ÁREA DE SALUD 1
MURCIA-OESTE
Arrixaca

PROTOCOL

TITLE:

Abdominal drainage in the postoperative period of liver transplantation (DRALIT): multi-institutional randomized clinical trial

Drenaje abdominal en el postoperatorio del trasplante hepático (DRALIT): Ensayo Clínico multicéntrico aleatorizado.

Protocol code:
Version: v.1
Date: 24/5/2022
EudraCT:

PROMOTER: Department of General Surgery and Digestive Diseases

PRINCIPAL RESEARCHER / COORDINATOR: Víctor López López / Álvaro Cerezuela Fernández de Palencia

CONFIDENTIAL

This document contains confidential information that should not be disclosed or published to other people other than clinical researchers, members of the Clinical Research Ethics Committees of the participating hospital centers and Spanish Health Authorities.

ABSTRACT

Title:

Abdominal DRAinage in the postoperative period of LIver Transplantation (DRALIT): multi-institutional randomized clinical trial

Promoter: Department of General Surgery and Digestive Diseases

Principal researchers:

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Justification of the study: Classically, in the postoperative period of liver transplantation (LT), abdominal drainage has been used as a way to make the early diagnosis of hemorrhages, bile leaks and other postsurgical complications, as well as an evacuation route for ascites. The use of it routinely is currently under discussion due to the morbidities associated with its use.

Objectives: The objective of the clinical trial is to evaluate whether the routine use of abdominal drainage in the postoperative period of LT is associated or not with an increase in postoperative complications. Also evaluate the quality of life in relation to the presence or not of abdominal drainage.

Trial design: After signing the informed consent of those patients who meet the inclusion criteria, they will be randomized into two groups for placement of an abdominal drain or not. On the third day, the abdominal drainage will be removed except for signs of bleeding, postoperative infection or bile leakage, and abdominal postoperative complications will be evaluated according to the Clavien-Dindo scale in the first 90 postoperative days.

Randomization: 2 groups of equal size, total n = 365 patients. Simple intraoperative randomization prior to closure of the abdominal wall after fulfilling all the inclusion criteria and none of the exclusion criteria.

Masking: no masking.

Study population: liver transplants for all etiologies.

Variables analyzed:

- **Recipient preoperative** variables: gender, age, pre-transplant stay, BMI, ASA, diabetes, HTN, dialysis, MELD, Child-Pugh, serology, albumin, bilirubin, INR, CRP, creatinine, ascites, SBP, prothrombin time, encephalopathy, time from SSI to LT (months), retransplantation, previous surgeries, cirrhosis etiology, indication for transplantation, sarcopenia.
- **Donor** characteristic variables: age, stay in ICU, vasoactive drugs, cultures, antibiotics, CIT, WIT, type of donation (DBD / DCD), previous immunosuppression.
- **Intraoperative** variables: placement or not of abdominal drainage, surgical time (min), transfusions, blood loss, surgical technique, arterial anastomosis type, biliary anastomosis type, donation with extended criteria, recipient with extended criteria, clamping times.
- **Postoperative** variables: ICU stay, hospital stay, abdominal complications (collection, bile leak, hematoma, hemorrhage, paralytic ileus, ascites, bleeding, wound drainage complications, vascular anastomosis complications, mechanical obstruction, hollow viscus perforations, wound complications surgery), graft function, post-transplant antibiotic therapy, post-transplant immunosuppressive regimen, number of post-LT HC, mortality at 90 days, global complications at 90 days.
- **SF-36:** Physical function, physical role, body pain, general health, vitality, social function, emotional role, mental health (on inclusion in the waiting list, one month after surgery, 4 months after surgery).

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LIST OF ACRONYMS AND DEFINITION OF TERMS

- **ASA:** American Society of Anesthesiologists Classification
- **BMI:** Body Mass Index
- **MELD:** Model For End-Stage Liver Disease
- **INR:** International normalized ratio
- **LT:** liver transplantation
- **CRP:** C-Reactive Protein
- **SBP:** Spontaneous Bacterial Peritonitis
- **ILQ::** Inclusion in Surgical Waiting List
- **ICU:** Intensive Care Unit
- **CIT:** Cold Ischemia Time
- **WIT:** Warm Ischemia Time
- **DBD:** Donation after brainstem death
- **DCD:** Donation after circulatory death
- **CH:** Red blood cell concentrates
- **RETH:** Spanish Registry of Hepatic Transplantation
- **ERAS®:** Enhanced Recovery After Surgey
- **CRD:** Data Collection Notebook
- **RCT:** Randomized Clinical Trial
- **CEIC:** Clinical Research Ethics Committee

- **GENERAL INFORMATION**
  - **Trial identification**

Abdominal drainage in the postoperative period of liver transplantation: multi-institutional randomized clinical trial.

Acronym (if applicable): DRALIT

Version: v.1

Date: 12/7/2021

Eudra CT number:

  - **Type of clinical trial**

Randomized without masking.

