IMPACT OF EXOCRINE PANCREATIC INSUFFICIENCY ASSOCIATED WITH ACUTE PANCREATITIS AND PANCREATIC ENZYME REPLACEMENT THERAPY ON GUT MICROBIOTA, IMMUNOLOGICAL CHANGES AND QUALITY OF LIFE

INFORMED CONSENT

MARCH 17TH, 2021

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Gastroenterology Department, Centro Hospitalar e Universitário de Coimbra, E.P.E., Coimbra, Portugal

INFORMATION FORM AND

INFORMED CONSENT

TITLE OF THE RESEARCH PROJECT:

Impact of Exocrine Pancreatic Insufficiency associated with Acute Pancreatitis and Pancreatic Replacement Therapy on Gut Microbiota, Immunological Changes and Quality of Life

STUDY PROMOTER : Prof. Dr. Nuno Almeida

RESEARCH COORDINATOR	Nuno Almeida
STUDY CENTRE	Serviço de Gastrenterologia do CHUC
PRINCIPAL INVESTIGATORS	Elisa Gravito-Soares, Marta Gravito-Soares
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PATIENT'S NAME (Press Letter) _____

Participants are voluntarily invited to be included in this study, in which will be necessary to take blood and stool samples before and after Helicobacter pylori (Hp) eradication therapy to study the intestinal flora and immunological profile. This procedure, so-called **informed consent**, describes the purpose of the study, the procedures to be performed and the possible benefits and associated risks. The participation of the patient may contribute to improve the knowledge and optimize the therapy of gastric Hp infection.

Participants will receive a copy of this Informed consent to review and seek advice from family and friends (if desired). Investigators and other members of research team will clarify any questions about the consent form. Once the study

is understood and there is no doubt about it, the participant should make the decision to participate or not. If the patient agrees to participate, he/she will be asked to sign and date this form. After the participant and investigator's signatures have been obtained, a **copy** of signed informed consent will be given to the participant. In case of no participation, there will be no penalty for the health care provided to the patient.

1. GENERAL INFORMATION AND OBJECTIVES OF THE STUDY

This study will take place at the **Gastroenterology Department** of the **Centro Hospitalar e Universitário de Coimbra, E.P.E.** (medical consultation, collection of blood and stool samples) and **Faculties of Medicine and Pharmacy** of the **University of Coimbra** (analysis of gut microbiota in feces and laboratory analysis of blood samples), with the aim of evaluating changes related to the development of exocrine pancreatic insufficiency (EPI) after acute pancreatitis and when to start pancreatic enzyme replacement therapy (PERT), the efficacy and safety profile of PERT and the response to PERT therapy in terms of nutritional deficits, changes In gut microbiota and immunology and quality of life. This is a prospective multicenter and longitudinal study, so no changes will be made to your usual medication or treatment other than PERT, if EPI is diagnosed after acute pancreatitis.
This study was approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra (FMUC) in order to ensure the rights protection, safety and wellbeing of all included participants and to guarantee public proof of such protection.
In order to ensure participants' safety, the **surveillance** and **support** from a **Gastroenterologist** will be provided before, during and after PERT.
This study aims to evaluate the diagnostic evaluation and predictors of EPI following acute pancreatitis, to evaluate the need for PERT, duration of PERT, as well as, the efficacy, in terms of clinical reversal and associated nutritional deficits and safety profile. Note that the therapeutic regimen to be employed is not experimental, in the sense that it is approved and currently being used for other indications, however its use in the context of EPI after acute pancreatitis is not well established, and there are no formal recommendations for its use. We will also evaluate changes before and after TSEP in nutritional deficits, gut microbiota, immunological changes, and quality of life.

2. PROCEDURES AND STUDY DESIGN

2.1. Procedures

A Gastroenterologist of the study will conduct a review of medical history and chronic medication from all participants. After the patient accepts to participate in this study, blood and stool samples will be taken after acute pancreatitis adiagnosis and before and after the diagnosis of EPI, as well as before and after the start of PERT. The therapy to be used, approved for EPI associated with other causes, includes pancreatic enzymes, with an anticipated treatment time required to reverse the clinical and nutritional deficits associated with this clinical condition.

2.2. Schedule of hospital visits and duration

This study consists of 3-7 gastroenterology medical appointments (depending on when the diagnosis of EPI will be made after the inaugural episode of acute pancreatitis), lasting about 10 to 20 minutes each, that would already take place for post-hospitalization acute pancreatitis surveillance, EPI development, and assessment of compliance and response to PERT. In all consultations you will be accompanied by a Gastroenterologist, involving the collection of blood/stool samples during the in-hospital phase and on 2 subsequent visits (at diagnosis of EPI and 6 months after starting PERT). The treatment with pancreatic enzymes will take place from the time of diagnosis of EPI (at hospitalization or follow-up visits at 1, 3, 6, 12 and 18 months) until 6 months after the start of PERT. During and after hospitalization for acute pancreatitis until the diagnosis of EPI and evaluation of PERT, you will perform tests to evaluate EPI, with the need for stool sampling and/or breath test, to evaluate response to therapy after your diagnosis, depending on the test that was positive at diagnosis of EPI. Blood samples will also be taken to diagnose endocrine pancreatic insufficiency, which may also occur after acute pancreatitis, and the patient will be treated accordingly.

