Vital Therapies Inc.

Protocol

Protocol No.	VTIC-301
Study medical device	ELAD® （Extracorporeal Liver Assistance Device）
Subject	Multi-center, randomized, controlled and open-label study of ELAD® biological artificial liver in the treatment of ACLF patient with hepatic insufficiency and hepatic failure
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Glossary of terms and list of abbreviations

List of abbreviations	Defination
AAG	Alpha1-acid glycoprotein
AAT	Alpha-1 Antitrypsin
ACLF	Acute on chronic liver failure
AE	Adverse event
AFP	Alpha fetoprotein
ALB	Albumin
ALP	Alkaline phosphatase
ALSS	Artificial liver support system
ALT	Alanine aminotransferase
AMG	Alpha 2 macro globin
ANA	Anti nuclear antibody
APACHE	Acute physiology and chronic health evaluation
APOB	Apolipoprotein B
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CER	Ceruloplasmin
CHE	Cholinesterase
CHO	Cholesterol
CMV	Cytomegalovirus
CO_2CP	Carbon dioxide combining power
CRF	Case report form
CRO	Clinical research organization
CRP	C reactive protein
CSH	Chronic severe hepatitis
CTP	Child-Turcotte-Pugh score
DCF	Data clarification form

EBV	Epstein-Barr Virus
EC	Ethical committee
ELAD	Extracorporeal liver assistance device
GCP	Good clinical practice
GCS	Glasgow Coma Score
GGT	Gamma-glutamyl transpeptidase
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDV	Hepatitis D virus
ICF	Informed consent form
INR	International Normalized Ratio
ITT	Intent-To-Treat population
MELD	The model for end-stage liver disease
NEU	Neutrophil
PaO_2	Partial pressure of oxygen in arterial blood
PP	Per protocol population
PTA	Pro- thrombin activity
SAE	Serious adverse event
SAF	Safety population
SFDA	State food and drug administration
SOFA	Sepsis-related organ failure
TBil	Total bilirubin
TRF	Transferrin
ULN	Upper limit of the normal range
VTI	Vital Therapies，Inc.
WBC	White blood cell

1.BACKGROUND

It is widely known that China has 120 million HBV carriers and chronic hepatitis B patients, and 38 million hepatitis C patients. Approximately 0.1%～0.5% of these patients would experience severe hepatitis due to acute hepatocellular necrosis or hypofunction, which results in hepatic insufficiency and hepatic failure. The acute developed hepatic failure that develops on the basis of chronic viral hepatopathy, is named as “chronic severe hepatitis” in China, or referred to “acute on chronic liver failure，ACLF” on some international publications. This is one of most common type of hepatic failure in China, whose pathogenesis, treatment and prognosis are quite different from those of drug-induced acute liver failure, which is commonly seen overseas. The chronic severe hepatitis is difficult to treat with poor prognosis. Currently, the primary treatment strategy is comprehensive physical treatment in combination with non- biological artificial liver support therapy in order to promote the spontaneous recovery of liver and help the patient go through the crisis of the disease; if the liver damage is difficult to be recovered, the artificial liver support should be transferred into liver transplant. Currently, the total effective rate of comprehensive treatment which refer to physical treatment plus non- biological artificial liver still stays around 50％～70％.

Artificial liver technique is a recently-developed extracorporeal liver support technique. With extracorporeal mechanical, chemical or biological equipment, it could temporarily replace or partially replace the function of liver, thereby, to provide assistance in the treatment of hepatic insufficiency or relevant diseases. The primary difference between artificial liver and general physical medication lies in that, the former is by “functional replacement” and the latter is by “functional reinforcement”. Since the artificial liver takes extracorporeal support and functional replacement as its priorities, it is also known as artificial liver support system (ALSS). According to the formation and properties of the artificial liver, it could be classified into three types, ①non-biological type, also known as physical artificial liver. It works mainly by physical or mechanical means, including plasma exchange, direct hemoperfusion/plasma absorption, hemofiltration, molecular adsorbent recycling system (MARS) and etc. ②biological type bind the biological parts, such as homogenous or heterogeneous liver cells, with synthesized materials to form a specific equipment, the blood or plasma of patients would experience substance exchange and detoxification with extracorporeal cells through this equipment; ③mixed type, with the combination of both biological and non-biological types, this type of ALSS has both of their functions. Some suggest that since method like plasma exchange, supplements some biological active components like clotting factors while eliminating harmful substances, it could be classified as one type, i.e. intermediate or transiting artificial liver. Several clinical evidences have demonstrated that, compared with physical medication, the artificial liver could significantly improve the survival rate of early and middle stage liver failure, with a total

effective rate of 51％～69%. However, the clinical efficacy of all of these artificial liver techniques which work mainly by detoxification but can not replace other function of liver such as synthesis, transforming, secretion is unsatisfactory. Therefore,it is a common goal for both clinician and biomedical engineering researcher to develop a kind of liver support system that can fully imitate normal function of human liver.

Recently-developed ELAD® liver support system, Vital Therapies，Inc. US, is a biological artificial liver that applies ELAD® cartridge which contains C3A human hepatocellular strain for continuous liver support therapy. The C3A cell strain (US patent No. 5,290,684) ,originated from liver tumor, is a kind of well-differentiated and immortal cell strain, and it has been proved by experiments to have several normal functions of hepatocyte: such as synthesizing albumin, transferring, clotting factor Ⅴ and Ⅶ, antifibrinolysin 3, complement C3, α-1antitrypsin, alpha-fetaprotein and etc. Moreover, the cell also has many important metabolizing passages that are close to the normal level, such as gluconeogenesis, urea synthesis and the metabolism of glucose, galactose and lidocaine. Further cell examination indicates that the cell doesn't contain any foreign human pathogenic microorganisms. Up to now, about 80 patients have been treated with ELAD biological artificial liver in phase Ⅰ and Ⅱ clinical trials in US and Europe. Results indicate that, ELAD is safe, effective and tolerable in the treatment of acute hepatic failure.

As mentioned above, the type of hepatic failure in China is quite different from that overseas, therefore, though ELAD biological artificial liver has been preliminarily demonstrated to be safe and effective overseas, its safety and efficacy in patients with chronic severe hepatitis, hepatic insufficiency & hepatic failure which is common in China has still not be evaluated by clinical study. In order to furtherly evaluate the safety and efficacy of ELAD® biological artificial liver, a multi-center, randomized, control clinical study, approved by the State Food and Drug Administration, will be conducted.

2. OBJECTIVE

To study the efficacy and safety of ELAD® liver support system in the treatment of acute severe hepatic insufficiency and hepatic failure developed on the basis of chronic viral hepatopathy. To emphasis on efficacy。

3. PROTOCOL

3.1 STUDY SUBJECTS

Patients on early or middle stage of severe hepatitis.

Obvious gastrointestinal and/or systemic toxic symptoms; PTA> 20％ and ≤ 40%;

TBil＞10mg/dL, or the daily increase of TBil > 1mg/dL.;with minimal-moderate volume ascites; Without hepatoencephalopathy, or encephalopathy below Grade II（including Grade II）.

Patients of chronic hepatitis B (severe): PTA> 40％and ≤ 50%; TBil＞5XULN,

The diagnosis criteria are based on the “Guidelines for the treatment and prevention of viral hepatitis”, conference of national viral hepatitis, 2000.