  - **Promoter**

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- **Name and addresses of clinical laboratories and medical or technical departments or other institutions involved in the trial.**

Progressively, different centers at the European level will join the clinical trial.

- **JUSTIFICATION**

LT has become in recent years a procedure with an increasing number of indications and with a greater number of donations given the social knowledge of the donation process and donation in controlled asystole. The Spanish Registry of Liver Transplantation (RETH) shows a total of 28,609 TH in the period 1986-2019, which represents an average of 867 TH per year in Spain. These data place Spain among the first countries in terms of HT.

In LT, abdominal drainage has historically been used prophylactically as a way to identify early intra-abdominal postoperative complications such as hemorrhage, bile leakage, and others.

In transplant patients, the use of post-surgical abdominal drains on a routine basis has shown an increase in total protein losses in patients with refractory ascites, an increase in ascending infections secondary to drainage, infection and pain at the insertion point of the drain, as well as as, an increase in hospital stay. Nor can a higher rate of postsurgical bleeding and bile leakage be ruled out in patients with abdominal drainage.

Currently, in the few studies that there are in reference to the systematic use of abdominal drains in lTH, the need for them prophylactically is being discussed as an early diagnosis of postoperative intra-abdominal complications is not observed, but complications are seen to increase secondary to drainage. Therefore, the need to use it systematically in all patients is currently under discussion.

Currently, we are facing an increase in ERAS® (Enhanced Recovery After Surgey) programs, which began in 2008 with colorectal surgery and are currently expanding to other surgical procedures. These programs advocate reducing the number of drains and even not using them in patients with a low risk of post-surgical complications.

In the current bibliography, the methodology of the studies is varied, with the majority being non-randomized retrospective studies, which is why it is a subject that requires studies with a better methodological design and a higher number of patients to obtain

conclusions of clinical relevance. that can set the direction in this area that is in constant discussion.

Given the absence of any randomized non-inferiority clinical trial that studies the routine use of abdominal drainage in the postoperative period of liver transplantation, we consider that it is necessary to carry it out to increase the evidence.

The number of HT performed in each center is limited and variable annually, which is why we consider that the best design for this clinical trial is a European multicenter.

- **OBJECTIVE AND PURPOSE OF THE TEST**

The objective of our randomized clinical trial is to evaluate whether the prophylactic use of intra-abdominal drains in LT patients reduces postoperative intra-abdominal complications, compared to their routine use.

  - **Main goal.**
  - To assess whether the prophylactic use of abdominal drains in the postoperative period of LT increases the number of abdominal complications in the 90 postoperative days (Clavien-Dindo)
  - **Secondary objectives.**
  - To evaluate the possible improvement in the quality of life of the transplanted patient derived from the absence of postsurgical drainage (SF-36).
  - Evaluate the postoperative stay in both groups.

- **STUDY DESIGN**

Unmasked European multicenter randomized clinical trial with two arms parallel to the study.

Patients who meet the inclusion criteria will be offered to participate in this study by signing an informed consent. An informed consent approved by the Research Ethics Committee of the Virgen de la Arrixaca University Hospital will be used.

Patients who give their consent for the study will be randomized to the drainage group (D) and the control group without drainage (ND) before the beginning of the abdominal wall closure.

In the drainage group (D), it will be placed on the right flank / right iliac fossa. The drain will be connected to a bag and fixed to the skin with a silk. Said drain will be placed at the level of the surgical bed.
Regarding the control group, intraoperative drainage will not be placed, except when the surgeon's discretion considers it necessary due to the high risk of bleeding, bile leakage or any other process / complication in which it may benefit from intra-abdominal drainage.

All patients, regardless of the randomization group, will receive a quality of life questionnaire (SF-36) prior to surgery that they must complete.

All patients will receive routine antibiotic prophylaxis 60 minutes before surgery, repeating the number of doses that are required according to blood loss and surgical time. Antibiotic prophylaxis will be adjusted according to the resistance protocols of each participating center.

- **DATA COLLECT**

The following variables will be collected for each patient:

- **Recipient preoperative** variables**:** gender, age, pre-transplant stay, BMI, ASA, diabetes, HTN, dialysis, MELD, Child-Pugh, serology, albumin, bilirubin, INR, CRP, creatinine, ascites, SBP, prothrombin time, encephalopathy, time from SSI to HT (months), retransplantation, previous surgeries, cirrhosis etiology, indication for transplantation, sarcopenia.
- **Donor** characteristic variables: age, stay in ICU, vasoactive drugs, cultures, antibiotics, CIT, WIT, type of donation (DBD / DCD), previous immunosuppression.
- **Intraoperative** variables**:** placement or not of abdominal drainage, surgical time (min), transfusions, blood loss, surgical technique, arterial anastomosis type, biliary anastomosis type, donation with extended criteria, recipient with extended criteria, clamping times.
- **Postoperative** variables**:** ICU stay, hospital stay, abdominal complications (collection, bile leak, hematoma, hemorrhage, paralytic ileus, ascites, bleeding, wound drainage complications, vascular anastomosis complications, mechanical

obstruction, hollow viscus perforations, wound complications surgery), graft function, post-transplant antibiotic therapy, post-transplant immunosuppressive regimen, number of post-HT HC, mortality at 90 days, global complications at 90 days.

