PLIEGO DE PRESCRIPCIONES TÉCNICAS

QUE HA DE REGIR EL CONTRATO DE SERVICIOS DE "CONTRACT RESEARCH ORGANISATION" (CRO), A LA FUNDACIÓN PARA LA INVESTIGACIÓN BIOMÉDICA DEL HOSPITAL UNIVERSITARIO RAMÓN Y CAJAL (FIBIO-HRC), PARA EL DESARROLLO DEL PROYECTO "ENSAYO CLÍNICO PROSPECTIVO, ALEATORIZADO Y MULTICÉNTRICO PARA EVALUAR LA EFICACIA DEL TIPS FRENTE AL TRATAMIENTO ESTÁNDAR EN PACIENTES DE ALTO RIESGO TRAS UN EPISODIO AGUDO DE HEMORRAGIA VARICOSA", MEDIANTE PROCEDIMIENTO ABIERTO CON PLURALIDAD DE CRITERIOS.

EXPEDIENTE: PA1-26-CRO

I. OBJETO Y FINALIDAD DEL CONTRATO

El presente Pliego de Prescripciones Técnicas (PPT) tiene por objeto definir los trabajos de CRO (Contract Research Organization) a contratar por la Fundación para la Investigación Biomédica del Hospital Universitario Ramón y Cajal, para la puesta en marcha, desarrollo, seguimiento y cierre del estudio asegurando:

- La calidad metodológica y documental del proyecto
- El cumplimiento de los requisitos regulatorios y éticos aplicables
- La homogeneidad operativa entre los centros participantes
- La correcta captura, custodia y explotación de los datos del estudio
- La adecuada coordinación y seguimiento del proyecto durante toda su duración

El contrato se celebra para la realización del proyecto de investigación con número de expediente: PI24/01769, financiado por el Instituto de Salud Carlos III y cofinanciado por la Unión Europea.

Titulo del proyecto: ensayo clínico prospectivo, aleatorizado y multicéntrico para evaluar la eficacia del tips frente al tratamiento estándar en pacientes de alto riesgo tras un episodio agudo de hemorragia varicosa *(prospective, randomized, multicenter clinical trial to evaluate the efficacy of tips versus standard of care in high-risk patients after acute variceal bleeding)*

Objeto del proyecto: se ha diseñado un estudio pragmático, de fácil realización e integrado en la práctica clínica diaria, en el que proponemos aleatorizar a los pacientes con ascitis que presentan una segunda descompensación en forma de hemorragia varicosa, cuyo riesgo de muerte es muy alto con el tratamiento convencional, a recibir dicho tratamiento o TIPS. Nuestra previsión es que los pacientes tratados con TIPS van a tener mayor supervivencia, menos complicaciones de la cirrosis y mejor calidad de vida. Además, los pacientes tratados con TIPS tendrían menos necesidad de trasplante hepático, menos hospitalizaciones y visitas a urgencias y menor número de días de baja laboral, entre otros.

II. SERVICIOS A CONTRATAR.

El servicio a contratar es el de puesta en marcha y la gestión CRO del ensayo clínico asociado al proyecto público con código PI24/01769, realizando todas sus actividades según la legislación vigente sobre EECC en la Unión Europea.

El contratista, aportando a su riesgo y ventura los medios que resulten necesarios, actuará como soporte en la ejecución del estudio para el equipo investigador, realizando las tareas técnicas necesarias y las regulatorias que le sean delegadas por la Fundación contratante, según la mencionada legislación y las normas de buena práctica clínica e investigadora.

Las actividades a realizar por el contratista, a título enunciativo y no limitativo, son:

1. Redacción del protocolo del estudio y de su documentación asociada, incluyendo justificación, objetivos, metodología, aspectos éticos, plan de análisis estadístico, hoja de información al paciente y consentimiento informado.
2. Diseño, configuración, implantación y puesta en funcionamiento del Cuaderno de Recogida de Datos electrónico (CRDe), incluyendo la definición de contenidos y variables, la elaboración del CRD anotado, la creación y configuración de la plataforma, su revisión funcional, pruebas, validación y control de calidad, el registro y gestión de accesos de usuarios, la formación del equipo investigador y la exportación de datos para su análisis estadístico.
3. Preparación y envío de la documentación al CEIm de referencia, seguimiento de su tramitación y gestión de una enmienda, en caso de resultar necesaria.
4. Gestión de las aprobaciones con los 17 centros participantes, incluyendo cumplimentación de acuerdos, negociación, seguimiento documental y circuito de firmas.
5. Seguimiento trimestral del proyecto mediante newsletters, teleconferencias con la persona coordinadora e informes periódicos de avance.
6. Gestión de las tasas contractuales de los 17 centros participantes, excluidos los costes derivados de posibles adendas.
7. Gestión administrativa asociada a los pagos vinculados al estudio, incluyendo alta de proveedor, contabilización, tramitación, gestión fiscal, incidencias de facturación y certificados, cuando proceda.
8. Servicio de hosting, soporte técnico y mantenimiento del CRDe, con resolución de incidencias durante la vigencia del contrato.
9. Organización y realización de la reunión de inicio del estudio, con revisión del protocolo, herramienta de recogida de datos, farmacovigilancia, logística y dudas iniciales.
10. Monitorización telefónica de la recogida de datos, con al menos una llamada semestral por centro durante la vigencia del contrato, para seguimiento del estudio y resolución de incidencias y dudas.
11. Realización de la llamada o reunión de cierre del estudio, con monitorización final, cierre operativo y resolución de incidencias pendientes.

III. PROTECCIÓN DE DATOS PERSONALES EN LA EJECUCIÓN DEL CONTRATO.

El adjudicatario, en la medida en que acceda y trate datos de carácter personal de los sujetos participantes en el Proyecto queda obligado a la más estricta observancia de lo establecido en el artículo 6.1.b) del Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos y por el que se deroga la Directiva 95/46/CE (RGPD).

El adjudicatario es, asimismo, responsable de garantizar la más estricta observancia de lo establecido en la normativa citada por el personal por él contratado para la realización del objeto del contrato, debiendo gestionar las autorizaciones de acceso a la documentación clínica,

que resultaran pertinentes, de los pacientes incluidos en los ensayos con cada uno de los centros bajo la supervisión del/la investigador/a responsable y a los solos efectos de comprobar los datos aportados por éste en lo referente al cumplimiento del protocolo, garantizar que los datos son registrados de forma correcta y completa, así como asegurarse de que se hayan obtenido el consentimiento informado de todos los pacientes antes de su inclusión en el ensayo.

El adjudicatario tendrá la consideración de encargado de tratamiento en relación con los centros de realización de los ensayos clínicos y únicamente tratará los datos conforme a las instrucciones del responsable del tratamiento, que no los aplicará o utilizará con fin distinto al que figura en este contrato, ni los comunicará, ni siquiera para su conservación, a otras personas, debiendo aplicar medidas de seguridad de nivel alto.

ANEXO: memoria de ejecución del proyecto de investigación PI24/01769

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Madrid a la fecha de la firma

La Directora

44908140L LAURA BARREALES (R: G83726984)

Firmado digitalmente por 44908140L LAURA BARREALES (R: G83726984)
Fecha: 2026.05.21 11:48:53 +02'00'

Laura Barreales Tolosa

MEMORIA DE EJECUCIÓN DEL PROYECTO DE INVESTIGACIÓN PI 24/01769

Expediente Nº PI24/01769

INVESTIGADOR/A PRINCIPAL: LUIS TÉLLEZ VILLAJOS

MEMORIA DE SOLICITUD PROYECTO DE I+D+I EN SALUD
SECCIÓN ANTECEDENTES Y ESTADO ACTUAL DEL TEMA

Finalidad del proyecto, antecedentes y estado actual de los conocimientos científico-técnicos, grupos nacionales o internacionales que trabajan en la línea específica del proyecto o en líneas afines. Indicar si el proyecto forma parte de una línea de investigación estable y si es así desde cuándo. Indicar si existen resultados preliminares en el ámbito de la propuesta y proyectos relacionados. Citar las referencias en el apartado siguiente: Bibliografía más relevante y actualizada **(Max. 3 páginas. 15700 caracteres)**

Acute variceal bleeding (AVB) is a common cause of decompensation in cirrhosis, only preceded in frequency by ascites (D'Amico et al, 2006). In the absence of treatment, AVB carries risks of rebleeding and death as high as 60% and 30%, respectively, at 1 year (Bosch J et al, 2003). The current standard of care (SOC) far rebleeding prevention combines non-selective beta-blockers (NSBBs), specifically carvedilol or propranolol, with endoscopic band ligation (EVL) (García-Tsao G et al, 2017; EASL CPG 2018; De Franchis Retal, 2022), reducing rebleeding and death risks to 21% and 23% at 2 years, respectively (Puente A et al, 2014; Albillos A et al, 2017). In contrast to endoscopic therapy that only acts on rebleeding risk, NSBBs reduce portal pressure and, by this mean, decrease rebleeding as well as other complications of portal hypertension, such as ascites. Indeed, responders, those achieving significant portal pressure reduction, exhibit better outcomes, emphasizing the pivotal role of portal hypertension in cirrhosis (Turco L et al, 2020). The efficacy of the combination of EVL plus NSBB is heterogeneous, depending on factors such as the stage of cirrhosis and the portal pressure response to NSBBs, with rebleeding and death ranging, respectively, from 17 to 40% and from 22 to 79% (D'Amico G et al, 2014; Turco Letal, 2020; La Mura V et al, 2020). Transjugular intrahepatic portosystemic shunt (TIPS) is reserved far patients that fail first-line therapy to prevent rebleeding. In this setting, covered stents effectively reduce rebleeding from 29% in the SOC group to 0% at about 2 years' follow-up (Holster IL et al, 2016). The greater efficacy of TIPS to prevent rebleeding is closely related to its greater portal pressure-lowering effect with rebleeding risk markedly reduced by reaching an absolute porto-systemic gradient lower than 12 mmHg (Boike JR et al, 2022).

