1 TITLE PAGE

Study title: Coagulation in Cirrhosis ("COUCH") – a pilot study

Name of investigational product: Prothromplex

Indication studied: Restrictive vs liberal substitution of coagulation factors prior to minor liver interventions in cirrhosis patients

Name of Sponsor: Prof. Stefan Schaller; Prof. Oliver Kimberger; Department of Anesthesiology, General Intensive Care Medicine and Pain Therapy, Medical University of Vienna.

Protocol No.: V5.0

EudraCT-Number: 2021-006870-22

Development Phase of Study: IV

Study Initiation date: 12/01/2023

First patient in: 08/03/2023

Last patient out: 31/10/2024

Study completion date: 13/01/2025

Investigator(s): Prof. David Baron, Department of Anesthesiology, General Intensive Care Medicine and Pain Therapy, Medical University of Vienna.

Name of Author/Company:

Dr. Armin Langauer, armin-andreas.langauer@oegk.at

Dr. Kristina Nieding, kristina.nieding@meduniwien.ac.at

Date of report: 27.12.2025

The clinical trial was performed in accordance with the International Council for Harmonisation E6 (Good Clinical Practice), the regulatory requirements, and the ethical principles that have their origin in the Declaration of Helsinki.

Sponsor

Prof. Stefan Schaller

29. Jan. 2026
EES Einfache elektronische Signatur
Signiert auf Skribble.com

Signature

29.01.2026

Date

Investigator

Prof. David Baron

Signature

5.1.2026

Date

Authors

Dr. Armin Langauer

Signature

27.12.2025

Date

Dr. Kristina Nieding

Signature

28.12.2025

Date

2 SYNOPSIS

Name of Sponsor/ Company: Department of Anaesthesiology, General Intensive Care Medicine and Pain Therapy, Medical University of Vienna.	
Name of Investigational Medicinal Product: Prothromplex	
Name of active ingredient(s): Coagulation factors II, VII, IX, X, Protein C	
Title of Study Coagulation in Cirrhosis – a pilot study	
Investigator(s): Prof. David Baron	
Study Center: Medical University of Vienna	
Publication (reference): study not published at date of report	
Studied period (years): *(08/03/2023 – 31/10/2024)*	**Phase of Development:** IV
Objectives: Restrictive vs liberal substitution of coagulation factors prior to minor liver interventions in cirrhosis patients	
Methodology: randomized controlled trial	
Number of patients (planned and analysed): 20 planned, 13 included, 12 analysed, 1 dropout	
Inclusion Criteria: Patients at the University Hospital of Vienna with diagnosed liver cirrhosis and deranged coagulation parameters (INR >1,5 AND/ OR platelet count <50 G/L) who are planned for one of the following elective invasive interventions of the liver: - biopsy or puncture - microwave ablation (MWA) or radiofrequency ablation (RFA) - transjugular intrahepatic portosystemic shunt (TIPS) - percutaneous transhepatic cholangiography drain (PTCD).	
Exclusion Criteria: - Missing informed consent or inability to consent - age < 18 years - pregnancy or breastfeeding - chronic kidney injury KDIGO stage G4 or G5 - not paused anticoagulant therapy, except for acetylsalicylic acid (ASA)	

- history of bleeding or clinical signs of a haemorrhagic diathesis in the physical examination (e.g., petechia, ecchymosis, mucosal bleeding, haemorrhagic diathesis within the family, menorrhagia, prolonged bleeding after surgery).

Test product, dose and mode of administration, batch number:

n.a. the intervention is withholding the reference therapy (see below)

Duration of treatment: single shot administration prior to intervention

Reference therapy, dose and mode of administration, batch number:

Prothromplex, dose (I.U.) = (measured INR – 1,5) x 20 x body weight (kg),

intravenous

Criteria for Evaluation:

Incidence of bleeding complications or other substitution related complications

Statistical Methods:

Descriptive due to low number of participants.

Summary-Conclusion:

Efficacy Results:

Due to the small sample size of this pilot study, no reliable statement can be made about the efficacy of withholding Prothromplex for the selected group of patients.

Safety Results:

Due to the small sample size of this pilot study, no reliable statement can be made about the safety of withholding Prothromplex for the selected group of patients.

Conclusion:

Our pilot study did not suggest clear superiority of either regimen. A non-inferiority study with a larger sample size is needed to draw further conclusions. There were no major bleeding events in either study group when INR was between 1,5 and 2,0.

Date of report: 27.12.2025

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
AKH	Vienna General Hospital, University Hospital of Vienna
AMG	“Arzneimittelgesetz” (pharmaceutical law)
BASG	Austrian Federal Office for Safety in Health Care
CRF	Case Report Form
EC	Ethics Committee
GCP	Good Clinical Practice
GI	Gastrointenstinal
ICH	International Council for Harmonization
IMP	Investigational Medicinal Product
KDIGO	Kidney Disease – Improving Global Outcome
KKS	Clinical Trials Coordination Center
MWA	Microwave Ablation
PT	Preferred Term
PPSB	Prothrombincomplex concentrate
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SOC	System Organ Classes
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEG	Thromboelastography
TIPS	Transjugular Intrahepatic Portosystemic Shunt
vWF	von-Willebrand Factor
WHO	World Health Organization

5 ETHICS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The Ethics Committee of the Medical University Vienna, defined as central EC for this trial, reviewed study documents as required by ICH-GCP and the AMG including study protocol and informed consent form in all their ethical, legal and medical aspects.

5.2 Ethical Conduct of the Study

The study was conducted in accordance with the protocol, the principles of the "Declaration of Helsinki" in its current version and the requirements of the Austrian law (AMG).

