding different indications for TIPS.

10.3. Sample Size Determination

A sample size of 1000 patients will provide an acceptable range of indications for TIPS (approximately 400 for refractory ascites, 300 for variceal bleeding, 100 for both ascites and variceal bleeding 50 for hepatic hydrothorax, 50 for treatment of portal vein thrombosis and 100 for treatment of portal hypertension management prior to elective invasive procedure such as abdominal surgery.

10.4. Data Analysis

10.4.1. Timing of Analyses

No a priori interim analysis will be planned as this is a registry study, however, ongoing data analysis will be performed for quality control and for generating preliminary data for abstract submissions and future grant proposals.

10.4.2. Analysis Populations

The data set will be analyzed based on etiology for liver disease, primary/secondary indications for TIPS, MELD sore before TIPS, intentions for liver transplant (listed/evaluated before TIPS vs not formally listed/evaluated for transplant).

10.4.3. Statistical Analysis of Primary/Secondary Endpoint(s)

Analyses of the registry cohort will involve estimation of primary/secondary outcome incidence event rates. These event rates will be calculated for all subjects as well as stratified among the indications for TIPS, MELD sore before TIPS, intentions for liver transplant (listed/evaluated before TIPS vs not formally listed/evaluated for transplant).

Risk factors for primary and secondary endpoints will be assessed. These risk factors will include medical history (including severity and etiology of underlying liver disease), laboratory results, technical factors associated with the TIPS procedure. The longitudinal analyses will utilize established methods of statistical models for longitudinal interval-scale responses, longitudinal categorical responses, and survivorship.

Relative risk estimates will be calculated for the entire cohort as well as subgroups outlined above.

11. Ethical and Regulatory Considerations

11.1. Statement of Compliance

The study will be conducted in compliance with this protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), ISO 14155:2011 and in accordance with Good Clinical Practice (GCP) requirements described in the current revision of ICH Guidelines and all applicable regulations, including current United States Code of Federal Regulations (CFR), Title 21, Parts 50, 54, 56, and 312 and Title 45, Part 164. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. This study will also be carried out in accordance with local legal requirements.

11.2. Compliance Responsibilities

The Investigator will conduct the study in accordance with all applicable regulations and laws, any relevant agreements, the study protocol, and all approval conditions of the reviewing IRB. The Investigator will verify IRB approval is obtained prior to enrollment, maintained throughout the course of the study, and that all IRB reporting requirements are met. The Investigator is responsible for protecting the rights, safety, and welfare of Subjects under the Investigator's care and for the control of devices under investigation. The Investigator is also responsible for ensuring that informed consent is properly obtained.

The study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

11.3. Informed Consent

The Investigator shall verify that all potential Subjects for this study are provided with a consent form describing this study and sufficient information to make an informed decision about their participation.

The formal consent of a Subject, using the IRB approved consent form, must be obtained by the Investigator before that Subject undergoes any study-related procedure. The consent form will be signed and personally dated by the Subject and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the Subject records. A copy of the informed consent document will be given to the Subject for his or her records. Any significant, new information which emerges while the study is in progress that may influence a Subject's willingness to continue to take part in the study will be provided to the Subject.

The Investigator shall verify that documentation of the acquisition of informed consent is recorded in each Subject's records in accordance with applicable regulations.

11.4. Independent Ethical Review

The Investigator shall not enroll any Subjects prior to obtaining approval for the study from a properly constituted independent IRB.

The Investigator will submit the protocol, informed consent forms, other information to be provided to Subjects such as survey instruments or questionnaires, and any proposed advertising / recruitment materials, to the IRB for written approval.

11.5. Conflict of Interest

All Investigators will follow applicable laws and regulations as well as the conflict of interest policies of their Site and the reviewing IRB.

11.6. Confidentiality

All Subject records will be kept confidential to the extent provided by applicable laws and regulations. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to medical records.

Such records may also be reviewed by the Site's IRB as applicable.

The Investigator will inform the Subjects that their records will be reviewed.

11.7. Study Discontinuation or Suspension

There are no anticipated study related events that would result in study discontinuation or suspension given this is a registry study. In the event the study sponsor withdrawals funding, then all new subject enrollment and subject follow up will cease.