Risk stratification after AVB could be refined using clinical and hemodynamic information to allow far treatment individualization. Villanueva et al. showed that a strategy of preventing variceal rebleeding based on the hepatic venous pressure gradient (HVPG) response to therapy reduced rebleeding at 2 years from 31% to 19% compared with standard treatment (Villanueva C et al, 2017). In a more recent series of 193 patients with AVB, La Mura et al. reported that patients with variceal bleeding associated with ascites or hepatic encephalopathy, baseline HVPG >16 mmHg, and non-response to NSBB had risks of bleeding and death as high as 40% and 70%, respectively, at 4 years (La Mura V et al, 2020). The same figures were of 17% and 44% in the low-risk group composed of patients not fulfilling one of these criteria. Risk stratification in this study required HVPG measurement, a technique not available in most centers, which limits the applicability of the findings. Importantly, in this study presence of ascites or encephalopathy at the time of variceal bleeding, i.e., bleeding as further decompensation, identified patients with risks of bleeding and death of 21% and 52% at 4 years, respectively.

A further step in the prevention of rebleeding is to consider it in the context of other complications of cirrhosis. The stage of disease largely influences prognosis in cirrhosis, with a dramatic decrease when acute decompensation develops (D'Amico G et al, 2006 and 2014). Within the decompensated stage, the prognosis is different if the first decompensation is due to variceal bleeding or ascites and, more importantly, if variceal bleeding occurs alone or in a patient with ascites ("further decompensation"). The 2-year mortality of patients with variceal bleeding as the first decompensating event is 25% but rises to 35% when bleeding occurs in a patient previously decompensated, most often because of ascites (D'Amico G et al, 2023). Consistent with this result, another recent series has reported a mortality of 30% and 56% at 18 months and 3 years, respectively, in patients in whom AVB occurs after ascites (García-Guix Metal, 2023). Similarly, a recent meta-analysis has shown that after AVB, patients at higher risk of death are those who were decompensated, mainly because of ascites, with creatinine >1.8 mg/L and sodium <131 mEq/ at the time of hemorrhage. This means that the risk of death after an AVB episode is more associated to the presence of ascites and circulatory dysfunction, than on the recurrence of rebleeding. In other words, the presence of decompensation, such as ascites, identifies a subset of patients with decompensated cirrhosis at high risk of death after bleeding in whom the goal of any intervention should be improve survival rather than to prevent rebleeding.

Despite the poor long-term survival of patients with ascites at the time of AVB, current guidelines recommend a

combination of EVL and NSBBs to all patients after an episode of variceal bleeding, regardless the presence of ascites. This recommendation is based on the fact that the prevention of recurrent rebleeding is the primary endpoint of trials supporting available evidence (García-Tsao G et al, EASL CPG 2018, De Franchis et al, 2022). An alternative strategy would be to anticípate second-line therapy, i.e., TIPS, in this patient population instead of using itas rescue therapy after the failure of standard treatment. Accordingly, it can be hypothesized that the pronounced portal-pressure lowering effect of TIPS corrects the circulatory dysfunction and could modify the natural course of decompensated cirrhosis. The strategy of anticipating TIPS decisions in patients at high risk of failure to standard treatment has improved survival in other settings such as AVB and difficult-to-treat-ascites, where TIPS is increasingly acknowledged as a disease-modifying "upstream" therapy (Garcia-Pagán JC et al 2010; Nicoara-Farcau O et al, 2021; Bureau C et al, 2017). Specifically, advancing TIPS decision in patients with recurrent ascites increased survival from 52% to 93% at 1 year compared to standard treatment with large volume paracenteses and albumin, and reduced portal hypertensive-related bleeding without increasing risk of hepatic encephalopathy (Bureau C et al, 2017).

In summary, current international guidelines recommend the combination of EVL and NSBBs to prevent rebleeding to all patients after AVB, independently of cirrhosis stage or previous decompensations. Recent data support that patients with ascites and AVB have a poor prognosis, even applying this strategy. In the context of patients with two or more decompensating events, they may benefit from a greater portal pressure-lowering effect that controls ascites and prevents rebleeding and other life-threatening complications, such as hepatorenal syndrome and spontaneous bacteria! peritonitis (Abraldes JG et al, 2019). **Anticipating TIPS in this scenario may substantially benefit transplant-free survival and quality of life without increasing the risk of hepatic encephalopathy.**

Additionally, our study propases a comprehensive **nested pilot study with an innovative approach (proteomics profile in plasma).** This approach aims to address the lack of knowledge about the pathophysiological mechanisms underlying further decompensation in liver disease. Analyzing the proteomic profile in the plasma samples of these patients will allow the characterization of the stage of further decompensation and provide deeper insights into the response to portal hypertension treatments (TIPS vs. standard of care with NSBBs). The identification of the primary pathways involved in the early stage of further decompensation, as proposed in this study, offers insights into the main immunological pathways and suggests opportunities for personalized therapies targeting them.

What is clear to us so far is that inflammation plays a significant role in driving the progression of liver disease across different stages and is implicated in liver-related complications and mortality. In recent years, the evaluation of pro-inflammatory cytokines, acute-phase proteins, and immune activation markers has been employed to enhance risk prediction in both compensated and decompensated cirrhosis (Costa D, et al. 2021; Groenbaek H, et al. 2016; Gurbuz B et al. 2023). Recent data indicate a close relationship between preoperative serum IL-6 levels and the occurrence of hepatic encephalopathy post-TIPS (Li JY et al. 20203). Additionally, elevated venous levels of CXCL11 and IL-8 have been linked to shortened survival in TIPS-receiving patients (Berres ML et al. 2015; Liu G et al. 2022). In the same line, focusing on the innate immune response, it has been suggested that dysregulated biomarkers of innate and adaptive immunity predict disease progression. This study showed that complement levels and immunoglobulins may serve as surrogates of cirrhosis-associated immune dysfunction and associate with cirrhosis severity and systemic inflammation. In fact, low complement C3c predicted decompensation and liver-related death, whereas high lgG-1 indicated an increased risk for infections (Simbrunner B et al., 2023). However, it is unknown whether the liver-specific proteins of patients with further decompensated cirrhosis could provide information on the state of immune system dysregulation at the time of AVB, and subsequently, their variation after TIPS treatment (1-month post-intervention) could offer insights into the degree of progression or regression of liver disease. Circulation markers capable of showing the dysregulation of the immune system in patients treated and untreated with TIPS are urgently needed in clinical practice. However, the characterization of the proteomic profile in inflammation-mediating proteins in decompensated cirrhosis patients treated with TIPS remains underexplored.

Therefore, in this pilot study, we will collect not only suprahepatic and peripheral plasma before and after TIPS placement treatment but also peripheral blood mononuclear cells (PBMC). The primary focus of this pilot protein study is to characterize major up-regulated and down-regulated proteins in plasma, comparing suprahepatic vs. peripheral profiles and examining changes over time (before vs. after TIPS). Depending on the identified up-regulated or down-regulated pathways, we will explore their association with specific mononuclear cells (monocytes, lymphocytes, or neutrophils). This approach will enable us to profile the corresponding cell line through single-cell RNA sequencing (scRNA-seq) in subsequent studies. PI and co-PI extensive expertise in experimental immunology ensures our ability to conduct this protein analysis and profile the involved cell line for single-cell studies in the upcoming ISCIII call (2027).

In conclusion, conducting this multicentre clinical trial is pertinent and represents the best way to generate the needed evidence to anticípate the indication of TIPS in decompensated cirrhosis. Moreover, this study offers a unique opportunity to explore innovative a proteomic analysis to enhance our understanding of TIPS intervention. Additionally, it allows for the identification of new predictive biomarkers for poor prognosis, enabling precise individual risk stratification in alignment with precision medicine principies.

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SECCIÓN ANTECEDENTES Y ESTADO ACTUAL DEL TEMA

Citar las referencias incluidas en el apartado anterior: Antecedentes y Estado actual. **(Máx 1 página. 5250 caracteres)**

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MEMORIA DE SOLICITUD PROYECTO DE I+D+I EN SALUD
SECCIÓN HIPÓTESIS Y OBJETIVOS

(Ajústese al espacio disponible)

HIPÓTESIS

We propase a groundbreaking hypothesis that challenges the conventional approach to patients recovering from an episode of acute variceal bleeding as a further decompensated event. Our working theory suggests that this specific population remains at a heightened risk of subsequent decompensation and death, even when subjected to the existing standard of care. Traditionally, post-variceal bleeding care involves a combination of non-selective beta-blockers and endoscopic variceal ligation, with Transjugular lntrahepatic Portosystemic Shunt (TIPS) reserved as a last-resort measure for those experiencing additional rebleeding. In alignment with our hypothesis, an innovative strategy involving the proactive use of TIPS in this high-risk cohort is anticipated to significantly curtail further decompensation events, ultimately enhancing transplant-free survival rates. This hypothesis challenges the current paradigm and sets the stage for a paradigm shift in the management of these complex patients.

OBJETIVOS

Primary aim:
To assess the benefit of TIPS compared to standard treatment on liver transplant-free survival of patients with cirrhosis and clinically detectable ascites who survive/recover from an AVB episode.

Definition of clinical/y detectable ascites: moderate ar severe (grades 2 and 3) ascites that is present al admission far AVB ar controlled with ongoing diuretic therapy indicated due to clinically detectable ascites within the previous 12 months.