- **FOLLOW-UP**

The drain output will be evaluated daily after the surgical procedure. The quantity will be measured in milliliters and the appearance of the drainage will be categorized as serous, hematic, biliary or purulent. Its removal will be assessed on the 3rd postoperative day unless the patient shows signs of bleeding, bile leakage, intra-abdominal infection or any other complication that contraindicates its removal. When any of these complications that have delayed removal of the intra-abdominal drain are resolved, the drain should be removed.

Patients will be followed up during the postoperative period on a daily basis and complications will be observed at 90 days from discharge.
Calls will be made from discharge, the first 30 days every 15 days, from the month of discharge the periodicity will be monthly until 90 days from the intervention. The last follow-up call will be made on day 90. Subsequently, the follow-up protocol of each center will be followed.

The SF-36 quality of life questionnaire will be performed preoperatively, at one month and at 4 months after surgery.

- **Sampling methods and assignment of subjects to groups. Randomization.**

Subjects will be recruited at the pre-liver transplant consultation and/or at the time of inclusion on the transplant waiting list (Liver Transplant Committee - General Surgery Sessions Room - 3rd Floor Hospital Clínico Universitario Virgen de la Arrixaca, Murcia - Tuesday at 12h) among those patients who meet the criteria for participation in the study.
Once the individual has signed the informed consent document for the study and it has been verified that they meet all the inclusion criteria and none of the exclusion criteria, they will be considered eligible to be included in the study. In this first contact with the patient, you will fill out a first SF-36 health questionnaire.

Each patient will be assigned a numerical code consecutively as they are included in the trial. Randomization should be done in the operating room at the time prior to abdominal wall closure (optimal time for drain placement). This moment is chosen for randomization to avoid randomizing patients who ultimately require drainage due to intraoperative conditions by decision of the surgeon and not by randomization. Randomization will be performed using a spreadsheet with restricted access to participating centers through simple randomization. In order to carry out the randomization, the sheet will require filling in the initial data of the patient with which it will be verified that he meets the inclusion criteria in the study and none of the exclusion criteria. Subsequently, he will proceed to randomization and assign a number to the patient.

- **STUDY POPULATION**
  - **Definition of the study population**

    Patients will be recruited into the transplantation committee of the Hospital Clínico Virgen de la Arrixaca University. 365 individuals will be selected from both sexes, aged between 18 and 75 years, diagnosed with cirrhosis, liver disease, fulminant hepatitis or other indications specific to HT.
  - **Inclusion criteria.**
    - Patients of both sexes aged between 18 and 75 years included in the waiting list for HT by the committee of the Virgen de la Arrixaca University Hospital.
    - Sign Informed Consent.

  - **Exclusion criteria.**
    - Having been rejected for liver transplantation by said committee.
    - Age less than 18 years or greater than 75.
    - Any contraindication by the main surgeon that makes the placement of an intra-abdominal drain necessary.
    - Not having signed the Informed Consent.

  - **Abandonment and replacement of patients.**

Subjects can withdraw at any time, with or without reason, and without prejudice to them. The subject participating in the study may revoke his consent at any time, without expression of cause and without thereby incurring responsibility or harm to the participating subject. Individuals who drop out of the study will not undergo further follow-up or be substituted. The investigator may withdraw a subject from the study if he considers that the subject can no longer comply with all the requirements of the study or if any of the procedures is considered possibly harmful to him. Data that has already been collected on withdrawn subjects will be retained and used for analysis, but no new data will be collected after withdrawal.

- **Withdrawal criteria**

Those patients who meet any of these criteria will be withdrawn from the study:

- Presence of adverse events that at the discretion of the investigator implies the withdrawal of the patient.
- Deviation from the protocol that affects the interpretation of the study results and its scientific validity.
- Optional decision.
- Resignation of the individual to continue in the study.
- Loss of follow-up.

- **TREATMENT OF SUBJECTS**
  - **Description of the intervention**

In the intervention group, intra-abdominal drainage will be placed in the right flank / right iliac fossa. This drain will be placed on the surgical bed and the extracorporeal end will drain into a collection bag. Control of the amount drained and the appearance of the content will be carried out on a daily basis. If the clinical situation of the patient allows it, the drain should be removed on the 3rd postoperative day. If the clinical status or complications do not allow its withdrawal, consider withdrawing it as soon as said contraindications allow it.

The control group will not receive drainage. The evolution and the appearance of complications will be monitored in the ICU and ward on a daily basis.

The subjects will be closely monitored through the daily visit to the ICU and ward.

Regarding the assessment of quality of life (SF-36), the patient will complete a questionnaire at various points in the process:

- Inclusion on the waiting list.
- One month after surgery.
- 4 months after surgery.