Explanation:

- Various acute & chronic hepatic insufficiency and hepatic failure is the main life threating diseases in patients with hepatitis in China. Mortality is still high although non-biological artificial liver show some curative effects on these patients while physical treatment is not very effective .So it is necessary to conduct biological artificial liver study.
- The late stage of chronic severe hepatitis is too severe to be used for evaluation of ElAD. These kinds of patients will not be included.
- Patients of chronic hepatitis (severe) with PTA> 40％and ≤ 50% has tendency to develop into severe hepatitis. There is remarkable significance to stop the progress of hepatopathy. In order to study the effect of ELAD on stopping this process. This type of patients will be included.

3.2 CASE SELECTION

3.2.1 Inclusion criteria

- Chinese citizen, male or female, age range 16-65 y (including 16y and 65y); can afford the expense of basic treatments except ELAD.
- Acute, sub-acute, acute on chronic (i.e., chronic severe hepatitis) hepatic insufficiency and hepatic failure caused by various reasons; e.g., virus, alcohol, drug or inherited metabolic disease.
- Obvious gastrointestinal and/or systemic toxic symptoms
- TBil≥5XULN,, or the daily increase of total bilirubin > 1mg/dL（17.1μmol/L）.
- Prothrombin time activity（PTA）> 20％ and ≤ 50%; or INR> 1.6 and ≤ 4.0 , or PT ≥ 5 sec. and 20 sec. longer than control.
- Without hepatoencephalopathy, or encephalopathy below Grade II（including Grade II）.
- Without or minimal-moderate volume ascites/ pleural effusion.
- Patient or its legal representative could understand and sign the informed consent form, could exchange information with the investigator, could understand and cooperate the implementation of the clinical trial.

3.2.2 Exclusion criteria

- Primary or metastasis liver cancer.
- with medical history of Definite decompensated cirrhosis. (have one of followings : PTA<60%, TBil>2xULN; bleeding; hepatoencephalopathy; ascites).
- Slowly progressed hepatic cirrhosis and hepatic failure.

- Existence of uncontrolled severe infection, such as septicemia, pneumonia (after appropriate treatment of antibiotics, X-ray shows no improvement), abdominal cavity infection (after appropriate treatment of antibiotics, still have signs of peritonitis or White Cells of ascites>$0.1X10^9$ /L), and etc.
- Shock
- Active gastrointestinal bleeding (OB positive) or obvious bleeding in other sites within three days .
- Grade III and Ⅳ hepatoencephalopathy
- Platelet < 50×10^9/L
- Creatinine > 1.5mg/dL
- Severe esophageal varices; positive red signs while bleeding may occur in the near future.
- Besides liver damage, there exists any other severe active physical or mental diseases that might affect the treatment, evaluation or compliance on the discretion of the investigator, including any uncontrolled clinically significant primary renal, cardiac, pulmonary, vascular, nervous, digestive, metabolic diseases (obvious hyperthyroidism, severe diabetes and adrenal gland disease)and immune deficiency or cancer.
- Unable to cooperate in the trial or follow-up.
- Highly allergic to heparin or protamine.
- Planned to undergo liver transplantation or has undergone liver transplantation within 3 weeks before screening.
- Pregnancy or lactation
- Other non-biological artificial liver and relevant blood purification treatment within 3 days before screening
- Still in or has participated in any trials of investigational drugs within 3 months before screening.
- Unsuitable for the treatment according to other doctors.

3.2.3 Withdrawl of subjects from study

The trial will be discontinued permanenty for the following reasons:

- Ineligible for the inclusion criteria that is discovered during the trial.
- According to the principle of informed consent and the spirits of Declaration of Helsinki, those unwilling to cooperate with the investigator to complete the whole trial or requiring withdrawal could be dropped out.
- Any other conditions that might interfere with the evaluation on safety and efficacy of ELAD treatment occur during the trial.
- Liver transplantation
- Death

3.2.4 Discontinuation criteria of ELAD treatment

- ELAD has lasted for over 3 days, and the clinician believes that the medical condition has been significantly improved which needs no further treatment: e.g. symptom has been improved significantly PTA>60%, no hepatoencephalopathy, albumin >32g/L, no worsening or even decreased jaundice.
- Continuous worsening of the medical condition, the clinician believes that the

treatment needs to be changed or there is no need to continue with the treatment. After the consultation with the patient and its family, the treatment can stop.

- Comes to 10 days.
- Severe bleeding, shock or other severe adverse events that is life-threatening occur during the trial.
- Intolerable to the treatment.

3.3 TRIAL DESIGN

Trial type ： prospective, randomized, controlled, open-label, multi-center clinical trial
Sample size and grouping: 90 cases of patients with severe hepatic insufficiency and hepatic failure and who is eligible for the inclusion criteria (60 cases for treatment group, 30 cases for control group).
Sample size issues:
The minimum No. of case asked by statistics is 40 for each group. Considering the other factors such as withdrawl we select 60 cases as the minimum No. The minimum No.of case is based on the result of phase I and II clinical study in US which has 70 cases or more. Since there exists parallel control with control group and itself control before and after treatment in treat group 90 cases can meet the requirement of statistics.Based on the result of preceding study, patients will be randomized into treatment group or control one in a 2:1 ratio and the study will enroll 90 patients totally which could elementarily meet the statistics requirement.

Randomization:

A randomization list will be created by EXCEL Data Management Dept. with block randomization method before the clinical trial begins .Upon enrollment, each subject, who meets all the inclusion and exclusion criteria, will be assigned a unique number (subject randomisation No.) corresponding to the chronological order of study entry. This subject randomisation No. corresponds to the subject.Once assigned, patient numbers will not be reused.

The original randomization list and/or computer file will be kept securely at Excel data management Dept. and anyone could not access the randomisation list except for authorized persons who are not involved in the project.

3.4 TREATMENT PROTOCOL

Treatment group：

First step: plasma exchange: in terms of the principle of individuation（exchange volume: about 2500ml～3000ml）, blood velocity: 100ml/min, plasma velocity: 30ml/min, treatment duration: about 2 –3 hours.

Second step: continuous vein-vein hemofiltration: pre/post-dilution: blood velocity: 120ml/min, substitute fluid velocity: 2L/h, treatment duration: 2-8 hours, ultrafiltration volume depends on individual medical condition.

Third step: ELAD biological artificial liver treatment: blood velocity: 120ml/min～

150ml/min, plasma velocity:40 ml/min～50ml/min, treatment duration: 3-10 days according to medical condition on the discretion of doctor.ELAD will be provided by VTI freely.

Control group：only the first and second steps, no ELAD treatment.

Follow-up period: Both group will be followed for 12 weeks (start from first of plasma exchange)

Explanation:

The finally recovery of patients with chronic severe hepatitis and hepatic failure depend on the regeneration of the liver cell. Therefore the main function of the ELAD biological liver lie in partially replacing the function of liver temporary, stabilizing the inner environment and benefit from liver regeneration. Treatment duration should be adequate or else liver could not regenerate sufficiently. So the minimum duration of ELAD treatment is defined to 3 days The maximum treatment duration, limited by human resources, materials and study duration, is defined to 10days.Recent survival rate of severe hepatitis and hepatic failure is calculated by periods of 12 weeks, 24weeks and 48 weeks. Follow up duration is defined to 12 weeks with the limit of the study duration.