Definition of AVB recovery. absence of failure to control bleeding and of rebleeding within the first 5 days of the index bleeding with a period of hemodynamic stability of al leas! 48 hours.

Secondary aims:
- Overall mortality
- Liver-related mortality
- Hospital admission dueto further liver decompensation
- Days of hospitalization during follow-up
- Rebleeding of variceal origin and from any cause
- Clinically significan! hepatic encephalopathy (West-Haven grade 3 and 4)
- Hepatorenal syndrome (AKI-HRS>1A)
- Spontaneous bacteria! peritonitis and other bacteria! infections
- Number of large-volume evacuating paracentesis
- Serious adverse effects, specifically congestive heart failure.
- Quality of life and palien! reported outcomes.
- Socio-economic cost.

Nested pilot study aims:
- To evaluate changes in the profile on inflammation-mediating proteins (pro-inflammatory/anti-inflammatory) during follow-up in both study groups (treated with TIPS or with standard therapy).
- To explore whether changes in proteomics in paired-samples can predict liver-related outcomes and mortality.
- To compare suprahepatic vs. peripheral compartment profiles in patients treated with TIPS.

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MEMORIA DE SOLICITUD PROYECTO DE I+D+I EN SALUD
SECCIÓN PROYECTOS COORDINADOS/MULTICÉNTRICOS CON VARIOS CENTROS BENEFICIARIOS

En caso de Proyectos Coordinados/Multicéntricos con varios centros beneficiarios, el COORDINADOR deberá indicar:
- Objetivos globales del proyecto coordinado, la necesidad de dicha coordinación y el valor añadido que se espera obtener de la misma.
- Objetivos específicos de cada subproyecto (deben estar recogidos además en la memoria de cada subproyecto)
- Interacción entre los distintos objetivos, actividades y subproyectos.
- Los mecanismos de coordinación previstos para la eficaz ejecución del proyecto. **(Máx. 3 páginas. 15700 caracteres)**

N/A

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INVESTIGADOR/A PRINCIPAL: LUIS TÉLLEZ VILLAJOS

MEMORIA DE SOLICITUD PROYECTO DE I+D+I EN SALUD
SECCIÓN METODOLOGÍA

Diseño, sujetos de estudio, variables, recogida y análisis de datos y limitaciones del estudio.

Describir: Diseño, sujetos de estudio, variables, recogida y análisis de datos; describir limitaciones del estudio, sesgos de datos y mecanismo de compensación. Señalar riesgos de ejecución y plan de contingencia.
Describir la participación ciudadana en la propuesta
Justificar: alineamiento entre la hipótesis, objetivos, variables y metodología estadística de evaluación de variables.
Justificar: tamaño muestra! e incluir metodología de cálculo. Integración de la perspectiva de género en la metodología: describa si es preciso integrar perspectiva de género (entendido como análisis de género y sexo) referido a sus actividades. Justifique en caso de no ser necesario.
Justificar: novedad, originalidad, pertinencia y efecto incentivador sobre la institución si lo hubiese.

(Máx. 3 páginas. 15700 caracteres)

1. Study design
Phase III **randomized, controlled, open-label, multicenter trial with a pragmatic design,** comparing TIPS versus standard treatment in high-risk post-AVB patients.

2. Experimental treatment
The experimental arm is the use TIPS with controlled expansion stents (Viatorr endoprothesis). As per product specification sheet from W.L. Gore&Associates Inc., TIPS is indicated for patients with complications of portal hypertension, specifically AVB or ascites. **Therefore, the use of TIPS in the experimental arm aligns with the indications outlined in the technical data sheet.**

3. Study population
Patients with cirrhosis and ascites who recovered from an episode of AVB after successful treatment with vasoactive medication and endoscopic therapy. We considered for inclusion only patients fully recovered from AVB, defined as 5 days without clinical signs of rebleeding. **Patients treated with pre-emptive TIPS will be excluded.**

3.1 Inclusion criteria: Age between 18-80 years; cirrhosis of any etiology diagnosed by liver biopsy or by clinical, analytical, and imaging criteria; AVB (demonstrated endoscopically) treated with vasoactive and endoscopic therapy; clinically detectable ascites at the time of admission or controlled with ongoing diuretic therapy; written informed consent.

3.2 Exclusion criteria: prior TIPS or surgical portosystemic shunt; prior liver transplantation; AVB dueto isolated gastric varices (IGV1 and IGV2); terminal liver failure (i.e., Child-Pugh >13); active sepsis; moderate-severe porto-pulmonary hypertension; current congestive heart failure; portal cavernomatosis; hepatocellular carcinoma exceeding Milan; intrahepatic neoplasia other than hepatocellular carcinoma; debilitating extrahepatic disease with an estimated survival <12 months; current/desired pregnancy during the study period; severe uncontrolled psychiatric illness; inability to understand the information received; participation in another trial in the last 30 days.

3.3 Recruitment procedure
Patient recruitment will take place during hospitalization or in outpatient clinics. Collaborating investigators will consecutively invite all patients who meet the selection criteria. Patients who decline to participate will be registered in a database.

3.4 Sample size estimation
The sample size is based on assumptions of a 0.05 alpha significance level of 0.05, 80% power, two-sided analysis, and adjusted for an expected 5% loss to follow-up. Previous studies indicate an estimated 18-month survival of approximately 60% for patients with cirrhosis and ascites receiving standard treatment (PIMD: 28543862; PIMD: 31960441) and 85% for those with recurrent ascites treated with TIPS (PIMD: 27663604). To detecta significant 25% difference, a **minimum of 58 patients per group** (116 patients total sample size) is required.

4. Intervention
Patients between **days 5 and 12 after admission because an episode** of AVB will be randomized into two groups:

- **Group A (study group):** Patients will be treated with TIPS within the first 15 days after admission dueto index episode of AVB.
- **Group B (control group):** Patients will receive standard treatment with NSBBs (propranolol or carvedilol) plus EVL sessions every 2-4 weeks until complete variceal eradication, according to the current recommendations (PIMD: 35120736).

4.1 Intervention description
Patients will undergo a complete diagnostic work-up befare study inclusion, including blood tests echocardiogram, electrocardiogram, and abdominal imaging. No prohibited treatments exist. Upon informed consent, randomized patients will be aware of their assigned group.

- **Group A (TIPS):** Intrahepatic insertion of fully covered controlled expansion 8 mm stents, subsequently dilated according to hemodynamic response, aiming for a portal pressure gradient of 8-12 mmHg. Collateral vessels larger than 8 mm after TIPS placement will be embolized to reduce HE risk. After discharge, patients with prior history of overt HE will receive rifaximin during the first 6 months.

- **Group B (standard treatment):** Patients will receive the currently accepted treatment in clinical guidelines (PIMD: 35120736), involving NSBBs (propranolol or carvedilol) and EVL sessions every 2-4 weeks until complete esophageal varices eradication. Rescue TIPS will be considered in case of new AVB, recurrent/refractory ascites, recurrent hydrothorax, or progressive portal vein thrombosis.

5. Strategies to minimize bias
A 1:1 randomization will be conducted via the REDCap-SEPD electronic platform, utilizing a blind sequence in STATA Software version 16 befare starting the study. The randomization list, blind to investigators, will follow block criteria by center, with size and sequence concealed, and stratified by cirrhosis stage and prior NSBBs usage. The analysis, blinded to treatment, will be performed by an expert statistician. Sharing standardized operating procedures for patient management in each treatment arm will reduce potential variability among centers, ensuring consistency and minimizing biases. Regular monitoring and interim reviews allow adaptive adjustments to address unforeseen biases, ensuring study integrity and reliability.

6. Study definitions and outcomes.
6.1. Primary outcome
Liver-transplant-free survival, which includes death from any cause or transplantation for any reason.

6.2. Secondary outcomes
- **Global mortality**
- **Further liver-related decompensation,** as defined as the development of any of the following complications: acute gastrointestinal bleeding dueto portal hypertension; HE grade 3-4; worsening of ascites (at least 3 large-volume paracenteses within 1 year); hepatorenal syndrome spontaneous bacteria! peritonitis
- **Number of hospitalizations dueto further liver decompensations**
- **Days of admission due to further liver decompensations**
- **Change in liver function** (estimated by MELD and Child-Pugh seores)
- **Development of congestive heart failure,** only episodes requiring admission
- **Cost-effectiveness.** % of working days during follow-up
- **Patient reported outcomes (PROs),** which are pivotal to assess the impact of medical interventions on the patient's perspective of health and quality of life. Specifically, PROs will be evaluated by the EQ-5D. Additionally, we plan to collaborate with patient associations to identify PROs aligning with the lived experiences of patients with cirrhosis

7. Study visits and follow-up
The follow-up for each patient will be of 18 months since randomization. The following visits will be scheduled:

Screening and randomization visit (between days 5 and 12 since admission for the index AVB episode): written informed consent; randomization. Patients randomized to **group A** will be informed of TIPS procedure, and will receive NSBBs until TIPS. Patients assigned to **group B** will receive NSBBs and EVL sessions.

Visit O (up to day 15 since admission): **Group A:** TIPS procedure. **Group B:** Adjustment of NSBBs, if necessary. In both groups, clinical evaluation and sampling of a 1O ml of peripheral blood for storage in the Biobank for nested studies.

Visit 1 (+ 30 days since visit O; range: -10 to +1O days): abdominal Doppler US; clinical and laboratory evaluation; incidents, admissions, decompensations, and concomitant treatment recording; 10 ml blood sampling for the nested study collection.