- **Management of investigational medications / products.**

Investigational products will be supplied by the hospital. Said product will be administered intraoperatively and supplied to the surgical ward when its placement is confirmed depending on the group assigned after randomization.

- **Previous and concomitant treatments.**

Any pharmacological treatment carried out during the experimental period must be registered in the CRD. The principal investigator of the study will judge the suitability of the participant's continuity in the study.
The taking of drugs or other treatments that may modify the biological effects of the products under investigation will not be explicitly allowed.

- **Rescue medication**.

The use of rescue medication required by the patient is contemplated: analgesia, antipyretics, albumin in abundant ascitic losses, ...

- **Compliance evaluation.**

Following the randomization plan, all patients will be evaluated daily during their stay in the ward. All files must be available for review by the Promoter or the Promoter's representative.

- **STUDY VARIABLES.**

  The following variables will be collected for each patient:

- **Recipient preoperative** variables: gender, age, pre-transplant stay, BMI, ASA, diabetes, HTN, dialysis, MELD, Child-Pugh, serology, albumin, bilirubin, INR, CRP, creatinine, ascites, SBP, prothrombin time, encephalopathy, time from SSI to HT (months), retransplantation, previous surgeries, cirrhosis etiology, indication for transplantation, sarcopenia.
- **Donor** characteristic variables: age, stay in ICU, vasoactive drugs, cultures, antibiotics, CIT, WIT, type of donation (DBD / DCD), previous immunosuppression.
- **Intraoperative** variables: placement or not of abdominal drainage, surgical time (min), transfusions, blood loss, surgical technique, arterial anastomosis type, biliary anastomosis type, donation with extended criteria, recipient with extended criteria, clamping times.
- **Postoperative** variables: ICU stay, hospital stay, abdominal complications (collection, bile leak, hematoma, hemorrhage, paralytic ileus, ascites, bleeding, wound drainage complications, vascular anastomosis complications, mechanical obstruction, hollow viscus perforations, wound complications surgery), graft function, post-transplant antibiotic therapy, post-transplant immunosuppressive regimen, number of post-HT HC, mortality at 90 days, global complications at 90 days.
- **SF-36:** Physical function, physical role, body pain, general health, vitality, social function, emotional role, mental health (on inclusion in the waiting list, one month after surgery, 4 months after surgery).

- **SUBJECT FOLLOW-UP**

As we have previously indicated, patients will be evaluated daily by the research staff during their hospital stay. Those who were discharged before day 30 post-transplant will continue to contact the researchers by phone and report any event related to the insertion point of the drain.

Calls will be made from discharge, the first 30 days every 15 days, from the month of discharge the periodicity will be monthly until 90 days from the intervention. The last follow-up call will be made on day 90.

- **SAFETY ASSESSMENT (only for medicines, food or other therapeutic procedures).**

All patients assigned to the control group (DN) will be reevaluated intraoperatively. If, for obvious clinical reasons, the placement of the drain is required, said patient will be excluded from the study (randomization will not be carried out, so it would not be included in the RCT) and the drain will be placed.

Patient safety was not impaired at any point in the study, with the intervention group (D) being the routine procedure in LT and the control group (ND) re-evaluated intraoperatively.

- **STATISTICS**
  - **Data handling**

The data collection will be carried out through a Data Collection Notebook, capturing all the data in it legibly and in blue pen. Subsequently, said data will be dumped into a CRD through a spreadsheet. This sheet allows online access for the different study participants, to perform randomization and assign the patient code and to enter the data of each of the included patients. Patients will be included without personal data or identification documents, only an identification code that will be assigned to each one at the time of randomization. Once the trial is finished, all the data collected in the database will be evaluated for the writing of the final report.
All the documentation related to the study will remain stored in the Investigator's File, in the participating center, under the custody of the Principal Investigator until the end of the study. Once the study is finished, the documentation will be indexed and transferred to the general file of the center, complying with the recommendations established with respect to the Good Clinical Practice Standards.
The Principal Investigator will ensure that subject identification codes are kept for at least fifteen years after the trial has been completed or discontinued.

The data of all the CRDs will be entered into a database created for this purpose and equipped with safety margins and internal coherence standards. This database will be equipped with a double entry system and filters that prevent and detect any type of inconsistency or error in it. The information will be validated through internal consistency controls, studying the missing values. The data will be verified and corrected until the

database is fully validated. Once the database is purged, the variables will be recoded generating new variables (regrouping, sums, etc.).

- **Sample size.**

The hypothesis of this study was that the risk of postoperative complications at 90 days in the ND group would not be higher than in group D. A non-inferiority configuration was selected because the omission of drain placement is advantageous in terms of relieving to patients from discomfort and a decrease in medical cost. In calculating the sample size, the risk of an early postoperative complication related to LT was assumed to be 9% in the drain group and 6% in the no-drain group according to the literature review performed. Under a 4% non-inferiority margin, an alpha error of 0.05, and a statistical power of 80%, the sample was calculated as 174 patients in each arm. Assuming a 5% dropout rate, a total of 365 patients will be recruited into this study.