5.3 Patient Information and Consent

Investigators informed participants comprehensively regarding the nature, significance, impact and risks of this clinical trial. During this instruction the patients were made aware of the fact that they can withdraw their consent – without giving reasons – at any time, without their further medical care being influenced in any way. In addition, patients also received a written patient information sheet in comprehensible language, explaining the nature and purpose of the study and its progress. The patient information sheet was approved by the ethics committee. The consent form was signed and dated by the patient and the physician who conducted the informed consent discussion before any study related procedure was performed. Additionally, the patients were given a copy of the signed informed consent form.

The patients had agreed to the possibility of study-related data being passed on to relevant authorities. According to the stipulations of the Austrian Data Protection Law, confidentiality and pseudonymity of the volunteers were assured.

After giving written consent, the patient underwent the first screening investigations.

5.4 Insurance

During their participation in the clinical trial all patients were insured as defined by legal requirements. The investigator of the clinical trial received a copy of the insurance conditions and filed the copy in the Investigator Site file for reference. The sponsor provided insurance in order to indemnify (legal and financial coverage) the investigator/centre against claims arising from the study, except for claims that arise from malpractice and/or negligence. The compensation of the patient in the event of study-related injuries complied with the applicable regulations.

Details on the insurance, (i.e. insurance number: 07229622-2, Zürich Versicherungs AG, Leopold-Ungar-Platz 2, 1190 Vienna) were described in the patient information sheet.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor	Prof. Stefan Schaller, Prof. Oliver Kimberger
Monitor and Project Manager	Koordinationszentrum für Klinische Studien, KKS, Medical University of Vienna
Statistical planning	Prof. Martin Prosch
Investigator	Prof. David Baron

Table 1: Names and addresses of the persons who conducted the study; the members are listed according to their respective responsibilities

7 INTRODUCTION

Patients with cirrhosis often show deranged coagulation parameters, in particular thrombocytopenia and/or an increased INR. However, these findings do not necessarily constitute an increased tendency of bleeding. In fact, the defective synthesis of both pro- and anticoagulant factors often leads to a new equilibrium in the coagulation system. Nevertheless, out of fear of bleeding, liver cirrhosis patients with deviated laboratory coagulation parameters are often aggressively treated with coagulation products before minor interventions and punctures, especially platelet concentrates and coagulation factors, e.g. Prothromplex. Since the products mentioned can also have serious side effects, we were investigating whether patients with liver cirrhosis without a history of bleeding or clinical bleeding signs would benefit from a restrictive substitution regime. This study was a pilot study, carried out moncentrically at Vienna General Hospital (AKH, University Hospital of Vienna). We included 13 patients randomized into two groups: an intervention group with a restrictive use of coagulation products (these patients did not receive a prophylactic correction of their deranged coagulation parameters with Prothromplex) and a control group with a liberal regime. Our major endpoint was the incidence of major bleedings within the first 3 days of intervention.

8 STUDY OBJECTIVES

Our aim was to test a restrictive substitution regime in cirrhosis patients undergoing minor liver interventions on a small scale and to gather preliminary information on whether this was associated with a higher risk of major bleedings during or after intervention. As this was a pilot study, further research is required to sufficiently answer that question.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan – Description

Liver cirrhosis patients who were scheduled for a liver-related intervention were screened for in- and exclusion criteria. Patients considered eligible for the study were provided with detailed information and informed consent was obtained. Patients were carefully interviewed and physically examined for any signs of haemorrhagic diathesis.

Patients were then randomly assigned to one of two groups: One group ("liberal") received Prothromplex and/or platelet concentrates with the calculated goal of INR ≤ 1,5 or platelet count ≥ 50 G/l. The second group ("restrictive") received no substitution of Prothromplex, or platelet concentrate before intervention. Independently of randomization, patients were substituted with fibrinogen, if the level was less than 120 mg/dl at the time of baseline measurements. The dose of coagulation products was calculated using the following formulas:

- Calculation of fibrinogen:

  dose (mg) = (120 – measured Fib. level (mg/dl) x body weight (kg)) / 1,7

- Calculation of PPSB:

  dose (I.U.) = (measured INR – 1,5) x 20 x body weight (kg)

- Calculation of the content of platelet concentrates:

  Content (10^11/l) = (target value (109/l) – current value(10^9/l)) x total blood volume (l) / 0,66 x 100

Total blood volume is calculated as body surface (m²) x 2,21 for women and x 2,65 for men. The platelet concentrates with the appropriate content are individually provided by the Department of Blood Group Serology and Transfusion Medicine.

Substitution was administered about two hours prior to intervention. Parameters from a blood draw one hour prior to intervention (haemoglobin level, standard coagulation parameters, von-Willebrand factor (vWF), protein C and S, thrombin generation assay and thromboelastography (TEG)) were used as pre-intervention parameters for later comparison.

The occurrence of bleeding complications, as well as the need for coagulation and blood products, was documented over three days after the intervention. Upon discharge from the hospital, patients were handed out a diary that asks in detail for symptoms of thromboembolic events, bleeding, and transfusion-related complications. 28 days after the intervention, patients received a phone call from the study team in which the occurrence of complications was evaluated and documented.

The Clinical Trials Coordination Centre of the Medical University of Vienna (KKS) was appointed with the monitoring of the study and carried out the initiation visit and the closing visit.

9.2 Discussion of Study Design, including the Choice of Control Groups

The definition of the liberal substitution group was meant to replicate the routine procedure for cirrhosis patients undergoing minimally invasive interventions of the liver in a standardised way. Formulas for substitution of coagulation factors and platelets were selected to reach a goal of 1,5 INR and 50 G/l platelets in patients in the liberal group. The formulas mentioned in section 9.1. were used based on the patient's recent baseline laboratory measurements and a pre-intervention control blood draw was done in every patient to consider interindividual different substitution results in the analysis of our outcome parameters.

Since the intervention in this study is withholding the routinely administered substitution, the liberal substitution group can be considered to be the control group in this trial.

The restrictive substitution group did not receive any substitution for correction of INR or platelet count prior to the intervention.