Comprehensive and fundamental physical treatment：

Since subjects of the trial are patients with life-threatening hepatic insufficiency and hepatic failure, adequate and reasonable comprehensive physical treatment must be administered in combination with the treatment of artificial liver in order to ensure the vital interests of the subjects. The protocol of physical treatment is consistent between the treatment group and the control group.

①Try to ensure adequate oral/intravenous calorie supplementation, as well as adequate vitamins and microelements.

② Alternative drugs: VitK, hepatocyte growth-promoting factors, antiacids, glycyrrhizin preparations, vitamins, antiviral agents(Lamivudine 100mg/d，Adefovir Dipivoxil or entecavir Baraclude(0.5-1.0mg/d)could be used while virus variation occur caused by Adefovir Dipivoxil), anti-inflammation agents, hemostats, amino acid, potassium magnesium aspartate, immune modulators, intestinal flora regulators, lactulose, detoxification agents and etc.

③Albumin, plasma, Prothrombin Complex and Fibrinogen and etc. could be used according to medical condition But the time, times and total dosage used should be recorded clearly.

④Oxygen inhalation when necessary.

⑤Abdominal paracentesis when infection of abdominal cavity, severe abdominal inflation that affect respiration and circulation occur.

⑥ Record physical treatment timely. Concomitant drug's name, dosage, administration, duration should be recorded on both medical record and case report form in details as well as changes of dosage of concomitant drugs. Concomitant drug

record could be replaced by order sheet when necessary.

3.5 ITEMS AND MEASUREMENTS TO BE OBSERVED

Observed measurements：

Product reliability measurements: stability of each of the treatment parameters and etc. In order to keep the consistence with the current good clinical practice, Site will depend on the supplement of C3A biological reactor. The delivery, storage, application and return or disposing will be recorded carefully according to the standard operation procedure during product reliability test. Copies of product reliability test record will be provided to sponsor.

Safety measurements: adverse event (various hemodynamical parameters, uncomfortable symptoms, abnormal signs, abnormal lab examinations, various parameter s of instrument, circulation pipeline, tolerance to long treatment duration.

Efficacy measurements: including symptoms, signs, biochemical measurements, clotting measurements, immune measurements, blood-air analysis, Ammonia, GCS, MELD, CTP, APACHE and SOFA scores, abdominal ultrasonic, survival rate, survival time. (see appendix 2 for details).

.**Record schedule：** record various items and instrument parameters timely (see appendix 3 for details).

3.6. EVALUATION CRITERIA

3.6.1 Safety evaluation

- Treatment parameters and circulation pipe should be recorded regularly.
- All the adverse events should be recorded on the Case Report Form starting from the screening period to the end of trial.（including screening period）according to relative regulations. Including bleeding, blood pressure decrease, shock, fever, skin rash, infection, renal failure, hepatic carcinoma ,abnormal lab values and etc..
- The severity of the adverse events should be graded according to the “WHO toxicity grading criteria”.
- The tolerance of patient in such a long time.
- Serious adverse event.

3.6.2 Efficacy evaluation

Primary endpoint:

PTA of baseline VS PTA of fourteen days(the treatment duration will be calculated from the day when plasna exchange is conducted. PTA, which is no more than 24 hour prior to the initiation of plasma exchange, is defined as baseline.

Secondary endpoint:

1. MELD、CTP、APACHE、SOFA、Bilirubin,Albumin,, PA、CHE、INR、APTT、FIB、C3，C4， AAG， AAT， APOB，TRF， CER，ammonia，every symptoms,signs(fatigue, Anorexia, Nausea, vomiting, Abdominal flatulence：Hiccup, Nose/gum bleeding：Skin itching, hepatoencephalopathy, ascites of baseline VS these on day 14). The result of measurements above, which is conducted no more than 24 hour prior to the initiation of plasma exchange,are defined as baseline before treatment.

2．Survival time

3．Survival rate

4. Other items still should be valued by statistics according to clinical requirement.

3.7 STUDY PROCEDURE

First step: Screening period (day-14~day-1)

- Screen patient by inclusion and exclusion criteria firstly
- Sign informed consent form
- Collect Medical history: including current and previous medical history, system review, concomitant disease.
- Physical examination (including height,weight and vital signs)
- Lab examination and other assistant examination
- Record adverse event and concomitant drug;
- Recheck patient condition by inclusion and exclusion criteria
- Enrollment

Second step: Randomization（Day –1）:

- Recheck patient condition by inclusion and exclusion criteria;
- Disclose randomization letter, assign patient into different group according to the content of letter;
- Call VTI immediately for delivery of ELAD catridge once the patient is assigned into ELAD treatment group.
- Non biological artificial liver treatment will be conducted as soon as possible once the patient is assigned into control group (start within 24h in principle).
- Record adverse event and concomitant drug;

Third step: treatment period (day1-10)

Control group	Treatment group
Plasma exchange and continuous vein-vein hemofiltration Lab examinations before and after PE & CVVHF	Plasma exchange and continuous vein-vein hemofiltration on day 1. Lab examinations before and after PE & CVVHF but prior to ELAD treatment Biological artificial liver treatment initialtion on day 2 Record biological artificial liver treatment.
Symptoms,signs,lab examination and other assistant examination ((See fowchart for details)	Symptoms,signs,lab examination and other assistant examination(conduct and record blood routine,cloting measurement and serum examination on the preceding 5 days and then every 2 day until ELAD treatment finishes,if ELAD treatment stop in advance conduct examinations above every 3 day until day 14.Day 5,10,14 will has more,please has more in appedndix 3)
Record concomitant medication (daily)	Record concomitant medication (daily)

Record adverse event since last visit(daily)	Record adverse event since last visit(daily)
	Confirm dicontinuation criteria, stop ELAD treatment.

Fourth step: Follow up period (treatment group: from the end of ELAD treatment to the end of follow up period, control group: from day 14 to the end of follow up period)

The following evaluation will be done on second, forth, eighth and twelveth week:

survival rate, symptoms, signs, lab examination and other assistant examinations,

Record adverse event and concomitant drug,finish follow-up.

3.8 ADVERSE EVENTS THAT PROBABLY OCCURS

- Bleeding: Following medication could be used individually or collaboratedly according to the reason and the severity of bleeding: stop to use heparin, use protamine against heparin, prothrombin complex, platelet, Hemocoagulase, Etamsylate,Vitamin K and other hemostasis medication, antiacids, Trial will be discontinued and correspondent hemostasis and other emergent treatment will be conducted once bleeding occurs continually or massive haemorrhage occurs.
- Hypotension: increase blood volume, use drug that increase BP, if there is still no improvement after treated with these medication ELAD treatment will be discontinued temporary or permanently while blood in extracorporeal circulation will be returned to patient.
- Shock：ELAD treatment will be discontinued immediately, blood in extracorporeal circulation will be returned to patient while increase blood volume rapidly, adrenaline, dopamine , other vasoactive drugs and glucocorticoid will be used as necessary.
- Fever: Use physiotherapy for low-grade fever, NSAIDs for high-grade fever, Analyze reason of the fever and treat it correspondingly
- Skin rash: just care patient with mild condition, treat patient with severe condition using antihistamine drug
- Infection:Increase nutrition, body resistance, administer sensitive antibiotics against pathogens.
- Renal failure: avoid to administer renal toxic drug, keep enough blood volume, treat with hemodialysis or hemoperfusion as necessary.
- Hepatic carcinoma: follow up regularly, examine AFP monthly, ultrasonics examination on third months, conduct liver puncture and then analyze by histopathology if applicable, study the type of tumor cell and analyze its resource
- Blood coagulation: exchange the pipe.