12. References

1. Ascha, M., Hanouneh, M., Ascha, M. S., Zein, N. N., Sands, M., Lopez, R., & Hanouneh, I. A. (2016). Transjugular Intrahepatic Porto-Systemic Shunt in Patients with Liver Cirrhosis and Model for End-Stage Liver Disease ≥15. *Digestive Diseases and Sciences*, 1–9. http://doi.org/10.1007/s10620-016-4185-3
2. Lerrigo, R., Beste, L. A., Leipertz, S. L., Green, P. K., Lok, A. S. F., Kogut, M. J., & Ioannou, G. N. (2016). Characteristics and outcomes of transjugular intrahepatic portosystemic shunt recipients in the VA Healthcare System. *European Journal of Gastroenterology & Hepatology*, 28(6), 667–675. http://doi.org/10.1097/MEG.0000000000000604
3. Boike, J., Ge, J., German, M., Jest, N., Morelli, G., Spengler, E., ... & Lai, J. (2018). Contemporary practice patterns and outcomes after transjugular intrahepatic portosystemic shunt placement: A multicenter US experience of 1146 patients. *Journal of Hepatology*, *68*, S78.
4. Casadaban LC, Parvinian A, Minocha J, et al. Clearing the confusion over hepatic encephalopathy after TIPS creation: incidence, prog- nostic factors, and clinical outcomes. Dig Dis Sci 2015;60(04): 1059–1066
5. Srinivasa RN, Srinivasa RN, Chick JFB, Hage A, Saad WA. Transju- gular intrahepatic portosystemic shunt reduction using the GORE VIATORR controlled expansion endoprosthesis: hemodynamics of reducing an established 10-mm TIPS to 8-mm in diameter. Cardiovasc Intervent Radiol 2018;41(03):518-521
6. RiChard, J., & Thornburg, B. New Techniques and Devices in Transjugular Intrahepatic Portosystemic Shunt Placement. *Seminars in interventional radiology* 2018;35(03):206-214.

13. Study-Specific Appendices

Appendix 1. Schedule of Events

	Screening/ Enrollment (-2 Months)[1]	TIPS (Month 0)	Month 1 (Routine Clinical Visit)	Month 3 (Phone Call if no Visit)	Months 6, 12	Months 24, 36, 48, 60 (Routine Clinical Visits)
Informed Consent	X					
Demographics and Medical History	X					
Update Medical History	X	±	X	X	X	X
Physical Exam	X		X	±	X	X
TIPS procedural assessment		X				
Blood Tests[2]	X	X	X	X	X	X
Global Health Questionnaire - PROMIS® Scale v1.2 – Global Health	X	X[1]	X	X	X	X
PROMIS Item Bank v1.0 – Fatigue – Short Form 8a	X	X[1]	X	X	X	X
Short Form 36 – Version 2	X	X[1]	X	X	X	X
Chronic Liver Disease Questionnaire	X	X[1]	X	X	X	X
Hepatic Encephalopathy Staging Tool	X	X[1]	X		X	X
Clinical Hepatic Encephalopathy Staging Scale	X	X[1]	X		X	X
Liver Duplex Ultrasound	X[3]		X		X	X
Comprehensive echocardiogram	X		X	X	X	
Outcome assessment			X	X	X	X

1. Screening and enrollment visit may occur up to 2 months prior to the TIPS procedure. This visit can also include quality of life and hepatic encephalopathy assessments. These assessments should be repeated at the time of TIPS if there is a significant change in medical history such as a hospitalization for any reason or an unplanned visit to a healthcare professional (office visit, urgent care, etc.).

2. Standard of care blood work should ideally include complete blood counts, complete metabolic profile (including hepatic panel) and coagulation panel (prothrombin time and INR).
3. Liver duplex ultrasound should include the most recent ultrasound available – standard practice would suggest within 6 months of TIPS.
4. Standard of care serial echocardiography will be assessed for change in cardiac function over time. All images will be transmitted to the coordinating center (Northwestern University) for central review as part of an ancillary study on cardiac function after TIPS.

Appendix 2. PROMIS® Scale v1.2 – Global Health

PROMIS® Scale v1.2 – Global Health

Global Health

Please respond to each question or statement by marking one box per row.

		Excellent	Very good	Good	Fair	Poor
Global01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	In general, would you say your quality of life is:.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global05	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global09r	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A little**	**Not at all**
Global06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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PROMIS® Scale v1.2 – Global Health

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Global10r	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		None	**Mild**	**Moderate**	**Severe**	**Very severe**
Global08r	How would you rate your fatigue on average?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Global07r	How would you rate your pain on average?	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst pain imaginable**

Appendix 3. PROMIS Item Bank v1.0 – Fatigue – Short Form 8a

HI7		☐	☐	☐	☐	☐
AN3	_____	☐	☐	☐	☐	☐
FATEXP41		☐	☐	☐	☐	☐
FATEXP40		☐	☐	☐	☐	☐
FATEXP35		☐	☐	☐	☐	☐
FATIMP49		☐	☐	☐	☐	☐
FATIMP3		☐	☐	☐	☐	☐
FATIMP16		☐	☐	☐	☐	☐

Appendix 4. Short Form 36 – Version 2

Medical Outcomes Study Questionnaire Short Form 36 Health Survey

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey! For each of the following questions, please circle the number that best describes your answer.