Fibrinogen levels were substituted where necessary in both groups to attain normal levels. This was done to exclude bleeding due to lack of fibrinogen and to focus on the influence of platelet count and INR on bleeding in patients with liver cirrhosis.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Patients at Vienna General Hospital (AKH) with diagnosed liver cirrhosis and deranged coagulation parameters (INR >1,5 and/or platelet count <50 G/L) who are scheduled for one of the following elective invasive interventions of the liver:

- biopsy or puncture

- microwave ablation (MWA) or radiofrequency ablation (RFA)

- transjugular intrahepatic portosystemic shunt (TIPS)

- percutaneous transhepatic cholangiography drain (PTCD).

9.3.2 Exclusion Criteria

- Missing informed consent or inability to consent

- age < 18 years

- pregnancy or breastfeeding

- chronic kidney injury KDIGO stage G4 or G5

- not paused anticoagulant therapy, except for acetylsalicylic acid (ASA)

- history of bleeding or clinical signs of a haemorrhagic diathesis in the physical examination (e.g., petechia, ecchymosis, mucosal bleeding, haemorrhagic diathesis within the family, menorrhagia, prolonged bleeding after surgery).

9.3.3 Removal of Patients from Therapy or Assessment

Within the 13 included patients we had 1 dropout (death prior to intervention due to the underlying condition, not study related). Since the only intervention of this trial was administering or withholding a single dose of platelets or Prothromplex, no withdrawal from treatment was relevant at later stages. All patients received care according to standard of care protocols during and after the intervention, regardless of randomization.

9.4 Treatments

9.4.1 Treatments Administered

After randomization into either the liberal or the restrictive substitution group, patients in the restrictive study group received no Prothromplex prior to their liver intervention. Only fibrinogen was corrected if diminished. Patients in the liberal control group received Prothromplex (dose calculated following the formula mentioned above) about 2 hours prior

to intervention. We prepared the substance strictly according to the medical product information, using the solvent delivered within the same package. We then injected the medication slowly via an intravenous canula we had checked before.

No patients received the planned administration platelet concentrates during this trial. Randomisation and the particular laboratory measurements did not necessitate the application of platelet concentrates.

9.4.2 Identity of Investigational Product(s)

Prothromplex NF 500 by Takeda Pharmaceutical Company Limited was the sole used investigational product.

9.4.3 Method of Assigning Patients to Treatment Groups

Liver cirrhosis patients, who were scheduled for a liver-related intervention, were screened for in- and exclusion criteria. Patients considered eligible for the study were provided with detailed information and informed consent was obtained. Patients were carefully interviewed and physically examined for any signs of haemorrhagic diathesis.

Patients were then randomly assigned to one of two groups using the online available randomization service randomizer.at, which is owned by the Medical University of Graz, Austria. The software's GCP-compliance has been confirmed by the Austrian Federal Office for Safety in Health Care (BASG).

9.4.4 Selection of Doses in the Study

Formulas for calculating the dosage of Prothromplex, fibrinogen and platelet concentrates are given in section 9.1.

The calculation for Prothromplex- and fibrinogen substitution was derived from the manufacturer’s medical product information. Calculations for platelet substitution were provided by study team members of the Department of Transfusion Medicine and Cell Therapy.

9.4.5 Selection and Timing of Dose for each Patient

Prothromplex was given to patients randomized to the liberal control group 2 hours prior to the intervention. The timing was chosen to ensure sufficient effect at the time of the pre-intervention blood draw and at the intervention itself.

9.4.6 Blinding

The study was carried out semi-blinded. The interventionists were blinded to the randomization of the patients. The study team that administered the products, however, was not blinded. Due to the small sample size, no interim analyses requiring unblinding where planned.

9.4.7 Prior and Concomitant Therapy

Every patient's long-term medication was recorded in full in the CRF. Concomitant use of anticoagulatory medication at the time of intervention was considered an exclusion criterium. Acetylsalicylic acid was an exception from this rule and concomitant use was allowed peri-interventionally to reflect routine practice for patients undergoing minimally invasive surgery.

Since many of the included patients underwent their procedure under general anaesthesia, anaesthetic agents can also be considered concomitant medication and complete anaesthesia protocols were gathered for each patient to account for any effect of peri-interventional medication on the occurrence of bleeding, thrombosis and other adverse events. During the course of the intervention, patients did not receive any other coagulation factors or blood products, except for the occurrence of major bleeding (which constitutes the primary end point of this trial).

9.4.8 Treatment Compliance

As we used a single shot administration which was administered by the study team, treatment compliance was 100%. We did have 1 dropout though due to death prior to intervention (not study related). Completion of the diary was not checked in person. Participants were contacted via telephone and used the diary to answer any questions about relevant events in the 28-day period after the intervention. For participants that could repeatedly not be reached via telephone, a thorough search of our electronic patient records was conducted.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed

We used the formula mentioned above to calculate a Prothromplex dose that would correct the elevated INR >1,5 to the value of 1,5. We administered Prothromplex about 2 hours prior to intervention and checked the coagulation parameters 1 hour prior to intervention (INR, platelet count, protein C and S, vWF) and we also did thromboelastographic measurements.

The results of this examination were for study purposes only and the intervention was not delayed awaiting the results. The patients were closely monitored for bleeding or other complications according to the standard protocol for each intervention. The study team checked on the patients directly after intervention, on day 3 after intervention, and they received a phone call 4 weeks after intervention. On this phone call we checked on the patients' diary that was handed out to them with the focus on bleeding complications, thrombosis, allergic reactions or other transfusion or substitution related side effects.

9.5.2 Appropriateness of Measurements

All measurements - except for thrombin generation – were conducted using the equipment maintained by the University Hospital of Vienna or the Department of Anaesthesia, Intensive Care Medicine and Pain Medicine, respectively. Thrombin generation was assessed at a qualified external laboratory after completion of the inclusion period. The applicable measurements are routinely used parameters to indicate bleeding diathesis.