3.9 DATA MANAGEMENT

- Investigatior should complete CRF entry timely according to the data of source data and ensure its correctness, completeness and clearness.
- Monitor should inspect that the trial would be carried out in compliance with the protocol, confirm correctness and completeness of all CRF which should be consistent with source data, ask the investigator to correct the error and missing information timely while the original record corrected should be easy to seen. Any correctness should be signed and dated by investigator.
- Finished CRF should be transmitted between investigator, monitor and data management dept. with a spcial record. The record should be kept in study file.
- Double entry should be used for all CRF. Data audit should be conducted by computer programmme. Query and the answer to query will be conducted in the form of Data Clarification Form (DCF) which will be informed to monitor timely and be answered by investigator. DCF will be kept for inspection.
- Database will be locked once all of query has been clarified,quality control has been completed and qualified which means primary efficacy data and safety data are 100 percentage of correct, Error ratio of 10 percentage of non key data sampling is not over 0.5％.The data that has been locked will not be changed any more.

3.10 STATISTICS ANALYSIS

3.10.1 Selection of statistic analysis data

① Full analysis set(FAS): All randomised patients who have baseline record and receive treatment will be used for this efficacy analysis using the Last Observation Carried Forward (LOCF) according to Intent-to-Treat (ITT) Population.. The analysis of each efficacy variable will be performed on this data set.

② Per-protocol set(PPS): Patients without any major protocol violation will be included in the per protocol set, including those patients who have good treatment compliance, who do not take any prohibited medications during the study period and whose CRF are complete as requested.

③ Safety set（SFS）: Safety Population: All patients who were randomized and treated once will be used for this analysis set. The analysis of the safety variable will be preformed on this data set.

3.10.2 Statistics method

① For the classification data, non-parametric method should be applied for the comparison between pre-treatment and post-treatment conditions.

② Normality test should be applied in the analysis of the differences in quantitative measurements, and if it takes on normal distribution, central effect variance analysis should be applied; if it is non-normal distribution, non-parametric statistical method should be applied.

③ Safety data should be described statistically.

④ All the cases that have not completed the trial due to various reasons should be considered as withdrawl, cases that have experienced adverse events should be included in the statistics of adverse events.

⑤ Log－Rank test and COX proportional risk model should be applied in the survival analysis.

Detailed statistics method will be described on statistics analysis plan.

4. STUDY SCHEDULE

12 months

Feb.14, 2006 － Sep. 30th, 2006 case recruitment and enrollment

Oct. 1st, 2006 － Dec. 31th, 2006 follow-ups

Jan. 1st, 2007 － Jan. 31th, 2006 database establishment, statistical analysis and trial summary writing

5. RISKS AND BENEFITS OF THE TRIAL

5.1 RISKS

Just like any other developing product, known and yet unknown risks and side effects may occur during the trial process of ELAD artificial liver. These risks and side effects may be quite severe, lasting and even life-threatening. The possible special risks observed in previous animal and human trials include:

5.1.1 Severe hepatitis hepatic failure itself is a severe disease companied with several medical complications, sometimes even life-threatening. Each patient enrolled in the trial will be randomized into different treatment groups. For those receive ELAD artificial liver treatment, not very ideal therapeutic effects may be produced, or more adverse reactions may be developed compared with the routine therapies.

5.1.2 The placement of a double-lumen tube may develop complications: these complications include possible pulmonary collapse, bleeding on the puncture site, infection and etc.

5.1.3 Potential complications induced by the use of anticoagulation agents: intermittent administration of heparin will be applied during the treatment. Heparin is a kind of blood anticoagulation agent, which could prevent tube obstruction induced by the coagulation of the blood in the tube. Heparin administration may result in both external and internal bleeding at any time, including gastrointestinal, intracranial bleeding and etc., and it might be life-threatening when the bleeding is quite severe. Small amount of blood samples will be drawn at regular intervals to monitor the degree of anticoagulation, which is also a part of our standardized procedures. Still, extremely few patients may develop allergic reactions to heparin.

5.1.4 Hypotension: at the beginning of the ELAD artificial liver treatment, hypotension may be developed occasionally. After a period of treatment, the blood pressure could generally be stabilized successfully. Though the frequency of hypotension is not high, sometimes it may result in visceral impairment, such as heart, kidney and brain.

5.1.5 The following adverse reactions may be related with ELAD artificial liver:

① possibilities to develop tumor: the hepatocytes contained in the biological reactors of the ELAD artificial liver is originated from human embryonic hepatic tumor cells (between benign and malignant). These cells often adhere to the pillars in the extracorporeal biological reactors and will go through several filters for the prevention of the fell off cells entering into the human body. Theoretically speaking, if the leakage of the biological reactors occurs, few cells may enter into the body to develop tumors. However, the possibility is quite small, because the cells in the reactors generally will not enter into the body and the body generally will not develop tumors merely due to the infusion of a small amount of tumor cells with low-level malignancy. But in those patients with immunosuppression resulted from diseases or drugs, tumor induced by the fell off cells may be developed. Moreover, other tumors unrelated with artificial liver cells may be developed during treatment and follow-up periods.

② decrease in blood volume: since part of the intracorporeal blood will be drawn out for extracorporeal circulation during the ELAD artificial liver treatment, temporary decrease in blood volume may be induced.

③ other adverse reactions reported in studies include: vascular injury; acidosis; fever; hypothermia; thrombocytopenia, allergic reactions and etc. Most of these observed adverse reactions could be improved or would disappear spontaneously within a short period, whose definite clinical significance is not quite clear yet.

5.1.6 Pregnancy and fertility: currently, it is not very clear that whether or not ELAD artificial liver treatment will affect fetus or fertility. Thus, pregnant women will not be included in the trial.

5.2 BENEFITS

Severe hepatitis hepatic failure itself is a severe life-threatening disease. Case mortality rate is high even if patient is treated with current treatment which cost a lot(including physical plus non biological artificial liver treatment).

Patients assigned into treatment group will benefit as below:

①treated with advanced biological artificial liver,possibly get the chance to survive.

②treated with biological artificial liver freely, without any extra cost.

③It is possible to cut down the expense due to the application of biological artificial liver which could imitate function of the liver.

④Patients who complete the treatment and follow ups will get RMB 30,000 to 60,000 as assistant treatment fee which will be used to pay physical medication and etc..

Patients assigned into control group will benefit as below:

①Physical treatment will not be interfered.

②Patients who complete observation of 14 days and follow ups will get RMB 20,000 to 50,000 as assistant treatment fee.

6. ADMINISTRATION MATTERS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, last revised version, in accordance with the SFDA-GCP and applicable regulatory requirements.

6.1 ETHICS

6.1.1 Independent Ethics Committee

- The trial will not be initiated before the protocol and informed consent have been approved by Ethics Committee (EC).
- The constitution of EC must meet the requirements of SFDA. EC must also perform all duties outlined by the requirements of SFDA.
- The favourable opinion of all members of EC and the list of the EC members, with genders and qualifications, will be requested on the EC approval. Clinical monitors should not dispatch study medical divice to investigators before receiving EC approval.