2.3. Data processing

Data collected from the clinical history and lab results of blood and stool sample analysis will be submitted to a statistical analysis, with anonymity guarantee in all phases of the study.

3. RISKS AND POTENTIAL DRAWBACKS FOR THE PARTICIPANT

The risks of participating in this study are minimal and are the same as for venipuncture for blood collection (pain, bruising, or infection at the puncture site), the same as for blood testing for other purposes. There are no risks associated with stool sampling.

4. POTENTIAL BENEFITS

This study has the advantage of studying the EPI associated with acute pancreatitis, as well as the response to PERT, and will allow a better understanding of this disease, its treatment and associated complications. Furthermore, the information that will be collected will contribute to better inform physicians in order to improve the clinical care of patients with conditions similar to their own.

5. NEW INFORMATIONS

You will be made aware of any new information that may be relevant to your condition or that may influence your willingness to continue to participate in the study.

6. VOLUNTARY PARTICIPATION/ABANDONMENT

Participants are entirely free to accept or refuse to participate in this study, and may withdraw their consent at any time with no any consequence, penalty or loss of benefit and without compromising the relationship between participants and medical team involved in this study. Participants should inform the investigator of their decision to withdraw consent.

Study investigator may decide to end patients' participation, in case of not be in their health best interest to continue in this study. In addition, patients' participation may also be ended in case of no follow the study plan, by administrative decision or decision of the Ethics Committee. Study investigator will notify the participants if one of these conditions is met.

7. CONFIDENTIALITY

Without violating confidentiality rules, auditors and regulatory authorities will be permitted access to medical records to verify the performed procedures and the information obtained from the study in accordance with applicable laws and regulations. Participants' data will be kept confidential and anonymized and in case of study publication, their identity will remain confidential. By signing this informed consent, participants authorize this conditional and restricted access. Participants may also exercise their right to access the information at any time, having access to their medical information directly or through study investigators, and have the right to object to the data transmission that is covered by professional confidentiality.

Identifying medical records and the signed informed consent form will be checked for study purposes by the sponsor and/or representatives of the sponsor, and for regulatory purposes by the sponsor and/or representatives of the sponsor and regulatory agencies in other countries. The Ethics Committee responsible for this study may request access to participants' medical records to ensure that the study is being conducted in accordance with the protocol. Absolute confidentiality cannot be guaranteed due to the need for transmission of information to these parts.

By signing this informed consent form, participants allow that their medical data be verified, processed and reported as necessary for legitimate scientific purposes.

Confidentiality and processing of personal data

Personal data of study participants, including medical or health information, collected or created as part of the study (such as medical data or test results), shall be used for carried out the study, including for scientific research related to the condition under

study.

In giving consent to participate in this study, the participants' information, including clinical data, shall be used as follows:

1. The sponsor, investigators and others involved in the study will collect and use participants' personal data for the purposes described above.

2. Study data associated with participants' initials or other code with no direct identification (and no participants' name) will be communicated by researchers and others involved in the study to the study sponsor, who will use them for the purposes described above.

3. Study data associated with participants' initials or other code with no direct identification may be communicated to national and international health authorities.

4. Participants' identity will not be revealed in any reports or publications resulting from this study.

5. All persons or entities with access to participants' personal data are subject to professional confidentiality.

6. By giving consent to participate in this study, participants authorize the sponsor or study monitoring companies specifically contracted for this purpose and their employees and/or health authorities, to access the data contained in clinical files, to check the information collected and recorded by the investigators, namely to ensure data accuracy concerning participants and to guarantee that the study is being carried out correctly and the obtained data are reliable.

7. Considering law terms, participants have the right, through one of the study investigators, to request access to their data, as well as to request the rectification of their identification data.

8. Participants also have the right to withdraw their consent at any time by notifying the investigator, implying the end of participation in the study. However, non-identifiable data collected or created as a part of the study until that time may continue to be used for the purpose of the study, in particular to maintain the scientific integrity of the study, not being removed their medical data from the study file.

9. If participants do not give their consent, by signing this document, their participation in this study is not allowed. If and until the given consent is not withdrawn, it remains valid.

8. COMPENSATION

This study is the initiative of the investigator and therefore patient participation is requested without any financial compensation for its implementation, as is also the case with the investigators and the Study Centre.