9.5.3 Primary Efficacy Variable(s)

The primary outcome parameter of this trial was major bleeding during the intervention or within the first three days after the intervention. The occurrence of bleeding was assessed by the interventionist during the intervention and by performing routine follow up sonography depending on the type of intervention. In the recovery area, anaesthesiologists and nurses monitored the patient's vital parameters and controlled wound dressings before transferring the patient to the ward. At the ward, the responsible physicians and nurses documented the postinterventional course of the patients. Members of the study team visited the patients on the ward during their postinterventional observation to check for symptoms and signs of bleeding or other complications. Routine blood draws and the ward's complete documentation were assessed by the study team. In our centre, transjugular biopsies are routinely managed on an outpatient basis, which was not changed for patients included in this study.

Major bleeding was defined as an incidence of bleeding that fulfilled one or more of the following criteria:

- Bleeding requiring transfusion of blood products or coagulation factors
- Any intervention being necessary to staunch the bleeding
- Haemoglobin levels falling ≥ 2g/dl compared to the levels measured 1h prior to the intervention

The following secondary outcome parameters were defined:

- Use of coagulation and blood products in the first three days after the intervention
- Incidence of bleeding complications over a period of 28 days after the intervention

- Correlation of bleeding complications with van Willebrand factor-, TEG- and thrombin generation-analysis at the time of the intervention
- Incidence of transfusion related events and thromboembolic events over a period of 28 days after the intervention
- 28-day bleeding- or thrombosis associated mortality
- Overall mortality

Secondary outcome parameters were determined by conducting follow-up calls 28 days after the intervention. Patients received a diary before their release from stationary care, in which symptoms of thrombosis and bleeding were specifically asked for and could easily be documented. The study team additionally assessed the available documentation in our hospital's data management system.

9.5.4 Drug Concentration Measurements

No drug concentration measurements were conducted during this trial. Clinical outcomes and their correlation to laboratory values and substitution regimes were the focus of our research.

9.6 Data Quality Assurance

The KKS was appointed with the monitoring of the study. A data safety monitoring board was established additionally with the purpose of evaluating interim analyses.

Data was entered into paper form CRFs and via clincase (© 2019 Quadratek Data Solutions Ltd) into an eCRF created specifically for this trial by the Medical University of Vienna's IT Systems and Communications Department (ITSC).

Members of the study team were trained to use the relevant documentation forms before taking part in the procedures of this study.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

Since this trial has been redefined as a pilot study due to slow enrolment, the collected and analysed data will be presented descriptively. Absolute and relative incidence of recorded events, mean, and standard deviation will be given.

For the initially planned sample size of 400 participants, the calculation of a two-sided 95% confidence interval for the difference of bleeding incidences between both groups was

planned. This method of analysis will not be possible with our reduced sample size and has been removed from later versions of the study protocol.

9.7.2 Determination of Sample Size

The initially planned sample size for this trail was 400 participants in total (200 per group). This was based on the expected incidence of major bleeding determined in the available literature at the time. A non-inferiority study with a one-sided significance level of 2.5% would have required a sample size of 1507 participants per group. For reasons of feasibility, a sample size of 400 patients in total was decided on, which would have allowed the calculation of a two-sided 95% confidence interval for the difference of bleeding incidences between both groups.

Due to slow enrolment, the sample size was further reduced and the character of the trial changed to a pilot study with 10 patients per group.

9.8 Changes in the Conduct of the study or planned analyses

As described in section 9.7.2, the sample size was reduced from 400 to 20 total participants, i.e. 10 per group. For this redefinition of the study character, a substantial amendment was submitted to the competent ethics committee (EK) on 01/07/2024 and to the competent authority (BASG) on 26/07/2024. The decision was made by the investigational team after it became apparent, that the inclusion of a total of 400 participants will not be feasible at our institution.

The trial was started with ‘manifest ascites’ as an additional exclusion criterion. This criterion was removed from the protocol by an amendment submitted to the EK on 17/02/2023 and in the further course to the BASG. The decision was made after it became clear that the exclusion criterion of manifest ascites was not well defined, as most patients who were eligible for this trial showed ascites to some degree and in some cases, ascites is one of the indicating factors for the liver intervention in the first place. This protocol change was thoroughly discussed within the investigational team, including our members from the Department of Internal Medicine III and was concluded to not put our patients under additional risk.

Before enrolment of the first patient, the trial was planned with two investigational PPSB-Products: Beriplex (Beriplex® P/N 500 I.E., CSL Behring GmbH) and Prothromplex (Prothromplex TOTAL 600 I.E., Takeda Manufacturing Austria AG). Due to changes made by the General Hospital’s Pharmaceutical Department, Beriplex was replaced by Cofact (Cofact 500 I.E., Prothya Biosolutions Netherlands B.V.). This amendment to our protocol was submitted to the BASG and EK on 07/11/2022. No patient of this trial has received Cofact as investigational drug.