- Investigators should not enroll patients before receiving EC approval.
- Should a protocol amendment be made that needs EC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent (if appropriate) has been reviewed and received approval / favourable opinion from EC.
- EC should be informed if any serious adverse events or accidents, which might jeopardize the safety of patients and /or affect patient enrollment, occurred during the study. Opinions of EC must be obtained if reassessment of EC issues is required.

6.1.2 Informed Consent

- The investigator must explain to each subject (or the subject's legally accepted representative) the nature of the study, its purpose, and procedures involved, the expected duration before study initiation. Prior to subject participation in the trial, written informed consent must be obtained from each subject. Each informed consent form must be signed, dated and retained by the investigator as part of the study records.
- The subject must be informed that his / her medical records may be examined by inspector of SFDA, by sponsor(Vital Therapies Inc. VTI),by authorised monitors or Clinical Quality Assurance auditors appointed by VTI and by appropriate EC. members.

6.2 ADMINISTRAION OF STUDY MEDICAL DEVICE

6.2.1 Study medical device

Study medical device is named as ELAD® cartridge.The active ingredient within the ELAD® cartridge is the C3A cell line, which is a subclone of the human hepatoblastoma cell line HepG2. The C3A cell line has demonstrated liver-specific functions that include production of macromolecules and other cellular products such as albumin, Factor V, transferrin, antithrombin III, C3 complement, α-1-antitrypsin, α-fetoprotein, and others.

The cartridge that houses the C3A cell line is comprised of thousands of hollow fibers made up of a semi-permeable polysulfone material. The semi-permeable membrane permits a bi-directional flow, between the C3A cells and the ultrafiltrate. During ELAD® therapy, the patient's plasma ultrafiltrate is pumped through the lumen (ICS) of the hollow fiber cartridges allowing toxins, nutrients and dissolved oxygen from the ultrafiltrate to diffuse across the membrane into the ECS, where the C3A cells metabolize them. Metabolites, along with albumin and other proteins produced by the C3A cells, can then diffuse back across the membrane into the ultrafiltrate for return to the patient.

ELAD® cartridge will be provided freely by VTI for the trial.

6.2.2 Transportation and preservation of the study medical device.

Investigator will inform VTI immediately by telephone once the patient has been randomized and assigned to treatment group.VTI will be responsible for delivering ELAD® cartridge to the clinical site within 24 hours after received the call.

The ELAD® cartridges are packaged in an insulated shipping container which has been validated to maintain temperatures between 2°C and 8°C during shipment and delivered by courier to the clinical site. If the ELAD® cartridges have been compromised during shipment, VTI must be notified immediately for replacement ELAD® cartridges.

The ELAD® cartridges may remain between 2°C to 8°C for up to 48 hours, including time during shipment (i.e., 48 hours from the time of shipment from VTI to the investigative site) and prior to initiation of therapy in the ELAD® System. Investigator should treat the patient with ELAD as soon as possible after ELAD® cartridges come to site.

The ELAD® cartridges could only be used to treat patient after linked with the hardware component accurately to form a ELAD system.The hardware component, provided by VTI freely, is kept in special ward at room temperature by designated person to ensure its safety. Only the investigator or person designated by investigator will have access to the medical dvice.

Investigator should keep the records of trial relevant materials's delivery to site such as ELAD® cartridges, pipes needed for the system and etc. The unused materials shoud be returned to VTI after the trial finished.

6.2.3 Usage of study medical device

The ELAD® cartridges could only be used to treat patient after linked with the hardware component accurately. See ELAD® investigator brochure and operator manual for details of usage and way to link with the hardware component of ELAD. Investigator should operate medical device according to SOP regulated by these documents.

ELAD® cartridges is used to treat patient who is assigned to treatment group. The time of the treatment should not be later than the expiration date and time on the label.

6.2.4 Package and label of study medical dvice

Label of the medical device is designed by VTI as below according to applicable regulatory requirements. Concrete date and relevant items will be filled in the correspondent location of the label when medical device is produced.

ELAD®	ELAD®
(Extracorporeal Liver Assist Device)	(体外肝脏辅助装置)
Aseptically Processed	无菌化生产制造
Part #	产品号
Lot #	批号
Begin Use By:	开始使用日期
Actual Date and Time Started	实际开始使用日期
Complete Use By	结束使用日期

(10 days from Actual Start Date and Time or Date of Expiration, whichever comes first)	(实际开始使用日期后 10 天或根据到期日期)
Expiration Date	到期日期
Storage Conditions	储藏条件
Clinical Protocol #:	临床试验实施计划号
Dosage	剂量
Randomization No.	随机号
Investigator	临床试验负责人
Investigator Phone #	负责人电话
Caution: Investigational New Drug/Device.	注意: 试验性新药/器械
Limited by Federal (U.S.) Law to Investigational US	在试验中受美国联邦法律的限制
Vital Therapies, Inc., 15222C Avenue of Science, San Diego, California 92128	生命治疗公司, 美国加州 92128 圣地亚哥市科学大道 15222C 号

6.3 RANDOMIZATION

EXCEL pharmastudies Inc. will provide randomized letters for all subjects to investigators at every site.

6.4 CASE REPORT FORM

- The Sponsor will provide a 3-copy Case report form printed on non-carbon required paper for each individual subject. The original and the second copy should be returned to the sponsor, while the third copy should be kept by the investigator.

- Case report forms are used to record clinical trial data and are an integral part of the trial and subsequent reports. The case report forms, therefore, must be legible and complete. All forms must be filled in using a black ballpoint pen. Errors must be lined out but not obliterated and the correction inserted, initialled and dated.

- Whether the patient complete or withdraw from the study treatment, investigators must sign a declaration ensuring accuracy of data recorded on his/her CRF. Reasons should be noted on the CRFs of patients who prematurely discontinued study treatment.

- Case reports forms must be kept current to reflect subject condition at each phase during the course of trial. Subjects are not to be identified on the case report form by name. Appropriate coded identification (e.g. Randomization Number) and subject initials must be used. The investigator must make a separate confidential record of these details (subject identification code list) to permit identification of all subjects enrolled in a clinical trial in case follow-up is required.

- The investigator must maintain source documents, which are usually medical records of patients, for each patient in the study. Source documents consist of all demographic and medical information, including laboratory data, electrocardiograms, etc. Data reported on the Case Report Forms that are derived from source documents

must be consistent with the source documents.

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records – not just shadow charts – must be available.

- The following data to be reported on the CRF should be included and derived from the source documents:

- Case report forms, informed consents and all source documents must be available at all times for review by the sponsor's clinical trial monitor. These documents must be maintained for at least five years after the completion of this trial.

6.5 QUALITY ASSURANCE

A quality assurance audit of this trial may be conducted by the sponsor or sponsor's designees. The quality assurance auditor will have access to all medical records, the investigator's trial related files and correspondence, and the informed consent documentation that is relevant to this clinical trial.

6.6 ADVERSE EVENT REPORTING PROCEDURES

6.6.1 Adverse Events

- All adverse events occurring during the course of the clinical trial (i.e., from signing the informed consent onwards) will be collected, documented and reported to CRO by the investigator.

- An adverse event is defined as any untoward medical occurrence in a clinical investigation subject treated by study medical device and which does not necessarily have to have a causal relationship with this treatment. Adverse events will be recorded by the answers to "how have been feeling since last visit?" All adverse events should be reported whether reported by patients or observed by investigators.