- **Statistic analysis**

The subsequent statistical analysis will be performed with the SPSS v.25 software.

- **Descriptive analysis.**

The demographic data and other baseline characteristics of the trial subjects will be described using descriptive statistical indices, for the overall number of patients and for each of the groups of patients under study. Continuous variables will be described using measures of central tendency (mean) and measures of dispersion (standard deviation). While the categorical variables will be described through absolute and relative frequency tables. The baseline characteristics shown by the groups of participants included in the study will be compared. Statistical tests will be performed depending on the nature of the variables. To study the relationships between variables, standard chi-square tests have been used in the case of qualitative variables and Pearson's correlation in the case of quantitative variables. In each situation, any association in which the p-value was less than 0.05 was considered statistically significant. The magnitude of the association between qualitative variables will be made by calculating the relative risk, and between quantitative

variables using Pearson's correlation coefficient. In this multivariate analysis, the odds ratios will be obtained with a 95% confidence interval.

- **Analysis of the main variable**

The primary efficacy criterion is the comparison of the incidence of postsurgical complications according to the Clavien-Dindo classification.

- **Secondary variables analysis**

The univariate and multivariate study of all the included variables will be carried out.

- **ETHICS**

This study will be carried out in European hospitals in accordance with current European legislation that regulates the performance of clinical trials, for which this protocol is established as a reference document for review by the Ethics Committees, as well as for the taking of practical decisions in the management of included patients by participating investigators. The study will only begin after obtaining written authorization from the Clinical Research Ethics Committee.

With the exception of those emergency situations, no protocol changes or deviations will be allowed without documented approval. The CEIC must be informed of the possible changes and will approve in writing any change or deviation that may increase the risks of the subject and / or may adversely affect the rights of the volunteer or the validity of the research. This stipulation does not apply to those changes that are made to reduce inconvenience or avoid risks to the subjects and to changes that affect the administrative aspects of the study. Carrying out this study will respect at all times the rules of Good Clinical Practice and the regulations and recommendations that appear in the Declaration of Helsinki and that are included in the current legislation on the practice of clinical trials.

- **INFORMED CONSENT**

Before any specific test or study procedure is carried out, patients (or witnesses or legal representatives) who meet the participation criteria will be asked to sign the informed consent document approved by the Ethics Committee. Sufficient time should be given to them to review the informed consent document and to have their questions answered

before signing. Each individual will be informed orally and in writing of the study methodology, as well as the possible undesirable effects that may appear as a consequence of the different determinations that will be made. In the same way, they will be informed of the voluntary nature of the study both in terms of their participation and in terms of abandonment at any time during the study. Likewise, everyone will be aware of the possible undesirable effects that may appear during the study, regardless of the assigned group. All of them will sign an informed consent to participate in the project.

- **DIRECT ACCESS TO SOURCE DATA / DOCUMENTS**

Source documents are all original documents, data and records. All the data collected to carry out the study, both for the preparation of the subject's Clinical History, and for the rest of the study documents, will be archived in the participating centers, on paper or in digital format, in accordance with the procedures of each center. The data collected for the study will be identified by a numerical code and only the principal investigator / collaborators will be able to relate said data with the patient and with their medical history.

Access to the information of the participating subjects will be restricted to the study doctor and authorized collaborating team members. The researcher and the center will guarantee direct access to the data or source documents to the personnel authorized by the promoter (monitor, auditor), to the health authorities (Spanish Agency for Medicines and Health Products), and to the Ethical Committee for Clinical Research, when need it.

- **DATA MANAGEMENT AND RECORDS FILE**

Patient data will be collected in a CRD. The principal investigator or a sub-investigator of the center must ensure the accuracy and completeness of the data recorded and put their signature on the corresponding CRDs. These data will be exported to REDCap, which will be the platform on which all the data from the centers participating in the trial will be shared.

When the database has been considered complete and accurate, it will be closed by locking the database. The filing of all relevant documents in relation to the study will be

carried out according to the requirements of the ICH-GCP, Commission directive 2005/28 / EC of April 8, 2005, and according to the pertinent national laws.

- **DATA PROTECTION**

The data will be included in a database that must comply with Regulation 679/2016, of April 27, General Data Protection Regulation and Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights. Likewise, the transmission of said data will be done with the appropriate security measures in compliance with said regulation. During documentation and analysis, patients will only be identified by their individual patient code, while all subject names will be kept secret by the investigator.

- **FINANCING AND INSURANCE**

No extraordinary financing is necessary, since we will use available resources in daily clinical and surgical activity. This study would be exempt from the need to take out insurance since the patients will undergo two surgical techniques performed in routine clinical practice and do not pose an additional risk to the patient.

- **PUBLICATION POLICY**

Each researcher is free to publish data from their center. However, the collected data will be presented and published by the appropriate author according to the criteria established by the International Committee of Medical Journal Editors (ICJME). Data will be published regardless of trial results.