10 STUDY PATIENTS

10.1 Disposition of Patients

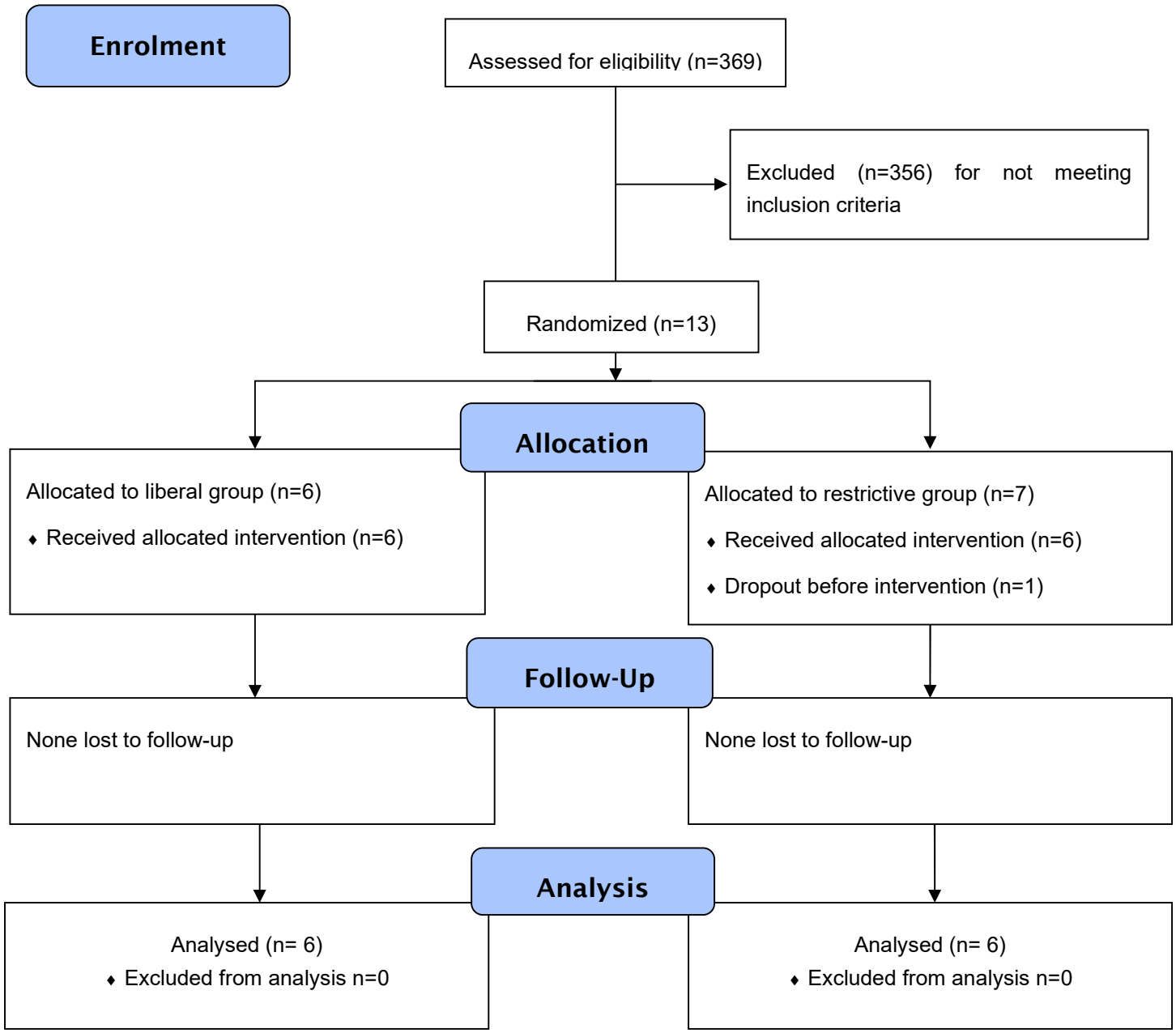

Figure 1 Disposition of patients

13 patients were included in this study and randomized. Of these 13 patients, 6 were assigned to the liberal and 7 to the restrictive substitution regime.

1 patient in the restrictive group died after randomization but before any study-related intervention.

1 of the 12 patients died 8 days after the intervention (not study related) and was not observed for the planned 28 days but was eligible for analysis, nonetheless.

10.2 Protocol deviations

No relevant deviations from the study protocol were observed. Time points for the administration of substitution (2 hours prior to intervention) and pre-intervention blood draw (1 hour prior to intervention) were adhered to as closely as possible in the course of peri-interventional patient procedures.

11 EFFICACY EVALUATION

11.1 Data Sets analysed

Due to the small study population, we were only able to perform a descriptive analysis of the data. Therefore, no exclusions (other than the 1 dropout before intervention) from our data set were necessary.

11.2 Demographic and Other Baseline Characteristics

11.2.1 Demography

Dropout not included in this table.

	Number of patients		
Age range	Male	Female	Total
18-39	1	0	1
40-59	5	1	6
60-79	4	1	5
>80	0	0	0

Table 2. Demographic patient data. Dropout not included in this table. Ethnicity was not recorded for this trial.

11.2.2 Anamnesis

All patients had a thorough anamnesis taken to assess possible exclusion criteria (see section 9.3.2). Conditions not listed in the exclusion criteria were not considered relevant for this trial.

11.2.3 Concomitant Medications and Diseases

Concomitant Medications were recorded in the CRF for every patient. Although permitted for inclusion in this trial, no patient was under therapy with acetylsalicylic acid. One patient under Apixaban had the medication paused for at least 48 hours before intervention and was therefore eligible for inclusion. One patient received Vitamin K1 prior to inclusion but still met the necessary laboratory parameters and was therefore kept in the trial.

11.3 Measurements of Treatment Compliance

As we used a single shot administration which was administered by the study team, treatment compliance was 100%. We did have 1 dropout though due to death prior to intervention (not study related).