- An serious adverse event is any untoward occurrence in a clinical trial which might: 1) result in death; 2) be fatal or life-threatening; 3) result in persistent functional or constructional damage 4) necessary medical treatment should be taken so as to avoid persistent damage or injury listed above. Persistent damage is defined as unrecoverable damage to body's function or construction not including minor injury or damage.

- All adverse events, serious and non-serious, will be fully documented on the appropriate case report form(s). For each adverse event, the investigator will provide the onset, duration, intensity, treatment required, outcome and action taken with the medical device. The investigator will determine the relationship of the medical device to all adverse events.

- Investigators must follow up all adverse events until the adverse symptoms are

resolved or become stable. Follow-up information on SAE should be reported to other participating investigators, VTI ,EC and SFDA.

- Sponsor and investigator should study the relevant informations including medical history, previous treatment, disease condition, concomitant medication and changes, treatment of ELAD® and etc when adverse events occur many times. If the adverse event is an unexpected one safety analysis report should be written and sent to SFDA , EC and all the investigators who attend the trial.The investigator brochure should be revised as it is necessary.

- The severity grade of adverse event
  - Mild: Awareness of sign or symptom, but easily tolerated
  - Moderate: Discomfort, enough to cause interference with daily activities
  - Severe: Incapacitating or inability to work or perform daily activities
- Outcomes of adverse events
  - Recovered: The participants recovered to his/her pre-trial condition and the AE was resolved without sequelae
  - Not recovered: The participant did not recover to his/her pre-trial condition and the AE was not resolved. However, hopefully the participant will recover without sequalae.
  - Sequelae: The AE may result in permanent sequelae to the participant.
  - Death: The participant died of AE. The patient's death date is the ending date of AE.
  - Unknown: The result of AE is unknown, including the participant has already died. However, the AE was not the cause of his/her death.
- Actions taken on study medical device in response to an adverse event
  - Continuation of treatment: The treatment method remained unchanged
  - Suspension of treatment: The study medical device was temporarily discontinued.
  - Discontinuation of treatment: The study medical device was permanently discontinued
  - Prolonging the treatment time: Maximum treatment time wil be 10 days.
  - Treatment completion: There was no change on the treatment. Usually, the adverse events occurred after the completion of treatment.
- The relationship of adverse events to study medical device
  - Unrelated: The adverse event obviously results from other medical factors, such as the subject's clinical conditions, other treatments or concomitant

medications.

- Unlikely: The adverse event is likely to result from other medical factors, such as the subject's clinical conditions, other treatment or concomitant medications and it is not consistent with the applicable product information.

- Possibly: The adverse event is consistent with the applicable product information and has a casual relationship with study medical device. However, its relationship with the other medical factors may not be ruled out.

- Probably: The adverse event is consistent with the applicable product information and has a casual relationship with the study medical device and can not be explained by other medical factors, such as the subject's clinical conditions, other treatment or concomitant medications.

- Definitely: The adverse event is consistent with the applicable product information and has a casual relationship with the study medical device. This relationship may not be explained by other medical factors such as the subject's clinical conditions, other treatment or concomitant medications. In addition, the adverse event reappears if the subject is re-exposed to the study product.

6.6.2 Principles for severe adverse events reporting

6.6.6.1 Fundamental principle: Severe event, that has led to death, severe injury of patient, user, or other person and possibly relate to study medical device, should be reported as suspected medical device adverse events.

6.6.6.2 When be close to report: Some events, according to medical staff, which did not cause the casualty when it occured but will be possible to result in death of patient or medical staff when it occurs again, should be reported as suspected medical device adverse events.

6.6.6.3 When in doubt-report

Report it as suspected medical device adverse events when it is unclear whether the adverse event is a adverse event or not. These events could be related with the medical device and could also be the events which could not exlude the relationship with the medical device.

6.6.6.4 Principles of exempt report

① Deficiancy of the medical device could be found by user before use;

② The occurrence of the adverse event is completely due to patient condition.

③ The adverse event occurs just because the medical device is over the period of validity.;

④ Safeguard procedure of medical device which had been designed in advance works well and could not injure the patient when event occurs.The event would not be reported.

6.6.3 SAE reporting procedures

- Any serious or significant adverse event, in compliance with principle of suspected medical device adverse event reporting, must be reported by investigator by telephone / fax to EXCEL clinical monitor within 24 hours after awareness of its occurrence; In case of death or life-threatening situations, the responsible investigator must inform both EXCEL clinical monitor and/or project manager VTI by phone or fax within 24 hours;Based on GCP guidelines, investigators should also be responsible for the timely report of SAE to EC and regulatory authorities (e,g, SFDA)

- Following such telephone / fax reports, EXCEL clinical monitor should make his/her best effort to be on site to assist investigators in the filling of SFDA SAE form and submit a copy of this form to EXCEL's project manager. Then EXCEL's project manager should fax the FSDA SAE form to VTI within 48 hours after learning this information from investigators.

- VTI will be responsible for reporting any SAE to SFDA as soon as possible. The contact address of sponsor and CRO are listed on cover.

6.7 REGULATION FOR PUBLICATION

Study results may be summarized and published in the form of paper by investigator after reviewed and then agreed with sponsor.

6.8 AMENDMENT AND REVISEMENT OF THE PLAN

Investigator should keep the trial in compliance with the protocol. Sponsor can edit and revise the protocol according to conditions. Except for the actions that can reduce damage to subject any protocol revised may be applied after reviewed and consented by EC.

6.9 STATEMENT OF CONFIDENTIALITY

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be ensured by utilising subject identification code number.

6.10 ENDING TRIAL IN ADVANCE BY SPONSOR

VTI reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The investigator will be reimbursed for reasonable expenses incurred if it is necessary to terminate the trial.

References

1. Guidelines for the treatment and prevention of viral hepatitis. National hepatitis,contagious disease and parasitic disease Society, Chinese Medical Society, 2000.
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3. Hepatic failure. Written by Gu Changhai,Wang Yuming.The peoples medical publishing house,2002.
4. Clinical hepathology,Written by Yao Guangbi,Shanghai Science and technology