Visit 2 to 6 (see "Anexo"; range: -15 to +15 days): clinical evaluation (visit 4 will be telematic); incidents, admissions, decompensations, and concomitant treatment recording; abdominal Doppler US (visits 3, 5, and 6)

8. Study duration
The duration of the study will be 3 years. Recruitment will be completed at month 30, so that all patients will have a mínimum follow-up of 6 months.

9. Statistical analysis
The statistical analysis will be conducted by independent biostatisticians from IRYCIS's Department of Statistics, blinded to the treatment in each study arm. Quantitative variables meeting normality assumptions will use mean and standard deviation; otherwise, median and interquartile range will be employed. Categorical variables will be described using relative and absolute frequencies, and 95% confidence intervals. The primary analysis, survival analysis, will follow an **intention-to-treat approach.** Comparative analysis will involve t-student or chi-square tests, and survival analysis will employ Kaplan-Meier curves and log-rank tests, with hazard ratios estimated through proportional hazards regression. Cox regression analysis will identify independent predictors for the primary endpoint. Secondary analyses, including logistic regression for death and decompensations, will adjust for baseline factors without p-adjustment for multiple comparisons. A significance level of p <0.05 will be adopted. **Externa! safety committee experts will conduct an interim analysis after 50% sample inclusion,** potentially leading to study discontinuation based on safety or survival differences. **The full Statistical Analysis Plan, detailing all planned analyses, along with the protocol of the study will be publicly available before study initiation.**

10. Monitoring and safety
To ensure project execution, we plan to enlist the support of an **externa! platform** (www.outcomes10.com). This platform will handle authorizations, monitor GCP adherence, oversee protocol-compliant data collection, and assist participating centers with **regulatory and externa! monitoring.** Additionally, it will provide training, review safety aspects, manage adverse event notifications, and prepare reports. The primary risk associated with the study treatment (TIPS) is hepatic encephalopathy (HE). Patients with a history of HE will receive rifaximin post-discharge, following EASL guidelines. An externa! safety committee will conduct an interim analysis at 50% sample inclusion, with recruitment discontinuation in case of safety concerns or survival differences. The study's continuation will depend on these analysis results

11. Feasibility
To ensure the clinical trial's feasibility, we have contacted **17 Spanish centers** experienced in cirrhosis, AVB and TIPS placement. **Pre-selection criteria encompassed an annual average of at least 10 TIPS, demonstrated capacity, infrastructure, and experienced personnel for multicenter studies in portal hypertension.** These centers, with a history of successful collaboration, showcase effective coordination. The included centers are expected to attract patient referrals, aiming for an average **inclusion of 4-5 patients per year** per center, aligning with the planned timeline in the multicenter design. Optimized patient selection plans reflecta pragmatic trial design mirroring usual clinical practice for follow-up in both study groups.

12. Limitations and risks
The main limitation of this clinical trial is the **absence of a blind control,** justified by ethical and safety concerns related to the nature of the experimental treatment involving a technical procedure under general anesthesia/deep sedation. This could introduce bias, potentially overestimating the intervention's effect. To mitigate bias, transplant-free survival was chosen as the **robust primary endpoint.** Another consideration is the potential competition with pre-emptive TIPS in patients with ascites surviving an AVB. While pre-emptive TIPS has established advantages, its applicability remains uncertain, with less than 10% of eligible patients receiving it in a French survey (PMID: 28918131). The proposed strategy applies after the 72-hour period, targeting a time frame where pre-emptive TIPS has shown an advantage. Additionally, the recruitment challenge posed by the large sample size will be addressed by involving 17 tertiary centers and implementing a **diffusion plan** to contact other referral centers.

13. Contingency plan
The contingency plan adopts a comprehensive strategy to tackle potential recruitment challenges. It diversifies sources

by establishing swift referral pathways with non-tertiary centers, engaging new investigators, and expanding the network of participating tertiary centers. Proactive measures such as targeted marketing, protocol adaptability, and regular communication are incorporated to optimize participant engagement. **The plan emphasizes immediate contact with non-tertiary centers and includes streamlined referral pathways.** Regular monitoring, virtual meetings, and open communication contribute to a dynamic approach. Additional strategies involve collaborations with advocacy groups, and potential adjustments to inclusion/exclusion criteria based on feedback.

14. Gender perspective, diversity, and environmental sustainability of the Project

Research team: Our research team prioritizes gender diversity, **with over 50% comprising talented women,** and fosters an environment of expertise and innovation regardless of gender. We are committed to nurturing, inclusivity and emerging **mentorship opportunities** to support the career growth of underrepresented groups. Our commitment to diversity extends beyond gender, encompassing a variety of areas of expertise, backgrounds, experiences, and perspectives. As we embark on this national multicentric study, our focus on **cohesion between the Health Services** of the different regions reflects our commitment to **building bridges** and uniting diverse talents in a shared vision.

Population: The study includes population of both biological sexes and genders.

Analysis: A comprehensive subgroup analysis by biological sex is planned to unravel potential variations in the impact of portal hypertension treatments, **adhering to Sex and Gender Equity in Research (SAGER) guidelines.** Data will be reported disaggregated by sex, considering anatomical, physiological, social, and cultural variables. The influence of sex and gender factors on enrollment, participation, discontinuation, loss-to-follow up, and outcomes will be assessed. **Raw data will be published disaggregated by sex and gender for future pooling and meta-analysis.**

Environmental sustainability: We prioritize environmental sustainability in our research by adopting a paperless approach and minimizing travel-related carbon emissions through virtual interactions (e.g. the 4th visit has been replaced by an eco-friendlier telephone-based alternative), online meetings, and optimized onsite visits.

15. Citizen engagement

Our commitment to citizen engagement is demonstrated through **integrating PROs to assess the impact of portal hypertension treatments in cirrhotic patients.** Collaborating with patient associations ensures the relevance of included PROs, tailoring assessments to matter to patients and emphasizing their perspectives in shaping outcomes.

16. Nested pilot analysis for proteomic

Blood sample collection

We plan to collect blood samples from all participants, ensuring compliance with GCP standards. These samples will be processed and stored at -80ºC in adherence to quality standards, with centralized storage managed by the IRYCIS Biobank.

Proteomic and bioinformatic analysis

We will select 40 patients (20 from each group) with plasma samples at baseline and at 1-month post-intervention, and 10 samples from healthy donors obtained from the Biobank. In this exploratory analysis, we will characterize the plasma proteome profile of inflammation-mediating proteins using **Olink Proteomics Biotechnology®** and a **specific bioinformatic analysis** (see "Medios disponibles" section).

Expediente Nº
PI24/01769

INVESTIGADOR/A PRINCIPAL: LUIS TÉLLEZ VILLAJOS

MEMORIA DE SOLICITUD PROYECTO DE I+D+I EN SALUD
PROPUESTA PARA EL PLAN DE GESTÓN DE DATOS

Describir la tipología y formato de los datos a recoger / generar en el marco del proyecto, procedimiento previsto para acceso a los mismos (quién, cómo y cuándo podrá acceder a ellos), titularidad de los datos, repositorio en que se prevé realizar su depósito, y procedimiento previsto para garantizar los requisitos éticos o legales específicos de aplicación. **(Máx. 1 página. 5250 caracteres)**

The study sponsor holds the responsibility far data processing and management. Data will be prospectively collected, standardized, and coded in a pre-designed electronic Case Report Form (CRF) hosted on the REDCap-SEPD online database. Information will be derived from patient interviews, clinical histories, telephone contacts, and the results of complementary tests.

Collaborating researchers or a designated collaborating study data manager will be tasked with entering data in the electronic CRF. Mechanisms are in place to detect and prevent unauthorized access attempts to the system. To align with ICH E6 Good Clinical Practice, trials using electronic data collection and management will necessarily consider a user's authentication (username and password) as the electronic signature, evidencing the user's authorization to alter information in the clinical database. The REDCap-SEPD platform manager will actívate a user far each researcher to input data, providing a username and prívate password to each research team member. AII data entries and modifications are recorded and stored in an audit lag (username, date, and time).

REDCap-SEPD, resulting from a consortium between the Spanish Society of Digestive Diseases (SEPD) and the Research Electronic *Research Electronic Database Capture* (REDCap), offers researches access to the online REDCap application. This platform aids in the management, design, and coordination of multicenter studies. REDCap enables the development of electronic data collection questionnaires valid far developing research studies. Compliant with current regulations on Personal Data Protection (Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on Data Protection and the Organic Law 3/2018, of 5 December, on Personal Data Protection and Guarantee of digital rights), this database facilitates the development of electronic data collection questionnaires far research studies.

The data review process begins any time after actual data are entered into the CRF. The goal of data quality activities, like the data validation process, is to obtain clinical trials with as few errors as possible to support the findings or conclusions drawn from the trials. In addition, data quality review is essential to meet regulatory requirements. While data quality measurement is important, it is equally, if not more, important to focus on error prevention early in the design stages of the protocol development and data management process.

Data cleaning activities encompass manual reviews and automated checks identifying inaccurate or invalid data, missing data, protocol deviations, and consistency checks. Discrepancies are generated far incorrect data, allowing investigators to respond and correct them. Investigators must correct discrepancies, and the data manager will verify changes during periodic database reviews. Any outstanding queries are forwarded to the appropriate manito and/or investigator until resolved or clarified.

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INVESTIGADOR/A PRINCIPAL: LUIS TÉLLEZ VILLAJOS

MEMORIA DE SOLICITUD PROYECTO DE I+D+I EN SALUD
SECCIÓN PLAN DE TRABAJO

Etapas de desarrollo y distribución de las tareas de todo el equipo investigadorc-Describir para cada persona del equipo investigador sus competencias y la adecuación entre estas competencias y las actividades experimentales que va a desarrollar.
Explicite el momento de recogida de las variables en las diferentes etapas de desarrollo del proyecto; justifique el marco temporal de realización del proyecto y el método de cálculo para esta justificación; identifique los riesgos de ejecución y de la planificación de su control; describir las asignaciones previstas para el personal técnico que se solicita.