11.4 Results and Tabulations of Patient Data

11.4.1 Tabulation of Patient Data

	Restrictive (n=6)	Liberal (n=6)
Age (years; mean (sd))	56 (9)	56 (15)
Sex (number (%))		
Male	6 (100)	4 (67)
Female	0 (0)	2 (33)
Height (cm; mean (sd))	181 (5)	178 (9)
Weight (kg; mean (sd))	83 (25)	84 (17)
BMI (kg/m2; mean (sd))	25.6 (7.8)	26.3 (3.9)
INR (mean (sd))	1,8 (0,3)	1,9 (0,3)
Fibrinogen (mg/dL; (sd))	248 (62)	175 (76)
Platelets (G/L; mean (min,max))	141 (35,288)	90 (59,114)
Hemoglobin (g/dl; mean (min,max))	12.4 (9.3,14.8)	9.6 (7.8,12.3)
VWF (%; mean (sd))	410 (128)	339 (73)
Protein C (%; mean (sd))	41 (23)	45 (17)
Protein S (%; mean (sd))	87 (40)	78 (14)
EXTEM CT (s; mean (sd))	69 (21)	69 (17)
EXTEM MCF (mm; mean (sd))	49 (12)	48 (6)
INTEM CT (s; mean (sd))	118 (67)	159 (51)
INTEM MCF (mm; mean (sd))	44 (15)	45 (5)
FIBTEM CT (s; mean (sd))	73 (20)	90 (57)
FIBTEM MCF (mm; mean (sd))	14 (4)	11 (4)

Table 3. Mean and standard deviation (sd) of demographic data and laboratory measurements of patients in both study groups.

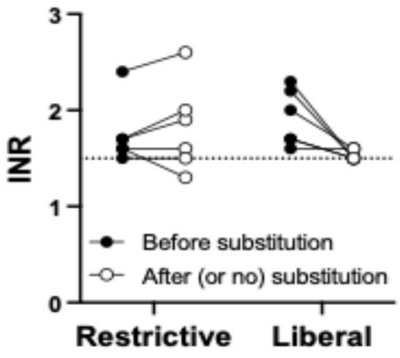

Figure 2. INR development from enrolment to intervention (with or without substitution).

11.4.2 Statistical/analytical issues

The small sample size precluded us from further statistical analysis.

11.4.2.1 Handling of Dropouts or Missing Data

We had one drop out before intervention and excluded this patient from any further analysis (beyond recording baseline blood values at the time of inclusion, which were available from routine laboratory investigations). We did not exclude patients from analysis due to missing data.

11.4.2.2 Interim Analyses and Data Monitoring

The KKS was appointed with the monitoring of the study. A data safety monitoring board was established additionally with the purpose of evaluating interim analyses. Due to the reduced sample size, no interim analyses were performed.

11.4.3 Drug Dose, Drug Concentration, and Relationships to Response

As shown above (section 11.4.1), substitution of PPSB using our INR-dependent formula reliably led to patients reaching the intended INR values.

11.4.4 Drug-Drug Interactions

We did not observe or suspect any drug-drug interactions in this trial.

11.4.5 Safety Conclusions

In our small sample size, we did not see any major bleeding in either study group when INR was between 1,5 and 2,0. One major bleeding occurred in the restrictive group with an INR of 2,6 (no substitution before intervention). One thromboembolic (portal vein thrombosis, seen on CT scan) occurred in the liberal group after administration of 252 I.U. of PPSB. Nevertheless, the remaining patients in this study group received up to 1520 I.U. of PPSB without clinical signs or incidental findings of thrombosis.

12 SAFETY EVALUATION

12.1 Extent of Exposure

The intervention of this trial consisted of withholding the routinely administered medical products. Patients were exposed to this intervention for a single administration or "non-administration" i.e. restriction at one specific time point during the course of their treatment or diagnostic procedure.

Treatment:	Number of patients:
liberal	6
restrictive	6
dropout before exposure	1

Table 4. Cumulative patient exposure

12.2 Adverse Events (AEs)

12.2.1 Brief Summary of Adverse Events

We observed a total of two adverse events and three severe adverse events during the course of this trial. One major bleeding occurred in the restrictive group, which ultimately ended in the patient's death. A thromboembolic event (incidental finding on routine CT scan) was ruled to be an adverse event, since no intervention was necessary, and the thrombosis resolved on its own without causing symptoms. Further, one incident of heart failure after the implementation of TIPS, one incidence of upper GI bleeding, occurring before any study related intervention, and one incidence of death due to Staphylococcus aureus sepsis during the 28-day observation period were recorded as adverse or severe adverse events, but do not suggest any relation to our intervention.

12.2.2 Display of Adverse Events

Patient ID	Event - Preferred Term	AE/SAE	Outcome	Group
COUCH-001	Thrombosis	AE	Resolved, no sequelae	Liberal
COUCH-003	Heat failure	AE	Resolved, no sequelae	Restrictive
COUCH-004	Major Bleeding	SAE	Death	Restrictive
COUCH-010	Upper GI Blood Loss	SAE	Death	Dropout before intervention
COUCH-011	Sepsis	SAE	Death	Restrictive

Table 5. Display of AE and SAE

12.2.3 Analysis of Adverse Events

We identified one major bleeding (COUCH-004) and one thromboembolic event (COUCH-001) as study related. The other AE or SAE (see 12.2.2) are not considered to be study related and are to be seen in the context of the severe morbidity of our study population and the high risk of the interventions themselves.

12.2.4 Listing of Adverse Events by patient

Patient ID: COUCH-001
Event: Thrombosis.
Male, 61 years, 168cm, 63kg. CRF locked in clinic archives.
Start AE 10.03.2023 (day 1 after intervention), **end** 17.04.2023.
Classification: Adverse event. **Action taken:** none. **Outcome:** resolved without sequelae.
Causality assessment: study related. The patient received 252 I.U. of PPSB to correct the INR before the intervention. This constitutes a relatively low dose of PPSB, but its contribution to the development of a thromboembolic event is still possible.
Randomisation and substitution: The patient was assigned to the liberal group and had received 252 I.U. of PPSB on 09.03.2023 prior to the intervention (MWA).
C**oncomitant medication:** Apixaban, Propranolol, Enalapril, Lorazepam, Spiolto, Substitol. Apixaban was paused for at least 48 hours before the intervention.

Patient ID: COUCH-003
Event: Heart failure.
Male, 43 years, 185cm, 93kg. CRF locked in clinic archives.
Start AE 14.04.2023 (day 1 after intervention), **end** 22.04.2023.
Classification: Adverse event. **Action taken:** ICU care. **Outcome:** resolved without sequelae.