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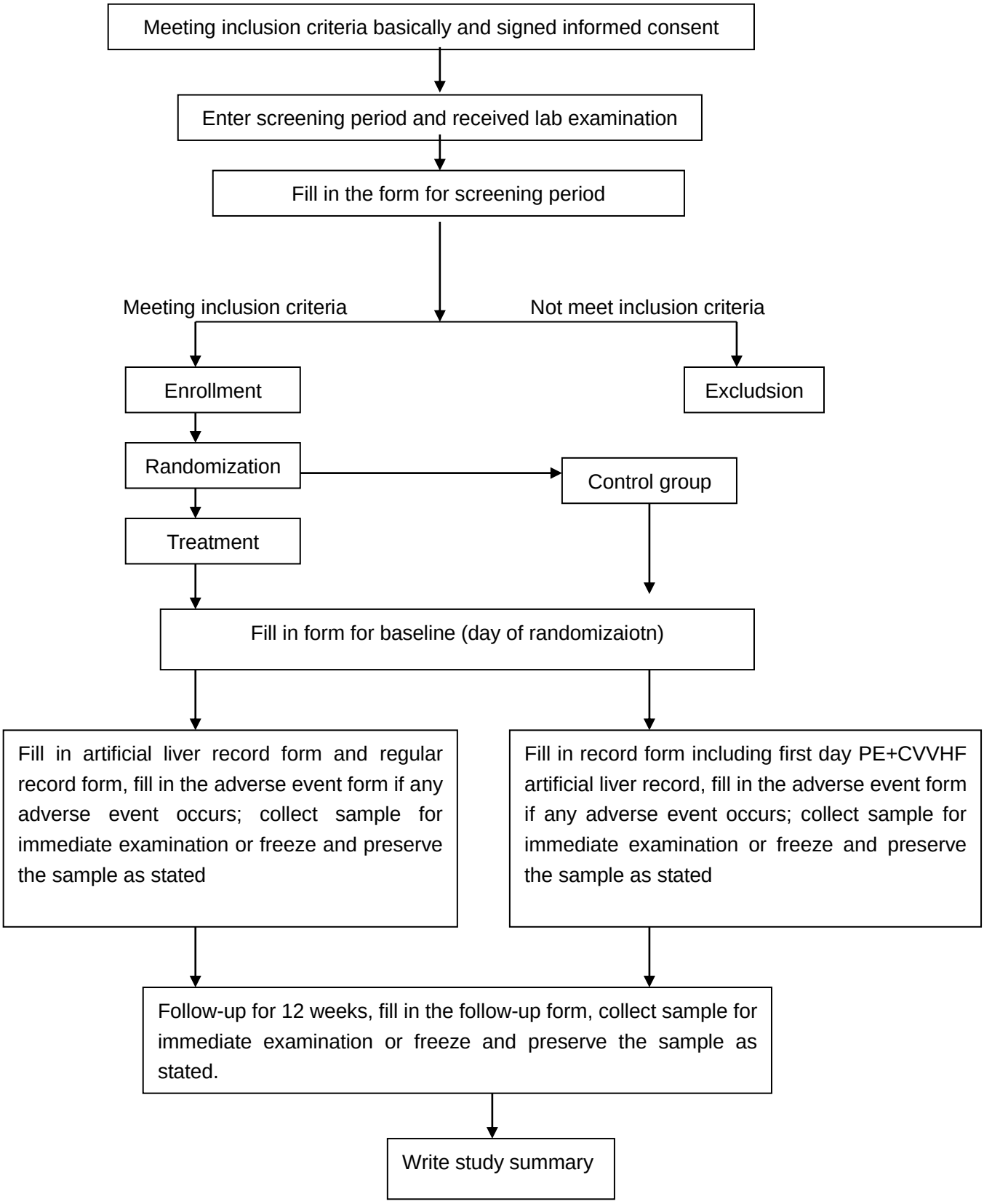
5. Kamath PS，Wiesner RH，Malinchoc M，et al. A model to predict survival in patients with end-stage liver disease. Hepatology，2001，33:464-470.

Appendix 1 Flowchart of ELAD Clinical Trial



Appendix 2 List of observed measurements

measurements	Contents
Clinical symptoms	hepatic encephalopathy: ● 0：non hepatic encephalopathy ● grade I-mild character change and anormal behavior, positive or negative flapping-wing tremor ● GradeII-consciousness confusion, somnipathy, inappropriate behaviour, computing and directional abilities subsidence,positive flapping,positive or negative pyramid sign, ● GradeIII-Lethargy,amentia,loss of partial consciousness,hallucination,positive or negative flapping, positive pyramid sign。 ● Grade Ⅳ-mild or deep coma,negative,wing- flapping tremor
Signs	● Vital signs：Temperature, pulse, blood pressure, respiration rate, hepatic encephalopathy, GCS score, ● Abdominal signs： shifting dullness,etc. ● Others：height, body weight, grip strength .

	Fatigue： ● Grade 1－mild（fell fatigued when do exercise bitterly, e.g. running） ● Grade 2 －moderate（fell fatigued when exercise mildly, able to manage daily activities independently） ● Grade 3 －severe（still fell fatigued when in bed, unable to manage daily activities independently） Food intake： ● Grade 1 －（food intake decreased by 1/4） ● Grade 2 －（food intake decreased by 1/2） ● Grade 3 －（food intake decreased by 2/3） ● Grade 4 －（food intake decreased by 3/4） Appetite: ● Grade 1 －（appetite decrease slightly） ● Grade 2 －（appetite is bad but feel hungary and hope to take some food）

	● Grade 3 －（appetite is very bad and not feel hungry） ● Grade4_－(anorexia,take little food) Nausea and vomiting： ● Grade 1 －mild（feel nausea, no vomiting, able to take some food） ● Grade 2 －moderate（nausea and vomiting, little food intake） ● Grade 3 －severe（no food intake, still nausea and vomiting ） Abdominal flatulence： ● Grade 1 －mild（occasional flatulence ,can relieve by self） ● Grade 2 －moderate（frequent flatulence, tolerable） ● Grade 3 －severe（severe abdominal flatulence, intolerable, require treatment ） Hiccup： ● Grade 1 －mild（occasional hiccup） ● Grade2－moderate（frequent hiccup, tolerable, not require treatment） ● Grade 3 －severe（frequent hiccup, intolerable, require treatment） Nose/gum bleeding： ● Grade 1 －little <2ml/d ● Grade 2 － medium 2～5ml/d ● Grade 3 － abundant >5ml/d Skin itching： ● Grade 1 －mild（occasional itching） ● Grade 2 －moderate（obvious itching, sleep unaffected） ● Grade 3 －severe（frequent itching, sleep affected）

Laboratory examinations	Biochemical measurements	ALT,AST,ALP,GGT,CHE,CHO,T-Bil,D-Bil,GLU,albumin,globulin, prealbumin, creatinine, urea nitrogen, uric acid, K^+ Na^+ Cl^- Ca^{2+} $Mg2^+$
	Clotting measurements	PT,PTA, INR,FIB,APTT,
	Routine measurements	Blood, urine and stool routines
	Special protein	AAG，AMG，AAT，TRF，CER，APOB，C3，C4，CRP，IgA，IgG，IgM
	Blood-gas analysis	PH , PaO_2, SaO_2, $PaCO_2$, actual HCO_3^- , BE
	Virus marker	HBV DNA quantification, HAV, HBV, HCV, HDV,HEV,CMV,EBV,HIV
	Thyroid	T3，T4，TSH
	Others	Ammonia, AFP, urinary volume
	Pregnancy test	Only for women of childbearing potential
Imaging examinations	Ultrasonic B	Liver size, echo, envelop, distribution/width of portal vein and splenic vein, splenic diameter, ascites/conclusion
	X ray	Chest X ray
	ECG	
Scores		MELD，CTP，APACHE II，SOFA
Others		Other significant measurements, such as oxygen inhalation, oxygen volume,central venous pressure, germiculture results and special symptom （e.g.,tri symptom of peritonitis）and etc. could be recorded.