(Ajústese al espacio disponible)

Study conception, methodology, design, and database creation
Participants: PI, Department of Biostatistics (IRYCIS), and externa! database manager (Consortium between REDCap and the Spanish Association of Digestive Diseases -SEPD-). For more detailed information about this database please see https://www.sepd.es/storage/cid/Normativa_ENCUESTAS.pdf; Timeframe: month 1
Study registration and IRB authorization
Participants: Externa! platform (Outcomes'10), and PI; Timeframe: months 2 and 3
Insurance sing-up process
Participants: IRYCIS-Research Support Unit, and PI; Timeframe: months 4 and 5
All centres activation
Participants: Externa! platform (Outcomes'10), PI, subinvestigators, and IRYCIS-Research Support Unit; Timeframe: months 6-8
Coordination, vigilance and monitoring, database management, and support:
Participants: Externa! platform (Outcomes'10), and externa! database manager; Timeframe: months 9-33
Patient enrollment, interventional procedure, follow-up, data entry in the electronic CRF, and procedures:
Participants: PI, and subinvestigators; Timeframe: months 9-33
Statistical analysis:
Participants: PI, and Department of Biostatistics (IRYCIS); Timeframe: months 33-end
Study diffusion:
All research team. The research team of the promoting institution (Hospital Universitario Ramón y Cajal) is responsible for the publication of the study protocol and its registration in Clinicaltrials.org; Timeframe: the last 6 months of the Project.
First draft of the final manuscript and authorship:
Those responsible for preparing the manuscript for the scientific communication of the results are Dr. Luis Téllez, who will be the first author, and Dr. Agustín Albillos (senior investigator), who will be the last author and corresponding author. The rest of the authorships will be established following the provisions of the International Committee of Medical Journal Editors (ICMJE) and will be based on the following four criteria:
- That there is a substantial contribution to the conception or design of the article or the acquisition, analysis, and interpretation of data.
- The author has participated in the design of the work or the critica! review of its intellectual content.
- The author has participated in the final approval of the manuscript to be published.
- The author can respond to all aspects of the article to ensure that questions related to the accuracy or completeness of any part of the work are adequately investigated and resolved.
Timeframe: the last 6 months of the Project.

Nested pilot proteomíc analysís and bíoinformatics:
Participants: Pis, and externa! platform (Olink®); Timeframe: months 26-31

Participants and roles of subínvestigators:
Hepatologists: H.U. Ramón y Cajal: L Téllez, A Albillos, A Guerrero, **MA** Rodríguez, J Martínez, B Mateas, **R** González, **R** Sánchez, E Tavío; H.G.U. Gregario Marañón: A Clemente; H. Clínic: S Shalaby; H. Sant Pau i la Santa Creu: A Brujats; H.U. Marqués de Valdecilla: A Puente; H.U. Vall d'Hebron: A Jiménez, J Bañares; H. Insular de Gran Canaria: AF Monescillo, CD Rodríguez; H.U. Río Hortega: 1 Peñas; Corporació Sanitária Universitária Pare Taulí: J Ferrusquía; H.U. de Canarias: C González Alayón; H. de Bellvitge: A Amador, M García; H.U. La Paz: M Abadía, N Gonzalo; H.U. La Fe: l. Conde; H.U. 12 de octubre: ML Manzano, 1 Calvo; H.U. Virgen del Rocío: A Giráldez; H.U. Puerta de Hierro: M López; H.U. Central de Asturias: L Franco
Interventional radiologísts: J Urbano, A Olavarría, 1 Diez, P Sanz, E Casanovas, E Villacastín, R Pintado
Nurses: L Oña, E Palacio, M Jiménez

Executíon risks and planníng to address them:
Given the extensive nature of this study, encompassing numerous centers, there is a possibility that during the study period, a center may be unable to meet the inclusion criteria or a sub-investigator may drop out. In such a scenario, we have explored the option of having backup centers that meet the criteria of performing >1O TIPS per year, and they will be invited to participate.

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INVESTIGADOR/A PRINCIPAL: LUIS TÉLLEZ VILLAJOS

MEMORIA DE SOLICITUD PROYECTO DE I+D+I EN SALUD
SECCIÓN PLAN DE TRABAJO
(Ajústese al espacio disponible. Puede incorporar hasta un máximo de 8 líneas de Actividad/Tarea)

CRONOGRAMA

ACTIVIDAD/ TAREA	PERSONA/S INVOLUCRADAS	MESES E F M A M J J A S O N D
Creación de base de datos	Ver imagen anexa	1° Año 0□□□□□□□□□□□ 2° Año □□□□□□□□□□□□ 3° Año □□□□□□□□□□□□
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ACTIVIDAD/ TAREA	**PERSONA/S INVOLUCRADAS**	**MESES E F M A M J J A S O N D**
Aprobación CEI y activación de centros	Ver imagen anexa	1° Año D00 □□000 □□□□ 2° Año □□□□□□□□□□□□ 3° Año □□□□□□□□□□□□
ACTIVIDAD/ TAREA	**PERSONA/S INVOLUCRADAS**	**MESES E F M A M J J A S O N D**
Reclutamiento y seguimiento de los sujetos incluidos	IPs y subinvestigadores	1° Año □□□□□□□□0000 2° Año 0 0 0 0 0 0 0 0 0 0 0 0 3° Año 0 0 0 0 0 0 0 0 □□□□
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Análisis de proteómica	IPs y plataforma externa	1° Año □□□□□□□□□□□□ 2° Año □□□□□□□□□□□□ 3° Año □□□00000D□□□
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Análisis estdístico	IPs y Unidad de Bioestadística del IRYCIS	1° Año □□□□□□□□□□□□ 2° Año □□□□□□□□□□□□ 3° Año □□□□□□□0000
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Difusión y publicación	Todo el equipo investigador	1° Año □□□□□□□□□□□□ 2° Año □□□□□□□□□□□□ 3° Año □□□□□□□0000

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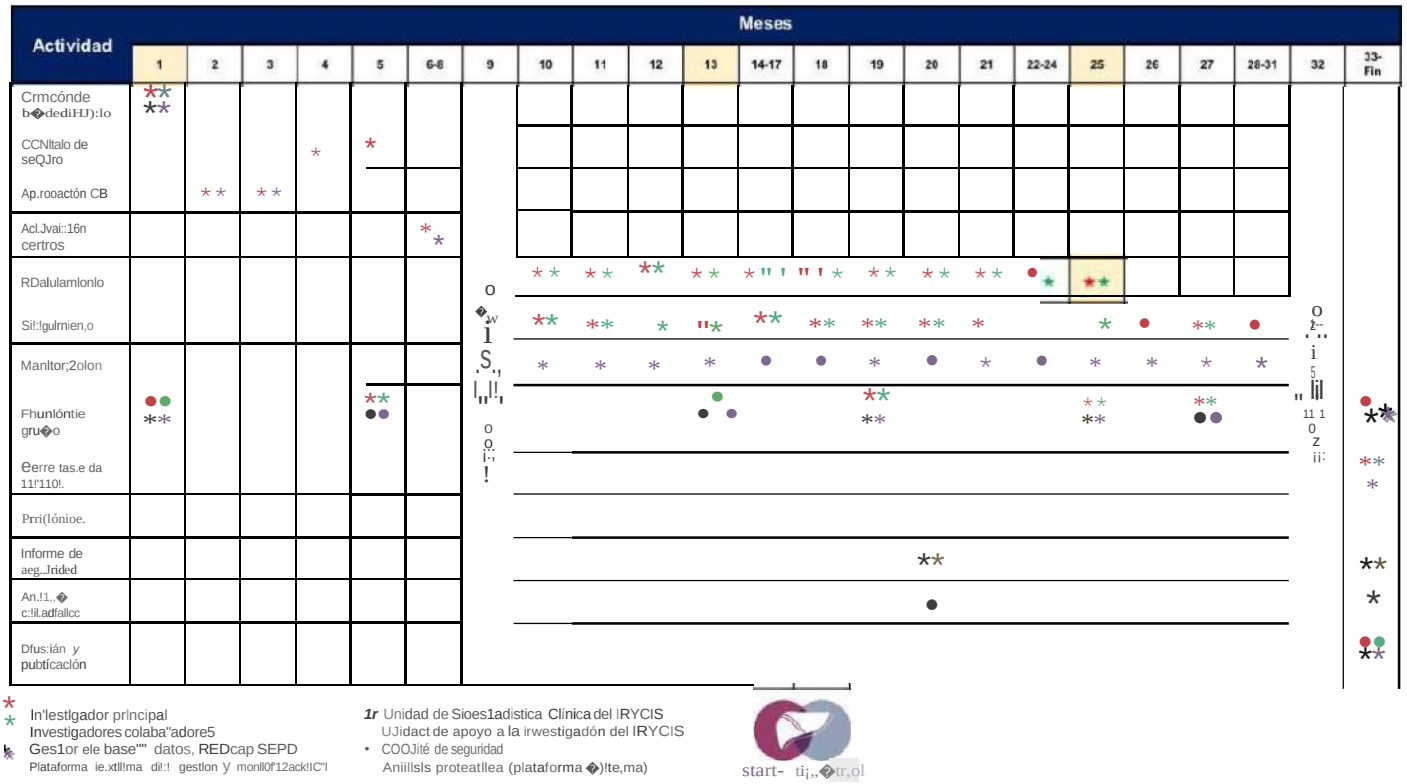
INVESTIGADOR/A PRINCIPAL: LUIS TÉLLEZ VILLAJOS