Causality assessment: not study related. Heart failure was deemed to have occurred due to volume overload in this patient, which is to be seen as a consequence of the altered circulation after TIPS implantation.
Randomisation and substitution: The patient was assigned to the restrictive group and received no study medication prior to the intervention (TIPS).
Concomitant medication: Pregabalin, Furosemid, Oxazepam, Morphin (Substitol).

Patient ID: COUCH-004
Event: Major bleeding.
Male, 55 years, 177cm, 70kg. CRF locked in clinic archives.
Start SAE 26.04.2023 (day 1 after intervention), **end** 11.05.2023
Classification: Severe adverse event. **Action taken:** ICU care, interventional and surgical bleeding control. **Outcome:** death.
Causality assessment: study related. The incidence of major bleeding events was the primary outcome parameter of this trail and, in this patient, occurred with an uncorrected INR of 2,6 prior to the intervention.
Randomisation and substitution: The patient was assigned to the restrictive group and received no study medication prior to the intervention (percutaneous liver biopsy).
Concomitant medication: Neurobion, Pantoprazol, Aldactone, Carvedilol, Lactulose, D3, Colidimin, Hepamerz, Fresubin.

Patient ID: COUCH-010
Event: Upper GI blood loss.
Female, 61 years, 164cm, 71kg. CRF locked in clinic archives.
Start SAE 28.05.2024 (drop out before study intervention), **end** 04.07.2024.
Classification: Severe adverse event. **Action taken:** information not available (drop out). **Outcome:** death.
Causality assessment: not study related.
Randomisation and substitution: The patient was assigned to the restrictive group, received no study medication and dropped out prior to the intervention.
Concomitant medication: Trimbow, Euthyrox, Ursofalk, Spironolacton, Carvedilol, Candesartan, Laevolac, Lasix, Bezalip, Serevent.

Patient ID: COUCH-011
Event: Sepsis.
Male, 71 years, 184cm, 111kg. CRF locked in clinic archives.
Start AE 12.07.2024 (estimated, patient discharged on 11.07.), **end:** 17.07.2024.
Classification: Severe adverse event. **Action taken:** readmission to hospital care, antimicrobial sepsis control. **Outcome:** death.
Causality assessment: not study related. Withholding substitution of coagulation factors is not related to sepsis.

Randomisation and substitution: The patient was assigned to the restrictive group and received no study medication prior to the intervention (TIPS).
Concomitant medication: Escitalopram, Lasix, Spironolacton, Laevolac, Tamsulosin, OleovitD3, Neuromultivit, Colidimin, HepaMerz.

12.2.5 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

COUCH-004

A male patient, 55 years old, was identified to fulfil the enrolment criteria and was assessed and randomized on 24.04.2023. The patient was assigned to the restrictive substitution group of the trial. He was scheduled to undergo CT-guided percutaneous biopsy of lesions in his liver on the following day (25.04.). The intervention was performed as planned and the patient was admitted to the ward for postinterventional care. A sonographic checkup on the ward showed no signs of bleeding.

During the night, the patient attracted attention for being hypotensive. Laboratory investigations showed reduced haemoglobin levels, which prompted immediate radiologic diagnostic measures that showed several active arterial and venous bleeding sites at the liver. Interventional measures to control the bleeding were started immediately and coiling of the culprit vessels was deemed successful. The patient did, however, remain unstable, was admitted to the intensive care unit and received extensive transfusion of red blood cell concentrates and coagulation products (without any study-related restrictions, as is the protocol once a bleeding complication is discovered). The patient subsequently underwent several interventions to control the recurrent bleeding using angiographic techniques and open surgery.

While at the intensive care unit, the patient's liver function further declined, and his condition was additionally complicated by renal and respiratory failure which culminated in multiorgan failure and his death on 11.05.2023.

COUCH-010

A female patient, 61 years old, was identified to fulfil the enrolment criteria and was assessed and randomized on 27.05.2024. The patient was assigned to the restrictive substitution group of the trial and was scheduled for MWA on the following day (28.05.).

Before the intervention could be performed, the patient showed signs of bleeding (significant reduction in haemoglobin levels pre-intervention), and the procedure was postponed to investigate the patient for the suspected bleeding. No study related intervention (except screening and assessment on 27.05.) had taken place at this time.

Acute upper GI-bleeding was diagnosed in the following investigation. The patient dropped out of the study as soon as bleeding was suspected on 28.05., since the elective MWA was no longer possible and any sign of recent or current bleeding is an exclusion criterion for this trial. The patient received standard care without any restrictions including endoscopic

bleeding control but died subsequently due to the combination of severe liver disease and acute intestinal bleeding on 04.07.2024.

COUCH-011

A male patient, 71 years old, was identified to fulfil the enrolment criteria and was assessed and randomized on 09.07.2024. The patient was assigned to the restrictive substitution group of the trial and was scheduled for TIPS later the same day.

The intervention was conducted without any reported events, the postinterventional observation took an unremarkable course and the patient was discharged from hospital care on 11.07.

On 15.07. (day 6 after intervention), the patient presented with hypotension and reduced general state of health. He was readmitted to stationary care and after an initial symptomatic therapy, the diagnosis of Staphylococcus aureus sepsis was made. The patient received standard care without any study-related restrictions but died two days later (17.07.) of sepsis.

12.2.6 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

The death of patient COUCH-004 has been thoroughly discussed within the study team. Since the major bleeding event was related to the intervention, the SAE is considered study related. The occurrence of major bleeding events was the primary outcome parameter of this trial and bleeding events are a well-known complication of the several elective interventions included in this study. The patient received intensive medical care without study related restrictions but died due to multiorgan failure several weeks after the intervention.