9. CONTACTS

If any questions regarding participants' rights in this study, please contact the Ethics Committee:

The Ethics Committee of the FMUC,

Azinhaga de Santa Comba, Celas – 3000-548 Coimbra

Phone number: (+351)239857707

e-mail: comissaoetica@fmed.uc.pt

In case of any question about this study, please contact:

Marta Gravito-Soares, Elisa Gravito-Soares

Gastroenterology Department, Centro Hospitalar e Universitário de Coimbra, E.P.E.

Praceta Prof. Mota Pinto, 3000-075 Coimbra, Portugal

Phone number: (+351)239400483

THIS INFORMED CONSENT FORM SHOULD NOT BE SIGNED WITHOUT THE PARTICIPANTS HAVING BEEN GIVEN THE OPPORTUNITY TO ASK AND RECEIVE SATISFACTORY ANSWERS TO ALL THEIR QUESTIONS.

INFORMED, FREE, AND CLARIFIED CONSENT for participation in Research Study

Please read the following information carefully. If you feel that anything is unclear, please feel free to ask for more information.

Study Title: Impact of Exocrine Pancreatic Insufficiency associated with Acute Pancreatitis and Pancreatic Replacement Therapy on Gut Microbiota, Immunological Changes and Quality of Life

Background: This clinical research study consists of a national multicenter prospective and longitudinal study and a blib randomized PERT placebo-controlled trial, with the purpose of knowing the changes in the gut microbiota induced by acute pancreatitis, EPI and PERT, knowing the efficacy and safety of PERT, when to start PERT and how for long and the impact on gut microbiota, immunological changes and quality of life of EPI diagnosis and response to PERT.

Explanation of the study: To carry out this study it is necessary to collect blood and stool samples (at acute pancreatitis diagnosis, after EPI diagnosis and after PERT) and your authorization to provide your clinical data, which will be deprived of any identification regarding the person in question, which will later be analyzed and published.

Conditions and funding: Your acceptance to participate in this research is voluntary and free of charge, and you will not suffer any prejudice, welfare or other, should you choose not to participate.

Confidentiality and anonymity: The data collected for this study are confidential and anonymity will be assured at all study phases.

I confirm that I have explained to the participant named below the nature, objectives and potential risks of the above Study.

Researcher:

Name:_____

Signature:_____ Date: _____ /_____ /_____

I, _____ (Full Name) give my consent for the clinical data concerning my person/relative _____ (Full Name) (delete as appropriate), regarding acute pancreatitis, EPI and PERT, as well as, changes of the gut microbiota, immunological changes and quality of life in follow-up in the Healthcare institution _____ in Portugal, to be made available for the research study entitled "**Impact of Exocrine Pancreatic Insufficiency associated with Acute Pancreatitis and Pancreatic Replacement Therapy on Gut Microbiota, Immunological Changes and Quality of Life**". The information provided is confidential, ensuring the anonymity of the person concerned.

Participant/Legal Representative:

Signature:_____ Date: _____ /_____ /_____

By signing this document, you declare that you have read and understood this document as well as the verbal information provided to me by the person/s signing above. I have been assured that I may, at any time, refuse to participate in this study without any consequences. Therefore, I agree to participate in this study and allow the use of the clinical data concerning the treatment of gastric infection by Helicobacter pylori and alteration of the intestinal flora, trusting that they will only be used for this research and the guarantees of confidentiality and anonymity given to me by the researcher.

In accordance with the Helsinki Declaration of the World Medical Association and its updates, the participants declare that:

1. Read this informed consent form and accept to participate in this study on a voluntary basis.
2. Receive all the study information about its nature, objectives, risks, likely duration as well as what is expected from the participant.
3. Have the opportunity to ask questions about the study and have understood the answers and the given information.
4. At any time can ask further questions to the study investigator and receive information about the study development. The investigator in charge of the study will give to participants all important information that comes up during the study that may change their willingness to continue to participate.
5. Agree to use information, including medical history and treatments with strict respect for medical secrecy and anonymity. Participants data will be kept strictly confidential. The authorization for consult their data will be given only to persons designated by the promoter and representatives of regulatory authorities.
6. Agree to follow all instructions given during the study and to cooperate with the investigator and to inform him/her immediately of changes in health and well-being and of all unexpected and unusual symptoms that occur.
7. Agree to use the results of the study for scientific purposes only and, in particular, I accept that these results will be disclosed to the relevant health authorities.
8. Accept that data generated during the study will be computerized by the sponsor or another person designated by him.
9. Can exercise their right of rectification and/or opposition.
10. Are free to withdraw from the study at any time, without having to justify their decision and without compromising the quality of health care provided. In addition, the investigator has the right to decide on their early withdrawal from the study, with information to the participants about the withdrawal cause.
11. Have been informed that the study may be interrupted by decision of the investigator, sponsor or regulatory authorities.

THIS DOCUMENT CONSISTS OF 2 PAGES AND IS MADE UP IN DUPLICATE:
ONE COPY FOR THE INVESTIGATOR, ONE FOR THE CONSENTING PERSON