1. In general, would you say your health is:	
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5
2. Compared to one year ago,	
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?
(Circle One Number on Each Line)

	Yes, Limited a Lot (1)	**Yes, Limited a Little (2)**	**No, Not limited at All (3)**
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3

g. Walking **more than a mile**	1	2	3
h. Walking **several blocks**	1	2	3
i. Walking **one block**	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?
(Circle One Number on Each Line)

	Yes (1)	**No (2)**
a. Cut down the amount of time you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the **kind** of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?
(Circle One Number on Each Line)

	Yes	**No**
a. Cut down the amount of time you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	
Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

7. How much bodily pain have you had during the past 4 weeks?	
None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6
8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	
Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. **(Circle One Number on Each Line)**

9. How much of the time during the **past 4 weeks** . . .

	All of the Time	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? (Circle One Number)	
All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

11. How TRUE or FALSE is each of the following statements for you. (Circle One Number on Each Line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

Appendix 5. Chronic Liver Disease Questionnaire

THE CHRONIC LIVER DISEASE QUESTIONNAIRE (CLDQ)—QUALITY OF LIFE INDEX FOR PATIENTS WITH CHRONIC LIVER DISEASE

This questionnaire is designed to find out how you have been feeling during the last two weeks. You will be asked about your symptoms related to your liver disease, how you have been affected in doing activities, and how your mood has been. Please complete all of the questions and select only one response for each question.

QUESTIONS

	All of the time	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**Hardly any of the time**	**None of the time**
1. How much of the time during the last two weeks have you been troubled by a feeling of abdominal bloating?							
2. How much of the time have you been tired or fatigued during the last two weeks?							
3. How much of the time during the last two weeks have you experienced bodily pain?							
4. How often during the last two weeks have you felt sleepy during the day?							
5. How much of the time during the last two weeks have you experienced abdominal pain?							
6. How much of the time during the last two weeks has shortness of breath been a problem for you in your daily activities?							
7. How much of the time during the last two weeks have you not been able to eat as much as you would like?							
8. How much of the time in the last two weeks have you been bothered by having decreased strength?							
9. How often during the last two weeks have you had trouble lifting or carrying heavy objects?							
10. How often during the last two weeks have you felt anxious?							

11. How often during the last two weeks have you felt a decreased level of energy?							
12. How much of the time during the last two weeks have you felt unhappy?							
13. How often during the last two weeks have you felt drowsy?							
14. How much of the time during the last two weeks have you been bothered by a limitation of your diet?							
15. How often during the last two weeks have you been irritable?							
16. How much of the time during the last two weeks have you had difficulty sleeping at night?							
17. How much of the time during the last two weeks have you been troubled by a feeling of abdominal discomfort?							
18. How much of the time during the last two weeks have you been worried about the impact your liver disease has on your family?							
19. How much of the time during the last two weeks have you had mood swings?							
20. How much of the time during the last two weeks have you been unable to fall asleep at night?							
21. How often during the last two weeks have you had muscle cramps?							
22. How much of the time during the last two weeks have you been worried that your symptoms will develop into major problems?							
23. How much of the time during the last two weeks have you had a dry mouth?							
24. How much of the time during the last two weeks have you felt depressed?							
25. How much of the time during the last two weeks have you been worried about your condition getting worse?							

26. How much of the time during the last two weeks have you had problems concentrating?							
27. How much of the time have you been troubled by itching during the last two weeks?							
28. How much of the time during the last two weeks have you been worried about never feeling any better?							
29. How much of the time during the last two weeks have you been concerned about the availability of a liver if you need a liver transplant?							

Appendix 6. Hepatic Encephalopathy Staging Tool

Hepatic Encephalopathy Staging Tool

Patients are to be staged for HE according to the criteria outlined below.