The clinical course of this patient needs to be seen in context of the severity of the preexisting liver disease including a periinterventional diagnosis of spontaneous bacterial peritonitis and the poor overall prognosis for patients with end stage liver disease without possibility for transplantation, as was the case in this patient. The difficulty to manage medical complications in patients with end stage liver disease becomes evident from the multitude of complications that followed in the weeks after the intervention.

The deaths of patients COUCH-010 and COUCH-011 are not considered study related and the relevant information is given in the sections above.

12.3 Clinical Laboratory Evaluation

12.3.1 Overview Over Laboratory Measurements

In this trial we measured several laboratory parameters related to haemostasis. In each patient, baseline parameters were checked for meeting inclusion criteria and, if applicable,

to calculate the dosage of coagulation products for substitution. The inclusion criteria and methods of substitution are found in the study protocol (Appendix 15.1.1).

The following laboratory parameters were measured and documented for each patient:

Baseline values (at the time of inclusion or recent values before assessment and inclusion in the trial): Platelet count, INR, fibrinogen.

Values 1h before intervention (i.e. after substitution, if applicable): TEG Parameters (INTEM, EXTEM, FIBTEM), platelet count, INR, fibrinogen, haemoglobin, vWF, protein C and S. A sample to measure thrombin generation was also taken and frozen for later analysis in an external laboratory.

Further laboratory diagnostics post intervention were performed at the responsible clinician's discretion and were not part of the study protocol.

12.3.2 Evaluation of Effect of Substitution of Coagulation Factors

Patient ID	Substituion	INR change	Fibrinogen (mg/dl) change	Bleeding/thrombosis?
COUCH-001	PPSB 252 I.U.	1,7 -> 1,5	-	Thrombosis
COUCH-002	Fibrinogen 123 mg, PPSB 980 I.U.	2,2 -> 1,5	117 -> 117	-
COUCH-003	-	-	-	-
COUCH-004	-	-	-	Bleeding
COUCH-005	-	-	-	-
COUCH-006	-	-	-	-
COUCH-007	-	-	-	-
COUCH-008	Fibrinogen 335mg, PPSB 1520 I.U.	2,3 -> 1,5	114 -> 119	-
COUCH-009	Fibrinogen 833 mg, PPSB 1090 I.U.	2,0 -> 1,6	107 -> 109	-
COUCH-010	**dropout**	-	-	-
COUCH-011	-	-	-	-
COUCH-012	PPSB 166 I.U.	1,6 -> 1,6	-	-
COUCH-013	PPSB 324 I.U.	1,7 -> 1,5	-	-

Table 6. Overview of the effectiveness of our substitution regime. Formulas for calculating the dose of PPSB and fibrinogen are found in the study protocol.

All patients who received PPSB to correct an elevated INR had an adequate response to our substitution regimen. We aimed for an INR of 1,5 in patients who received PPSB and observed INRs of 1,5-1,6 1h after substitution. Fibrinogen levels were only slightly reduced in our patients and therefore only relatively low doses of fibrinogen were substituted where necessary with a goal of 120mg/dl 1h after substitution.

Our results are displayed descriptively. Due to the low number of participants, no further statistical analysis was conducted.

12.4 Safety Conclusions

We observed one thromboembolic event in the liberal substitution group and one bleeding event in the restrictive substitution group of this trial. Participants in this trial had a severe underlying disease and are prone to spontaneous bleeding events as well as thromboembolic events.

It should be noted that the bleeding event occurred in a patient with a relatively high (compared to the study population) INR of 2,6 and that a concurrent diagnosis of spontaneous bacterial peritonitis was later made from the ascites of this patient.

One patient had a coincidental finding of portal vein thrombosis without clinical symptoms. It is unclear, whether the relatively low dose of 252 I.U. of PPSB contributed to or caused the thrombus formation in this case.

A spontaneous GI bleeding occurred in Patient COUCH-010, which therefore dropped out of the study and had no study related interventions (see 12.2.5 “Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events”). This event is not study related, but further underlines the severity of the underlying disease in our study population.

We observed no allergic reactions or unexpected adverse effects related to the study medication.

Due to the low number of participants, no further statistical analysis was conducted.

13 DISCUSSION AND OVERALL CONCLUSIONS

In this study, we included patients with severe liver cirrhosis, who were scheduled for an elective intervention of the liver. Patients with severe liver cirrhosis are prone to bleeding events as well as thromboembolic events due to impaired synthesis of both pro- and anticoagulatory factors in the liver. Standard laboratory testing, however, is neither appropriate nor intended to properly reflect the entirety of the rebalanced haemostasis in these patients. The implication of deranged standard laboratory coagulation tests for the peri-interventional management of these patients is not sufficiently understood.

Our goal was to assess the risk of bleeding in these patients when treated with a liberal vs. restrictive regimen of substitution of coagulation factors and platelets. Furthermore, we intended to gather data on the risks of thromboembolic events in liver cirrhosis patients after receiving coagulation factors.

During the course of this trial, we observed one peri-interventional major bleeding event in a patient with an INR of 2,6, one clinically non-significant thromboembolic event in a patient

after receiving a very low dose of PPSB, and several uneventful liver interventions in both restrictively and liberally substituted patients.

Due to slow enrolment, we had to greatly reduce the number of patients included in this study. Therefore, no statistical analysis beyond descriptive display of our results was conducted and further investigations are necessary to conclude whether a restrictive approach to coagulation substitution is safe in the described study population.

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15 APPENDICES

15.1 Study Information

15.1.1 Protocol

15.1.2 Protocol Amendments

15.1.3 Sample Case Report Form

15.1.4 Representative Written Information for Patient and Sample Consent Forms

15.1.5 List and Description of Investigators and Other Important Participants

15.1.6 Randomisation Scheme and Codes (Patient Identification and Treatment Assigned)

15.2 Patient Data Listings

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15.2.5 Adverse Event Listings