MEMORIA DE SOLICITUD PROYECTO DE I+D+I EN SALUD
SECCIÓN PLAN DE TRABAJO

Inserte (si lo desea) una imagen con un cronograma. Máximo un fichero de imagen formato jpg



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Expediente Nº
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INVESTIGADOR/A PRINCIPAL: LUIS TÉLLEZ VILLAJOS

MEMORIA DE SOLICITUD PROYECTO DE I+D+I EN SALUD

SECCIÓN MARCO ESTRATÉGICO

Relevancia, aplicabilidad y capacidad de transferencia del proyecto: Impacto en salud, económico y social.
Defina la necesidad no cubierta a la que el proyecto pretende responder, la dimensión de la misma y el método de cálculo de esa dimensión. Describa la contribución esperable al avance del conocimiento científico que resultaría de la ejecución del proyecto. Incluye una estimación del impacto en salud y su adecuación a la contribución esperable del proyecto. Defina la vulnerabilidad, en su caso, de la población sobre la que se pretende abordar el problema descrito en el proyecto, así como su método de estimación.
Establecer si la aplicabilidad del proyecto será inmediata o si precisará de estudios adicionales. Establezca si el proyecto generaría retos regulatorios y/o organizativos para su implementación en el SNS y, en su caso, la dimensión de las reformas que eventualmente se precisarían.
Explicar el tipo de transferibilidad del proyecto, ya sea en la clínica o en el sector productivo. Identificar posibles limitaciones para la implementación de los resultados.

(Máx. 1 página. 5250 caracteres)

Unique nature of the opportunity
It is crucial to highlight that **the 2024 AES 2021-2023 Call for "Proyectos de I+D+I en salud" is the only funding opportunity for our proposal.** The current call far "Proyectos de investigación clínica independiente" by AES 2021-2023 is specifically targeted towards 'human use drugs and/or advanced therapies', leaving a significant gap far trials exploring interventional procedures. In fact, our current proposal was rejected far this reason in the call far "Proyectos de investigación clínica independiente" in the 2023 AES call. Prívate funding far this project is also not possible, as the proposed intervention falls within the indications far prosthesis implantation and prevention of variceal bleeding. **Our project stands as an orphan in the landscape of clinical trials, and only this current call for "Proyectos de I+D+I en salud" can guarantee its successful execution.**

Relevance/ unmet need
Our project addresses a critica! unmet need in the realm of clinical trials, focusing on patients with decompensated liver cirrhosis, a population facing limited effective treatments and a dire prognosis. Cirrhosis ranks as the fifth leading cause of death in Spain, with a profound impact on the quality of life and healthcare resource consumption. The conventional treatments have shown limited efficacy, necessitating a novel approach.

Dimension/ calculation
The dimension of this unmet need is substantial, considering the prevalence of liver cirrhosis, its impact on working-age individuals, and the limited curative options available (i.e. liver transplantation). Improving survival from 60% at 18 months to >85% in patients with decompensated cirrhosis could have a profound impact on public health. The potential enhancement in survival rates signifies a substantial advancement in managing a condition with significant mortality. This improvement not only directly influences the well-being and life expectancy of affected individuals but also has broader implications far healthcare systems and societal outcomes. The study's outcomes, if successfully implemented, could result into a positive shift in public health indicators (years of life lost, quality of life, ...) and healthcare resource allocation.

Contribution to scientific knowledge
The project's execution is expected to significantly advance scientific knowledge by exploring the therapeutic repositioning of TIPS in earlier stages of decompensated cirrhosis. The impact on health is substantial, offering a potential shift towards a more effective and safer treatment paradigm far decompensated cirrhosis.

Vulnerability of the population
The population targeted by the project is highly vulnerable, characterized by the complexity and lethality of cirrhosis. Vulnerability is estimated through the limited available therapeutic options, high mortality rates, and the absence of curative options far most patients.

Applicability and transferability
The project's applicability is immediate, introducing a compelling alternative to standard treatments with the added advantage of TIPS, even in earlier stages. While the project anticipates the need far potential modifications in clinical

guidelines, it is important to note that these adjustments would be in response to the demonstrated efficacy and safety of TIPS in a broader range of indications. The expected regulatory considerations are manageable, as the proposed use aligns with the approved indications for TIPS, ensuring conformity with existing regulatory frameworks. The envisioned reforms are reasonable and justified, reflecting the project's commitment to advancing patient care within the bounds of evolving medical knowledge and practice. The project's transferability extends to healthcare sector as the economic and resource-saving aspects could influence healthcare policies and practices.

Biomarker discovery and personalized medicine

The nested pilot proteomic analysis aims to unveil pathophysiological pathways in response to diverse portal hypertension treatments for decompensated cirrhosis. The primary goal is to discover biomarkers predicting responses to TIPS and NSBBs, guiding personalized treatment for enhanced efficacy, minimal adverse events, and improved patient outcomes. The study also focuses on characterizing major plasma proteins, comparing suprahepatic vs. peripheral profiles, and assessing changes over time (before vs. after TIPS). Subsequent exploration of identified pathways and their association with specific mononuclear cells will enable cell line profiling through single-cell RNA sequencing in subsequent studies.

Limitations

Possible limitations for implementation include the need for specialized skills in performing TIPS procedures and potential resistance to change from established practices. Additionally, long-term follow-up studies may be required to assess the sustained effectiveness and safety of TIPS in this new indication. Regarding experimental studies, they have inherent limitations associated with the designed experiments (e.g., accuracy in determining inflammatory markers), and their extrapolation to clinical settings will similarly have inherent constraints.

Expediente **Nº**
PI24/01769

INVESTIGADOR/A PRINCIPAL: LUIS TÉLLEZ VILLAJOS

MEMORIA DE SOLICITUD PROYECTO DE I+D+I EN SALUD
SECCIÓN MEDIOS DISPONIBLESNIABILIDAD DEL PROYECTO

Medios disponibles para la realización del proyecto.

(Ajústese al espacio disponible)

Hospitalization and outpatient units (Hepatology)
The departments of Gastroenterology and Hepatology of all the institutions participating in the study provide careto inpatients with advanced chronic liver disease in specialized areas, where patients can be recruited. AII institutions provide ambulatory specialized medical and nurse visits, which guarantees adequate follow-up. The promoting institution has standardized work procedures and common management and information systems that can be easily shared with the research team.

Interventional radiology and endoscopy units
AII institutions have Interventional Radiology units where TIPS and other interventional therapeutic procedures are performed daily (range: 10-50 TIPS per year). Considering these numbers, we envision no recruitment problems. All Interventional Radiology units provide electronic report forms to patients and have prospective registries to record therapeutic procedure-related adverse events. The promoting institution has standardized work procedures and common management and information systems that can be easily shared with the research team. AII institutions have Endoscopy Units where endoscopic variceal ligation and other endoscopic therapeutic procedures are performed on daily basis.

Biobank
The processing and storage will follow the standards of good clinical practice and has the support of the Spanish Network of Biobanks. The Biobank of HU Ramón y Cajal-IRYCIS will centralize sample storage. This Biobank is authorized and listed on the National Register of Biobanks (No. B.0000678). It is a Central Support Unit for the investigation, which contributes to the Project by ensuring traceability, quality, and safety in terms of:
- Computer management: software application Bio-e-Bank (VITRO), with high-security conditions.
- Control of stores: continuous recording temperature (SIRIUS) with remole Access, telephone alarms of a power outage and increased temperature freezers (ZETRON), CO2 backups, the preferential line connected to the generator.
- Process control: System Quality Management according to ISO 9001:2015. Tested and certified SGC ICS (No. ES13/14407).
- Compliance with the Spanish regulatory framework for storage samples for research, with particular attention to the rights of the donor subject and obtaining informed consent for the incorporation into Biobank.

Research capabilities
The promoting research group has a Clinical Trials and Clinical Research Unit leaded by the PI dedicated to the coordination and monitoring of clinical trials that will collaborate with the externa! platform. The physical capabilities and human resources of the Unit are: one study coordinator, one data entry, two part-time nurses, medical consultation with the necessary equipment, work office and confidential documentation file, laboratory with refrigerated centrifuge and freezers of-20° and -80°, anda multipurpose room (meetings, monitoring, ...).

Externa! platform
In the study budget we include an externa! platform (Outcomes·1O) dedicated to monitoring, pharmacovigilance, and data management, specifically focused to for this clinical trial to guarantee the standardization and quality of the data obtained in all participating centers and in compliance with the Standards of Good Clinical Practice and applicable legislation (RD1090/2015). Outcomes·1O is a scientific and strategic consulting firm specialized in health outcomes research. They blend scientific methodology with a strategic vision to design and develop innovative research projects. The commitment to quality has driven them to seek methods for continuos improvement, leading to the implementation of an Integrated quality and information security management system. Both systems are certified by AENOR and IQNET.

Proteomic and bioinformatic analyses
Olink® Explore is a platform that allows the exploration and analysis of biological data at the protein level. It is based on the patented Proximity Extension Assay (PEA) technology by Olink, with data generation through NGS. This platform enables precise and simultaneous quantification of over 3000 protein biomarkers secreted in human bodily fluids. Key features of this technology include high sensitivity, exceptional specificity, parallelization, minimal sample volume (less than 8 microliters for analyzing over 3000 biomarkers), and a wide dynamic range (from femtograms to milligrams). Dueto these attributes, Olink® Explore has become an attractive technology for research projects and personalized medicine, facilitating the tracking and discovery of biomarkers for early diagnosis, prognosis, improved patient stratification, treatment response monitoring, anda better understanding of biological networks and functions.