- **BIBLIOGRAPHY**

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- **ANNEXES**

ANNEX 1. Clavien-Dindo Classification

(GRAVITY - POSTOPERATIVE COMPLICATION)

I. Any deviation from the normal postoperative period that does not require surgical or endoscopic reintervention. Includes additional use of electrolyte solutions, antiemetics, antipyretics, analgesics, and physical therapies. Includes superficial infection

II. Pharmacological treatment different from the previous ones. Blood transfusions or blood products and parenteral nutrition

III. Requires surgical, endoscopic or radiological reintervention:

   a. Without general anesthesia

   b. With general anesthesia

IV. Complications that threaten the life of the patient and require treatment in intermediate or intensive care:

   a. Organ dysfunction (includes hemodialysis)

   b. Multiple organ dysfunction

V. Death of the patient

Dindo D, Demartines N, Clavien PA. Classification of surgical complications, a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004; 240(2):205-213

ANNEX 2. CLASSIFICATION AMERICAN SOCIETY OF ANESTHESIOLOGIST (ASA)

I: No systemic disease.

II: Mild systemic disease.

III: Systemic disease that affects the activity of the patient.

IV: Serious disease, but not dying patient.

V: Dying patient, unexpected survival.

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ANNEX 3. INFORMED CONSENT

Servicio Murciano de Salud

INFORMED CONSENT SHEET

Study Title: Abdominal drainage in the postoperative period of liver transplantation (DRALIT): Randomized multicenter clinical trial.
Principal Investigator, service/unit and centre: Victor Lopez Lopez. General Surgery and Digestive System Service. University Clinical Hospital "Virgen de la Arrixaca", Ctra. Murcia-Cartagena s/n, CP 30120, El Palmar-Murcia,
Promoter/financier: Transplant Unit. General Surgery and Digestive System Service. University Clinical Hospital "Virgen de la Arrixaca"
Version number and date: v1. 12/16/2021

Participant/patient data
Name

Researcher or person providing the information
Name

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1. I have read, been informed and understand the content of this information sheet, which I certify with my signature as proof of my consent to everything contained therein.
2. I understand that my participation is voluntary and free of charge and I understand that I can request the revocation of this consent at any time, without having to offer explanations and without this affecting my present and/or future medical care.
1. I want the study doctor to communicate information derived from the research that may be relevant and applicable to my health or that of my family members:

   ▲ YES ▲ NO Telephone or contact e-mail.....
2. I consent to the storage of the associated data for future research under the conditions explained in this information sheet.

   ▲ YES ▲ NO
3. I consent to be contacted in the event that additional information is needed.

   ▲ YES ▲ NO Telephone or contact e-mail.....

Date: Signature of Participant/Patient

Date: Signature of the Investigator or person providing the information

REVOCATION OF CONSENT

I, Mr/Ms..... revoke the consent given on the date and do not wish to continue participating in the study"Abdominal drainage in the postoperative period of liver transplantation (DRALIT): Randomized multicenter clinical trial.".

Patient's signature:

Investigator Signature: Date:

ANNEX 4. PATIENT INFORMATION SHEET

Servicio Murciano de Salud

INFORMATION SHEET FOR PARTICIPANTS IN RESEARCH STUDIES WITHOUT SAMPLES

Study Title: Abdominal drainage in the postoperative period of liver transplantation (DRALIT): Randomized multicenter clinical trial.
Principal Investigator, service/unit and centre: Victor Lopez Lopez. General Surgery and Digestive System Service. University Clinical Hospital "Virgen de la Arrixaca", Ctra. Murcia-Cartagena s/n, CP 30120, El Palmar-Murcia,
Promoter/financier: Transplant Unit. General Surgery and Digestive System Service. University Clinical Hospital "Virgen de la Arrixaca"
Version number and date: v1.2 05/24/2022

INTRODUCTION

Considering the disease or process that you suffer from, we are writing to you to inform you about a study in which you are invited to participate. Our intention is that you receive the correct and sufficient information so that you can evaluate and judge whether or not you want to participate in this study. Before deciding whether you want to participate or not, please read this document carefully, which includes information about this project. You can ask all the questions that arise and request any clarification on any aspect of it. We will clarify any doubts that may arise at any time. In addition, you can consult with the people you consider appropriate.

The project has a favorable report from an accredited Research Ethics Committee in Spain.

VOLUNTARY PARTICIPATION

You should know that your participation is voluntary and that you can decide not to participate or change your decision and withdrawconsent at any time, without altering the relationship with your doctor or causing any damage to your treatment.

PURPOSE AND PROCEDURES OF THE STUDY:

We request your participation in this research project whose main objective is to deepen the knowledge of the use of abdominal drains in the immediate postoperative period of liver transplantation.