Stage 0/1	**Patient to be considered Stage 0/1 if any of the following apply:** • No Disorientation (i.e., correct answers to all questions below) • Mild Disorientation (i.e., correct answers for questions 1 and 2, however patient may answer one question incorrectly for questions 3–7) 1. What is your name? *(must be answered correctly to be considered Stage 0/1)* 2. What year were you born? *(must be answered correctly to be considered Stage 0/1)* 3. What city or town do you live in? 4. What type of place is this? 5. What is the year? 6. Who is the current president (or country-specific leader)? 7. What is the month? • **Note:** Patients who respond incorrectly to question 1 (name) and/or question 2 (year of birth) should be rated as Stage 2
Stage 2	**Patient to be considered Stage 2 if the following applies:** • Disorientation (i.e., incorrect answer to EITHER questions 1 or 2 OR two or more incorrect answers for questions 3–7) 1. What is your name? 2. What year were you born? 3. What city or town do you live in? 4. What type of place is this? 5. What is the year? 6. Who is the current president (or country-specific leader)? 7. What is the month? • **Note:** Patients who are sleepy, but easily arousable and responsive to questions should be rated as HEST Stage 2
Stage 3	**Patient to be considered Stage 3 if any of the following apply:** • **Severe drowsiness** (can be aroused by moderate stimuli but then almost immediately drifts back to sleep) • **Stupor** (unresponsiveness from which the patient can be aroused only by vigorous and repeated stimuli; incomprehensible speech) • **Obvious confusion/gross disorientation** (inattention to questions; inappropriate response to commands or questions; bewilderment)
Stage 4	**Patient to be considered Stage 4 if coma is present.** • A coma is defined as a state of unarousable unresponsiveness.

Hepatic Encephalopathy Staging Tool

The Hepatic Encephalopathy Staging Tool (HEST) is being developed for use in clinical trials and research where it is important that the stage of HE be accurately and consistently determined among investigators and researchers. The HEST is to be used as an aid to study investigators and researchers in determining the stage of HE.

This instruction manual details how to administer and interpret the HEST. Please read this document carefully before beginning your patient evaluation. Importantly, it is useful to have the HEST printed out and with you when you begin your patient assessment. The HEST is based on patient orientation status.

Similar to the West Haven criteria, the HEST places patients in the following stages of HE (Stage 0/1, 2, 3 and 4). Stages 0/1 and 2 are determined by the patient's level of orientation to person, place, time and current events. Patient orientation is assessed by a series of seven questions. If the patient answers at least two of the seven questions incorrectly, they will be classified as having Stage 2 HE. As orientation to person or self is most critical to a patient's cognitive status and level of awareness, if a patient answers incorrectly to either (or both) of the person-orientation questions (What is your name? What year were you born?), the patient should be classified as Stage 2.

Please review the tool below.

Appendix 7. Clinical Hepatic Encephalopathy Staging Scale

Clinical Hepatic Encephalopathy Staging Scale (CHESS)

In order to assess clinical severity of hepatic encephalopathy, Ortiz et al. (Aliment Pharmacol Ther. 2007) developed a scale initially composed of 48 items easy to categorize. Their analysis leads to the establishment of a Clinical Hepatic Encephalopathy Staging Scale of nine items (CHESS), ranged from normality (Hepatic Encephalopathy Clinical Staging Scale = 0) to deep coma (Clinical Hepatic Encephalopathy Staging Scale = 9).

The total score is the sum of the answers to the 9 items. Minimal score= 0. Maximal score= 9. For indication, CHESS score of 3 correlates with a grade 2 in West Haven criteria.

Patient Name: _____ **Date:** _____

			SCORE	
			0	1
1	Does the patient know which month he/she is in (i.e.: January, February)?	Yes	☐	
		No or he/she does not talk		☐
2	Does the patient know which day of the week he/she is in (i.e.: Thursday, Friday...)?	Yes	☐	
		No or he/she does not talk		☐
3	Can he/she count backwards from 10 to 1 without making mistakes or stopping? (the patient is asked between item 2 and 3 to count forward from 1 to 10 and is helped if necessary)	Yes	☐	
		No or he/she does not talk		☐
4	If asked to do so, does he/she raise his/her arms?	Yes	☐	
		No		☐
5	Does he/she understand what you are saying to him/her? (based on the answers to questions 1 to 4)	Yes	☐	
		No or he/she does not talk		☐
6	Is the patient awake and alert?	Yes	☐	
		No, he/she is sleepy or fast asleep		☐
7	Is the patient fast asleep, and is it difficult to wake him/her up?	Yes	☐	
		No		☐
8	Can he/she talk?	Yes	☐	
		He/she does not talk		☐
9	Can he/she talk correctly? In other words, can you understand everything he/she says, and he/she doesn't stammer?	Yes	☐	
		No, he/she does not talk or does not talk correctly		☐
		TOTAL		