The proteomics data will be pre-processed and normalized, followed by statistical analysis to identify significan! changes. Data will be log2-transformed and proteins which quantified in at least 50% of all samples will be selected. To identify outliers, group-wise coefficients of variation will be calculated for each identified protein and features lower than 0.3 in at least one of the subgroups will be considered for further downstream analysis. A Student t-test and paired Student t-test will be performed to compare between different samples. P value less than 0.05 will be considered significan!. The results will be visualized using various software tools and interpreted to gain insights into the biological system under study. The ultimate goal is to gain a better understanding of the underlying biology and to generate !estable hypotheses for further experimental validation using the whole cohort or other cohorts in the future, incorporating other multiomics analyses.

Clinical Biostatistics Unit
The Biostatistics Unit of IRYCIS is located in the promoting center and is an Associated Cochrane Center. It is composed and equipped with software developed by the unit members, including Meta-DiSc, calculators, macros, PRESTA, etc. Additionally, it utilizes various statistical packages: SAS v9.3, SPSS v17, Stata v14, R v2.11, nQuery v7.0.

Expediente **Nº**
PI24/01769

INVESTIGADOR/A PRINCIPAL: LUIS TÉLLEZ VILLAJOS

MEMORIA DE SOLICITUD PROYECTO DE I+D+I EN SALUD
SECCIÓN ANEXOS

INTRODUZCA TEXTO COMO ANEXO **(Máx. 3 páginas)**

HOJA DE INFORMACIÓN AL PACIENTE

V1. 28/02/2024
TÍTULO DEL ESTUDIO: Ensayo clínico prospectivo, aleatorizado y multicéntrico para evaluar la eficacia del TIPS frente al tratamiento estándar en pacientes de alto riesgo tras un episodio de hemorragia varicosa aguda
INVESTIGADORES PRINCIPAL: Luis Téllez, Servicio de Gastroenterología y Hepatología. Planta 5 derecha. Hospital Universitario Ramón y Cajal.
CENTRO: Hospital Universitario Ramón y Cajal
Introducción
Nos dirigimos a usted para invitarle a participar un estudio de investigación dirigido a los pacientes con cirrosis y ascitis que se recuperan de una hemorragia varicosa aguda, como es su caso. El estudio ha sido aprobado por un Comité de Ética de la Investigación, de acuerdo a la legislación vigente (Ley de Investigación Biomédica 14/2007).

Nuestra intención es tan solo que usted reciba la información correcta y suficiente para que pueda evaluar y juzgar si quiere o no participar en este estudio. Para ello lea esta hoja informativa con atención y nosotros le aclararemos las dudas que le puedan surgir después de la explicación. Además, puede consultar con las personas que considere oportuno.

Participación voluntaria
Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar o cambiar su decisión y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su tratamiento.

Descripción general del estudio
El desarrollo de hipertensión portal conlleva complicaciones devastadoras como la hemorragia varicosa aguda o el desarrollo de ascitis, que tienen un marcado impacto en la supervivencia. Hasta el momento el tratamiento generalmente recomendado una vez acontecido un episodio de hemorragia es la combinación de un tratamiento farmacológico (propranolol o carvedilol) y endoscópico (ligadura con bandas de las varices). Este tratamiento disminuye el riesgo de nuevas hemorragias. Sin embargo, cuando la hemorragia acontece en pacientes con enfermedad hepática ya avanzada y con ascitis, el pronóstico es malo (aún con este tratamiento). Se sabe que la realización de una derivación portosistémica intrahepática percutánea o TIPS es la herramienta más eficaz para tratar las complicaciones de la hipertensión portal, ya que mejora drásticamente la hemodinámica hepática y resuelve la hipertensión portal. Sin embargo, este tratamiento se reserva para pacientes con enfermedad muy avanzada o aquellos en los que ya ha fracasado el tratamiento estándar antes citado.
Nuestro objetivo es investigar si la indicación anticipada del TIPS en los pacientes con ascitis y hemorragia varicosa aguda mejora el pronóstico global (menor riesgo de muerte) comparado con el tratamiento disponible hasta ahora. Además, contemplamos la posibilidad de que si nuestra hipótesis es cierta, esta mejoría en el pronóstico no se asociará a una mayor riesgo de eventos adversos, como el desarrollo de encefalopatía hepática. En el diseño del estudio han participado pacientes como usted, lo que nos ha permitido conocer algunos factores que también analizaremos relacionados con la calidad de vida y el bienestar.
Le invitamos a participar en este estudio aleatorizado en el que habrá dos grupos bien diferenciados: mediante una asignación al azar, a la mitad de los participantes se les va a hacer un seguimiento y tratamiento convencional y a la otra mitad se les propondrá la realización de TIPS.

Por otro lado, le proponemos participar en un estudio anidado, que persigue identificar marcadores en sangre que puedan ser de utilidad para predecir la evolución individual de cada paciente. En este sentido, se le solicitará una autorización específica para recoger una muestra de sangre. En resumen, por el hecho de participar en el estudio tiene que saber que se le realizarían las siguientes pruebas extraordinarias que no se harían si no participara en el estudio: un ecocardiograma transtorácico, un análisis con parámetros analíticos de función cardíaca y hepática, una muestra de sangre para estudios de biomarcadores (proteómica, metabolómica y análisis de miRNA). Se realizaran el mismo número de visitas tanto si le toca el grupo intervención como si le toca el grupo control, y serán aproximadamente 1 al mes y posteriormente cada 3-6 meses durante 18 meses.

Beneficios esperados
Una vez desarrollado este estudio, los resultados podrán ser directamente aplicados a nuestra práctica clínica habitual, pudiendo optimizar el tratamiento de los pacientes con cirrosis descompensada. De hecho, si nuestros resultados son los esperados, podremos proponer un enfoque novedoso que mejorará directamente la calidad de nuestro sistema sanitario disminuyendo el número de ingresos y consultas a urgencias de los pacientes con cirrosis descompensada. Hay que remarcar sin embargo que no podemos asegurar usted obtenga un beneficio concreto para su salud por el hecho de participar en el estudio.
Los resultados del proyecto serán difundidos mediante comunicaciones científicas y redes sociales, pero también se informará de forma activa a las sociedades de enfermos hepáticos para definir un plan de comunicación que llegue de forma amplia a la población

Confidencialidad
El Hospital Universitario Ramón y Cajal, como responsable del tratamiento de sus datos, le informa que el tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los participantes se ajustará al cumplimiento del Reglamento UE 2016/679 del Parlamento Europeo y del Consejo de 27 de abril de 2016 relativo a la protección de las personas físicas en cuanto al tratamiento de datos personales y la libre circulación de datos y a la Ley Orgánica 3/2018 de 5 de diciembre de Protección de Datos Personales y Garantía de los derechos digitales.
Los datos recogidos para estos estudios se recogerán identificados únicamente mediante un código, por lo que no se incluirá ningún tipo de información que permita identificar a los participantes. Sólo el médico del estudio y sus colaboradores con un permiso específico podrán relacionar

sus datos recogidos en el estudio con su historia clínica.
Su identidad no estará al alcance de ninguna otra persona a excepción de una urgencia médica o requerimiento legal. Podrán tener acceso a su información personal identificada, las autoridades sanitarias, el Comité de Ética de Investigación y personal autorizado por el promotor del estudio, cuando sea necesario para comprobar datos y procedimientos del estudio, pero siempre manteniendo la confidencialidad de acuerdo a la legislación vigente.
Sólo se cederán a terceros y a otros países los datos codificados, que en ningún caso contendrán información que pueda identificar al participante directamente (como nombre y apellidos, iniciales, dirección, número de la seguridad social, etc.). En el supuesto de que se produjera esta cesión, sería para la misma finalidad del estudio descrito y garantizando la confidencialidad.
Si se realizara una transferencia de datos codificados fuera de la UE, ya sea a entidades relacionadas con el centro hospitalario donde usted participa, a prestadores de servicios o a investigadores que colaboren con su médico, sus datos quedarán protegidos por salvaguardas como contratos u otros mecanismos establecidos por las autoridades de protección de datos.
Además de los derechos que ya contemplaba la legislación anterior (acceso, modificación, oposición y cancelación de datos, supresión en el nuevo Reglamento) ahora también puede limitar el tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercitar estos derechos, o si desea saber más sobre confidencialidad, deberán dirigirse al investigador principal del estudio o al Delegado de Protección de Datos del Hospital Universitario Ramón y Cajal a través del Servicio de Atención al Paciente. Así mismo tienen derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho/a.
Los datos ya recogidos no se pueden eliminar aunque usted abandone el estudio, para garantizar la validez de la investigación y cumplir con los deberes legales y los requisitos de autorización de medicamentos. Pero no se recogerán nuevos datos si usted decide dejar de participar.
El Investigador y el Promotor están obligados a conservar los datos recogidos para el estudio al menos hasta 5 años tras su finalización.
Posteriormente, la información personal solo se conservará por el centro para el cuidado de su salud y por el promotor para otros fines de investigación científica si el paciente hubiera otorgado su consentimiento para ello, y si así lo permite la ley y requisitos éticos aplicables.

Compensación económica
Su participación en el estudio no le supondrá ningún gasto y le serán reintegrados los gastos extraordinarios (por ejemplo comidas y traslados).