The main objective of the study is the evaluation of postoperative complications of liver transplantation and their relationship with the use of abdominal drains. It is wanted to evaluate if they suffer some type of relation with the drainage. The evaluation of the quality of life in the postoperative period in both groups and its relationship with the hospital stay is also the objective of the study.

EXPECTED BENEFITS:

It is possible that your participation in this study will not result in direct benefit, although your participation in this study will allow you to provide relevant information regarding abdominal drains in liver transplantation.

The need for the use of abdominal drains in the postoperative period of liver transplant patients and their relationship or not with the presence of postoperative complications is being studied.

The placement or not of the abdominal drain can have in both cases certain complications in an exceptional way (bleeding, biliary fistula, infections,...). A specific civil liability insurance policy has been contracted for the risks arising from this study.

RIGHT TO REVOCATE CONSENT

If you change your mind regarding the data provided, you have the right to request its destruction or anonymization, through your doctor/researcher/principal investigator. However, you should know that the data obtained in the analyzes carried out up to that moment may be used for the purposes requested and may be kept in compliance with the corresponding legal obligations.

CONFIDENTIALITY/PERSONAL DATA PROTECTION:

Your data will be associated with a code (encrypted) or anonymised. Process by which it is not possible to establish a relationship between a data or sample and the subject to which it refers. In addition, the data not associated with an identified or identifiable person by means of a code that allows the reverse operation. Only authorized personnel (liver transplant unit surgeons) may link the information derived from the analyzes performed with information about your identity.

Organic Law 3/2018 of December 5, on the Protection of Personal Data and guarantee of digital rights and Regulation (EU) 2016/6/9 of the European Parliament and of the Council of December 27 are fully applicable to this study. April 2016 Data Protection (RGPD). Therefore, it is important that you know the following information:

- Your personal data will be processed for the purpose indicated in the document to be signed and will be kept for the years necessary to comply with current applicable regulations.
- The Data Controller is the "Virgen de la Arrixaca" University Clinical Hospital (Area I de Salud-Murcia/Oeste), whose Data Protection Delegate (DPD) is Ms. Elena García Quiñones with address at Servicio Murciano de Salud, C. / Central nº 7, Habitamia I Building, 30100, Espinardo-Murcia (email: dpd-sms@carm.es).
- The legal basis that legitimizes the treatment is your consent.
- Applicable regulations: Regulation (EU) No. 536/2014 of the European Parliament and of the Council, of April 16, 2014, on clinical trials of medicinal products for human use, and by which Directive 2001/20/EC is repealed; Organic Law 3/2018, of December 5, on the Protection of Personal Data and Guarantee of Digital Rights, Law 14/2007, of July 3, on Biomedical Research; Royal Legislative Decree 1/2015, of July 24, approving the revised text of the Law on guarantees and rational use of medicines and health products; Law 44/ Law 44/2003, of November 21, on the organization of health professions, as well as Law 14/1986, of April 25, on General Health, Law 41/2002, of November 14, on autonomy of the patient, and other current legislation in health matters.
- Your data will not be transferred, except in cases required by law or in cases of medical emergency. However, at any time you can revoke the consent given, as well as exercise your rights of access, rectification, deletion, opposition, limitation of treatment and portability, to the extent applicable, through written communication to the Data Controller of the following way specifying your request, together with your DNI or equivalent document:
    - **Principal Investigator of the study / Coordinator**: Víctor López López / Álvaro Cerezuela Fernández de Palencia
    - **Home**: "Virgen de la Arrixaca" University Clinical Hospital, Ctra. Murcia-Cartagena s/n, CP 30120, El Palmar-Murcia,
- Likewise, we inform you of the possibility of filing a claim with the Spanish Data Protection Agency (C/Jorge Juan, 6 Madrid 28001)www.agpd.es

Access to your personal information will be restricted to the study doctor/collaborators, Health Authorities in matters of inspection, the Clinical Research Ethics Committee, when required to check the data and procedures of the study, but always maintaining their confidentiality.

The data collected for the study will be identified by a code, so that information that can identify you is not included, and only your study doctor / collaborators will be able to relate said data to you and your medical history.

The associated data will be kept under adequate security conditions and it is guaranteed that the subjects cannot be identified through means considered reasonable by persons other than those authorized.

Some additional data may be required. In that case, your doctor will contact you to request your collaboration again. You will be informed of the reasons and your consent will be requested again (see yes/no option at the bottom of the sheet).

From said data, scientific communications can be prepared to be presented at congresses or scientific journals, always maintaining the confidentiality of your personal data at all times.

You are informed that in accordance with the provisions of the seventeenth additional provision of Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights, as well as article 89 of the Regulation (EU) 2016/679, in the event that your data is processed for public health research purposes and, in particular, biomedical research, the following will be carried out:

- Carry out an impact assessment that determines the risks arising from the treatment in the cases provided for in article 35 of Regulation (EU) 2016/679 or in those established by the control authority. This evaluation will specifically include the risks of re-identification linked to the anonymization or pseudonymization of the data.
- Submit scientific research to quality standards and, where appropriate, to international guidelines on good clinical practice.
- Adopt, where appropriate, measures aimed at ensuring that researchers do not access identification data of interested parties. In the event that this separation between the data and the researcher cannot be guaranteed, an express commitment to confidentiality is guaranteed by the researcher as well as not to carry out any re-identification activity. Specific security measures will be adopted to prevent re-identification and access by unauthorized third parties.