Appendix 3 Flowchart for treatment group and control group

Procedure	**Screening**	**Randomization**	**Treatment**					**Follow up**		
Date	D-14～-1	D -1	D1	D2-4	D5	D7	D10	D14	D28	D56
Sign informed consent form	×									
Inclusion & exclusion criteria	×	×								
Randomization & grouping		×								
Medical history collection	×									
Virus markers	×n									
HBV DNA	×n									
Thyroid marker	×n									
Pregnancy test	×14									
Chest X ray	×7									
ECG	×14									
Symptom and physical	×	×	×	×	×	×	×	×	×	×
Urinary volume		×	×	×	×	×	×	×		
Blood routine	×1	×	×	×	×	×	×	×	×	×
Urine routine	×3						×			
Stool routine	×3						×			
Ascites routine	×3									
Liver function	×1	×	××	×	×	×	×	×	×	×
Creatinine , ions	×1	×	××		×		×	×	×	×
Coagulation items	×1	×	××	×	×	×	×	×	×	×
Blood gas		×			×		×	×		
Ammonia		×	××	D4×		×	×	×		
Specific protein		×					×	×		
AFP		×					×	×	×	×
Ultrasonic B	×7								×	×
MELD		×			×		×	×	×	×
CTP		×			×		×	×	×	×
APACHE II		×			×		×	×		
SOFA		×			×		×	×		
Adverse events		×	×	×	×	×	×	×	×	×
Concomitant medication	×	×	×	×	×	×	×	×	×	×

Explanations:

1. screening examination:Virus markers include HAV,HBV,HCV,HDV,HEV,CMV,EBV,HIV;Thyroid marker include T3，T4，TSH,pregnancy test only for women of childbearing potential,the patients with ascites should examine ascites routine if which could be drawn out.HBV DNA quantitative test only for patient with HBV infection and please specify examination date, trade name,dosage & duration of anti-virus medication.

2. X1-14, : data of day 1-14 prior to randomization day 1can be used as screening items.N means that examination result of item could be used as screening data no matter when it was done. D2-4： follow subject according to content of flowchart on day2,day3 & day4 respectively.

3. All examinations should be conducted on schedule stated above.The examinations could be conducted on±1 day duing hospitalization while on ±3 days after leaving hospital.

4. If treatment is discontinued prematurely (< 10d), all the examinations conducted on the discontinued

day should be the same as those conducted on Day 10 and then investigator should follow subject every 3 day until day 14 sharing the same items with day 2.

5. Total bilirubin, albium, ions and coagulation items will be conducted before and after PE and CVVH at day 1 as well as ammonia if ammonia is abnormal. The data before treatment will be defined as baseline data. Screening data will be used as randomizaion one if randomization begin within 24 hours after screening. Randomization data will be used as baseline one instead of data before treatment if treatment begin within 24 hours after randomization

6. Other items, considered to be necessary by other doctors, could be mearsured at any time. Significant results should be recorded at any moment.

Appendix 4 SOFA score criteria

Items	1	2	3	4
Respiration: PaO2/FiO2(kPa)	<53.3	<40.0	<26.7 with respirary assistance	<13.3 with respirary assistance
Clotting blood system: plt.(x109/L)	150	<100	<50	<20
Liver:TB umol/L)	20-32	33-101	102-204	>204
Cardiavascular system: hypotension	MAP<9.3kPa	dopamine ⩽ 5 or Dobutamine at any dose	dopamine>5 or Adrenaline ⩽ 0.1 or Noradrenaline ⩽ 0.1	dopamine>15 or Adrenaline>0.1 or Noradrenaline>0.1
Central nervous system (GCS score)	13-14	10-12	6-9	<6
Kidney: Cr (umol/L)	110-170	171-299	300-440	>440
Urinary volume ml:(24h)			<500	<200

Appendix 5 Criteria of MELD and CTP score

MELD score

MELD=3.8×ln bilirubin + 11.2×lnINR + 9.6×ln creatinine + 6.4×pathogeny

CTPscore

Variables	1	2	3
Hepatoencephalopathy grade	none	1～2	3～4
Ascites	none	little	moderate ～ severe
Albumin (g/L)	>35	28～35	<28
Prolonged prothrombin time (sec)	<4	4～6	>6
INR	<1.7	1.7－2.3	>2.3
Bilirubin	<2 folds	2～3 folds	>3 folds
Bilirubin (cholestasis type)	<4 folds	4～10 folds	>10 folds

CTP grading

Grade A: 5-6, Grade B: 7-9, Grade C: 10-15

Appendix 6 APACHE II score

APACHE II consist of APS，age and CPS3。APS include temprature, average artery pressure, heart rate, respiratory frequency, PaO2, pH, Na+,K+,creatinine concentration, HCT，WBC,and GCS coma index ,etc.Every item is still 0-4 score, total score is 0-60. Every parameter is the worst value of values within 24 hours prior to entering ICU. Age score is 0-6,CPS 2-5, total score of APACHE is 0-71.

Criteria for APACHE II acute biology score					
Parameter	Score				
	0	1	2	3	4
T(℃ rectum)	36.0-38.4	34.0-35.9 38.5-38.9	32.0-33.9	30.0-31.9 39.0-40.9	≤20.9 ≥41.0
MAP(kPa)	9.33-14.53		6.67-9.20 14.78-17.16	17.30-21.15	≤6.53 ≥21.30
HR/min	70-109		56-69 110-139	40-54 140-179	≤39 ≥180
RR/min Un MV or MV	12-24	10-11 25-34	6-9	35-49	≤5 ≥50
PaO2(kPa)	>9.33	8.13-9.33		7.33-8.00	<7.33
(A-a)DO2(kPa)	<.26.67		26.67-46.53	46.67-66.53	≤66.67
PH	7.33-7.49	7.50-7.59	7.25-7.32	7.15-7.24 7.60-7.69	<7.15 ≥7.70
Na(mmol/L)	130-149	150-154	120-129 155-159	111-119 160-179	≤110 ≥180
K(mmol/L)	3.5-5.4	3.0-3.4 5.5-5.9	2.5-2.9	6.0-6.9	<2.5 ≥7.0
Cr(umol/L)	53.04-123.76		<.53.04 132.6-167.96	176.80-300.56	≥309.40
HCl(%)	30.0-45.9	46.0-49.9	20.0-29.9 50.0-59.9		<20.0 ≥60.0
WBC(x10^9/L)	3.0-14.9	15.0-19.9	1.0-2.9 20.0-39.9		<1.0 ≥40.0
GCS		Equal to 15 minus actual GCS score			

Notes;MV—mechanic ventilation,record (A-a)DO_2 when FiO2≥0.5, record PaO2 only when FiO2<0.5;Cr score doubles when acute renal failure occurs.

APACHE II criteria for age and chronic health condition score

Age(year)	score	Chronic health	score

		condition	
⩽44	0		0
45-54	2	Planned operation	2
55-64	3		3
65-74	5	Non operation or emergency operation	5
⩾75	6		6

The form is only available for patients with severe organ function insufficiency or immune repression not for people with healthy history.

Appendix 6 GCS (Glasgow Coma Score)

The GCS is scored between 3 and 15, 3 being the worst, and 15 the best. It is composed of three parameters : Best Eye Response, Best Verbal Response, Best Motor Response, as given below :

Please select the best response to score since there may be difference between left body and right body while verbal reponse is scored. Improved GCS should be scored by both best response/worst response and left body/right body.

Best Eye Response. (4)

1. No eye opening.
2. Eye opening to pain.
3. Eye opening to verbal command.
4. Eyes open spontaneously.

Best Verbal Response. (5)

1. No verbal response
2. Incomprehensible sounds.
3. Inappropriate words.
4. Confused
5. Orientated

Best Motor Response. (6)

1. No motor response.
2. Extension to pain.
3. Flexion to pain.
4. Withdrawal from pain.
5. Localising pain.
6. Obeys Commands.