Obtención y utilización de muestras biológicas
La participación en este estudio conlleva la obtención de muestras de sangre para estudio de biomarcadores mediante técnias de proteómica, metabolómica y análisis de miRNA. De conformidad con lo que establece la Ley 14/2007 de investigación biomédica y el Real Decreto 1716/2011 por el que se regula la utilización de muestras biológicas en investigación, al firmar este documento usted acepta que se utilicen las muestras que se obtendrán para las finalidades del presente estudio.
Las muestras se mantendrán almacenadas en **Biobanco de Hospital Universitario Ramón y Cajal** hasta su utilización para los objetivos de este estudio. Una vez finalizado, las muestras sobrantes serán destruidas a no ser que usted firme un consentimiento específico para que puedan ser almacenadas y utilizadas en futuras investigaciones (se le proporcionará dicho consentimiento aparte).
Se utilizará un código para identificar su muestra y no se utilizará ningún dato suyo que pueda desvelar su identidad. Únicamente el médico del estudio y sus colaboradores podrán relacionar la muestra con usted.
Los datos que se deriven de la utilización de estas muestras se trataran del mismo modo que el resto de datos que se obtengan durante este estudio.
La cesión de muestras biológicas para este estudio es **gratuita y voluntaria.** Esto supone que usted no tendrá derechos sobre posibles beneficios comerciales de los descubrimientos que pudieran derivarse del resultado de la investigación biomédica.
Si se obtuviera información relevante que pudiera afectar a su salud o a la de sus familiares, se le notificará. En caso que fuera necesario contactar con usted, se utilizarían los datos que constan en su historia clínica. No obstante, se respetará su derecho a decidir que no se le comuniquen éstos, para lo que puede marcar la casilla que se encuentra en el formulario de consentimiento.
Asimismo, en caso que se realicen análisis genéticos no se le comunicarán ni a usted ni a su médico los resultados que se obtuvieran, aunque usted tiene derecho a solicitarlos dirigiéndose al médico del estudio. Tenga en cuenta que al tratarse de estudios de investigación exploratorios, no proporcionarán información útil ni se podrán utilizar para guiar su tratamiento ni para diagnóstico

Otra información relevante
Cualquier nueva información referente al tratamiento utilizado en el estudio y que pueda afectar a su disposición para participar, que se descubra durante su participación, le será comunicada por su médico lo antes posible.
Si usted decide retirar el consentimiento para participar en este estudio, ningún dato nuevo será añadido a la base de datos y, puede exigir la destrucción de todas las muestras identificables previamente retenidas para evitar la realización de nuevos análisis.
También debe saber que puede ser excluido del estudio si el promotor y/o los investigadores del estudio lo consideran oportuno, ya sea por motivos de seguridad, por cualquier acontecimiento adverso que se produzca y se considere relacionado con su participación en el estudio o porque consideren que no está cumpliendo con los procedimientos establecidos. En cualquiera de los casos, usted recibirá una explicación adecuada del motivo que ha ocasionado su retirada del estudio
Al firmar la hoja de consentimiento adjunta, se compromete a cumplir con los procedimientos del estudio que se le han expuesto.
Cuando acabe su participación recibirá el mejor tratamiento disponible y que su médico considere el más adecuado para su enfermedad.

HOJA DE CONSENTIMIENTO DEL PARTICIPANTE

Título del estudio: Ensayo clínico prospectivo, aleatorizado y multicéntrico para evaluar la eficacia del TIPS frente al tratamiento estándar en pacientes de alto riesgo tras un episodio de hemorragia varicosa aguda
V1 28.02.24

Yo, *(nombre y apellidos del participante)*

- He leído la hoja de información que se me ha entregado sobre el estudio.
- He podido hacer preguntas sobre el estudio.
- He recibido suficiente información sobre el estudio.
- He hablado con: *(nombre del investigador)*
- Comprendo que mi participación es voluntaria.
- Comprendo que puedo retirarme del estudio:

- Cuando quiera.
- Sin tener que dar explicaciones.
- Sin que esto repercuta en mis cuidados médicos.

- De conformidad con lo que establece el Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016 relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos y Ley Orgánica 3/2018, de 5 de diciembre, de protección de datos personales y garantía de los derechos digitales., declaro haber sido informado de la existencia de un fichero o tratamiento de datos de carácter personal, de la finalidad de la recogida de éstos y de los destinatarios de la información.

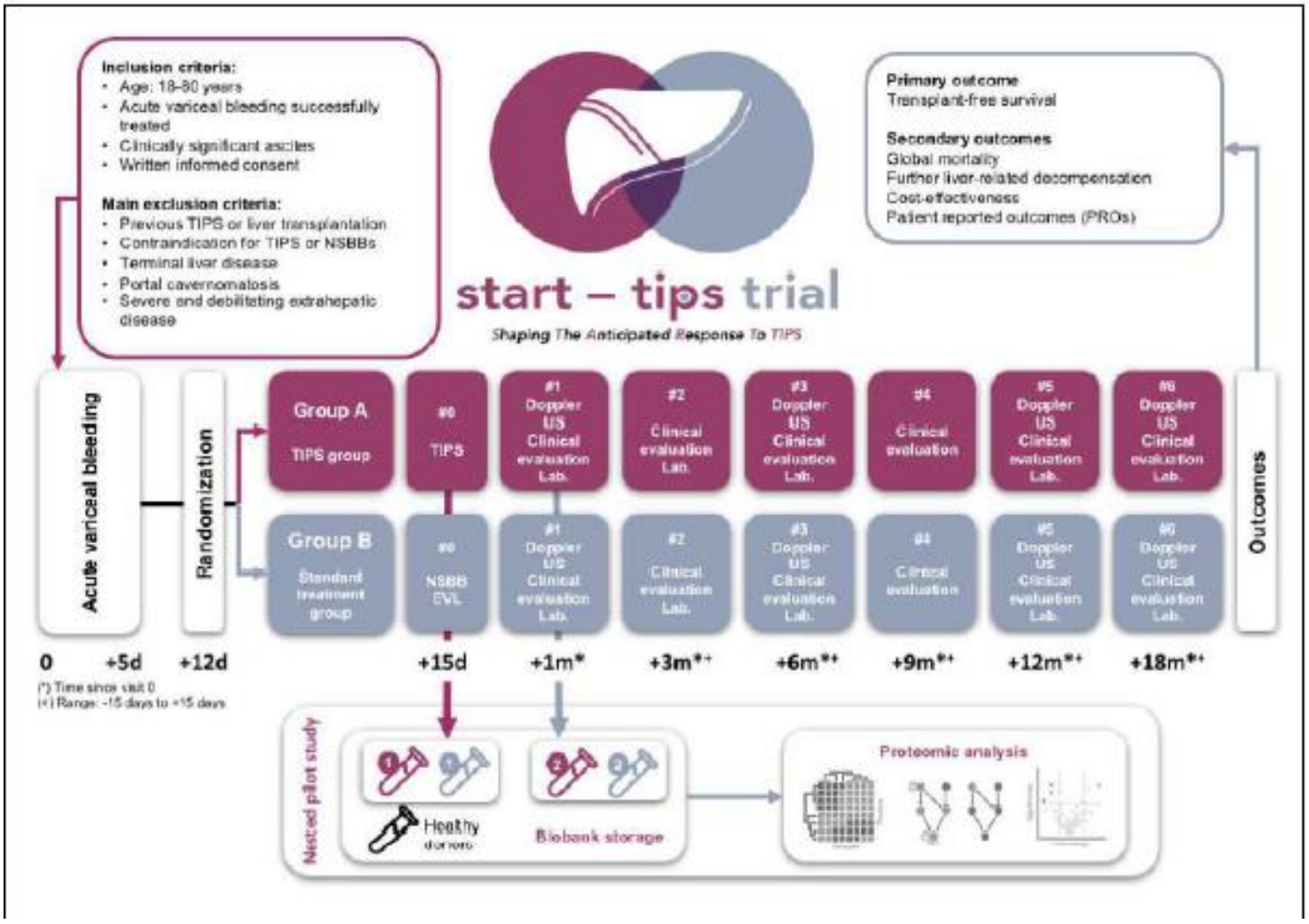
Ante la presente información que el Responsable del Tratamiento me ha otorgado, y habiendo entendido ésta, ofrezco mi consentimiento al tratamiento de:
☐ Mis datos personales para llevar a cabo el proyecto de investigación.
☐ Mis datos personales para llevar a cabo proyectos de investigación afines al presente o de la misma área de investigación
Presto libremente mi conformidad para participar en el estudio.

Firma del participante Firma del investigador

Fecha: ___ /___ /___ Fecha: ___ /___ /_

Deseo que me comuniquen la información derivada de la investigación que pueda ser relevante para mí salud:
SI NO
Firma del participante Firma del investigador

Fecha: ___ /___ /___ Fecha: ___ /___ /_


Inclusion criteria:
• Age: 18–80 years
• Acute variceal bleeding successfully treated
• Clinically significant ascites
• Written informed consent
Main exclusion criteria:
• Previous TIPS or liver transplantation
• Contraindication for TIPS or NSBBs
• Terminal liver disease
• Portal cavernomatosis
• Severe and debilitating extrahepatic disease
start – tips trial
Shaping The Anticipated Response To TIPS
Primary outcome
Transplant-free survival
Secondary outcomes
Global mortality
Further liver-related decompensation
Cost-effectiveness
Patient reported outcomes (PROs)
Acute variceal bleeding
Randomization
Group A
TIPS group
Group B
Standard treatment group
#0 TIPS
#0 NSBB EVL
#1 Doppler US Clinical evaluation Lab.
#2 Clinical evaluation Lab.
#3 Doppler US Clinical evaluation Lab.
#4 Clinical evaluation
#5 Doppler US Clinical evaluation Lab.
#6 Doppler US Clinical evaluation Lab.
Outcomes
0 +5d +12d +15d +1m* +3m*+ +6m*+ +9m*+ +12m*+ +18m*+
(*) Time since visit 0
(+) Range: -15 days to +15 days
Nested pilot study
Healthy donors
Biobank storage
Proteomic analysis