Only the data collected for the study will be transmitted to third parties, which in no case will contain information such as name and surname, initials, address, or social security number. In the event that this transfer occurs, it will be for the same purposes of the study described and guaranteeing confidentiality at least with the level of protection of the legislation in force in our country. If you want to know more about it, you can consult with the principal investigator or contact the Data Protection Delegate.

Appropriate measures will be adopted to guarantee the protection of your privacy and your data will not be cross-referenced with other databases that could allow your identification.

IMPLICATIONS OF THE INFORMATION OBTAINED WHEN ANALYZING THE DATA

In the event that you request it, you may be provided with specific information about the research study in which you have participated, as well as the general results of this study.

In the event that this study obtains data that could be clinically or genetically relevant for you, and of interest to your health or that of your family, you may request that they be communicated to you by your trial doctor if you indicate so in the box that appears at the end of this document. However, if the patient had indicated his refusal and when this information, in the opinion of the responsible physician, is necessary to avoid serious damage to his health or that of his biological relatives, a close relative or a representative will be informed, after consulting to the Healthcare Ethics Committee of the center. The communication of this information will be carried out by professionals who will be able to adequately explain its relevance and the options that may arise.

In the case of a minor donor, once they reach the age of majority, they will have the right to receive this information and to revoke their consent. In the event that she does not exercise it, it will be considered that the current document is still in force.

FUTURE RESEARCH

I authorize the possible reuse of personal data for health and biomedical research purposes for purposes or research areas related to this study.

ANNEX 5. QUESTIONNAIRE SF-36

SF-36 QUESTIONNAIRE

Name:_____ Ref. Dr:_____ Date: _____

ID#: _____ Age: _____ Gender: M / F

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:

In general, would you say your health is:

◯ Excellent ◯ Very Good ◯ Good ◯ Fair ◯ Poor

Compared to one year ago, how would you rate your health in general now?

◯ Much better now than one year ago
◯ Somewhat better now than one year ago
◯ About the same
◯ Somewhat worse now than one year ago
◯ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

◯ Yes, Limited a lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

◯ Yes, Limited a Lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Lifting or carrying groceries

◯ Yes, Limited a Lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Climbing several flights of stairs

◯ Yes, Limited a Lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Climbing one flight of stairs

◯ Yes, Limited a Lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Bending, kneeling, or stooping

◯ Yes, Limited a Lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Walking more than a mile

◯ Yes, Limited a Lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Walking several blocks

◯ Yes, Limited a Lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Walking one block

◯ Yes, Limited a Lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Bathing or dressing yourself
○Yes, Limited a Lot ○Yes, Limited a Little ○No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities
○Yes ○No

Accomplished less than you would like
○Yes ○No

Were limited in the kind of work or other activities
○Yes ○No

Had difficulty performing the work or other activities (for example, it took extra effort)
○Yes ○No

EMOTIONAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities
○Yes ○No

Accomplished less than you would like
○Yes ○No

Didn't do work or other activities as carefully as usual
○Yes ○No

SOCIAL ACTIVITIES:
Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

○Not at all ○Slightly ○Moderately ○Severe ○Very Severe

PAIN:
How much bodily pain have you had during the past 4 weeks?

○None ○Very Mild ○Mild ○Moderate ○Severe ○Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

○Not at all ○A little bit ○Moderately ○Quite a bit ○Extremely

ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
- ◯ All of the time
- ◯ Most of the time
- ◯ A good Bit of the Time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the Time

Have you been a very nervous person?
- ◯ All of the time
- ◯ Most of the time
- ◯ A good Bit of the Time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
- ◯ All of the time
- ◯ Most of the time
- ◯ A good Bit of the Time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the Time

Have you felt calm and peaceful?
- ◯ All of the time
- ◯ Most of the time
- ◯ A good Bit of the Time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the Time

Did you have a lot of energy?
- ◯ All of the time
- ◯ Most of the time
- ◯ A good Bit of the Time
- ◯ Some of the time
- ◯ A little bit of the time
- ◯ None of the Time

Have you felt downhearted and blue?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- All of the time
- Most of the time
- Some of the time
- A little bit of the time
- None of the Time

GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people
○ Definitely true ○ Mostly true ○ Don't know ○ Mostly false ○ Definitely false

I am as healthy as anybody I know
○ Definitely true ○ Mostly true ○ Don't know ○ Mostly false ○ Definitely false

I expect my health to get worse
○ Definitely true ○ Mostly true ○ Don't know ○ Mostly false ○ Definitely false

My health is excellent
○ Definitely true ○ Mostly true ○ Don't know ○ Mostly false ○ Definitely false