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Home care/outpatient vs hospital admission in mild acute pancreatitis: protocol of a multicentre, randomised controlled trial (PADI_2 trial)

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<td>Complete List of Authors:</td>
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Authors
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Running head

Outpatient in mild acute pancreatitis

Keywords

Acute pancreatitis; outpatient; homecare; early oral refeeding; length of hospital stay; pain relapse.
ABSTRACT

Introduction: Acute pancreatitis (AP) is the third cause of hospital admission for gastrointestinal disease and over 70% of AP admission are mild cases. In the United States, it represents an annual cost of 2.5 billion dollars. The most common standard management of mild AP (MAP) still is hospital admission. Patients with MAP usually achieve a complete recovery in less than a week and there are very reliable severity predictor scales. The aim of this study will be to compare of three different strategies for the management of MAP.

Methods/design: this is a randomized controlled three arm multicentre trial. Patients with MAP will be randomly assigned to groups A: outpatient; B: home care; C: hospital admission. The primary end point of the trial was the treatment failure rate of the outpatient/homecare management for patients with MAP compared with that of hospitalised patients. The following secondary endpoints will be to analyse: pain relapse; diet intolerance; hospital readmission; hospital length-of-stay; need for ICU admission; organ failure; complications; costs; patient satisfaction. The general feasibility, safety and quality checks required for high quality evidence will be adhered to.

Ethics and dissemination: The study has been approved by the Scientific and Research Ethics Committee of the ‘Institut d’Investigació Sanitaria Pere Virgili - IISPV’ (093/2022). This study will provide evidence as to whether outpatient/homecare are similar to usual management of AP. The conclusions of this study will be published in an open access journal.

Trial registration: The trial is registered at the ClinicalTrials.gov (NCT05360797).
STRENGTHS AND LIMITATIONS

1. Strength 1: This is a multicentre, randomised controlled three-arm trial which provides the first type A evidence regarding the new safe and effective outpatient treatment in selected patients with mild acute pancreatitis.

2. Strength 2: This protocol is written by a multidisciplinary team. The method is well detailed.

3. Strength 3: This study is suitable for clinical practice.

4. Strength 4: The established treatment is the usual one in patients with mild acute pancreatitis. There are no uncommon drugs/therapy used in this study, consequently no adverse events are expected.

5. Strength 5: Data will be managed by the Independent Data Manager Committee (IDMC). Data security and monitoring.

6. Limitation 1: The three-arm method of the study requires multidisciplinary team on the project which may limit the number of joining centres.

7. Limitation 2: Blinding is not suitable due to the characteristics of the three treatment arms.
BACKGROUND

Acute pancreatitis (AP) is one of the most common reasons for hospitalisation among gastrointestinal diseases in all over the world. The costs caused by severe AP are higher than mild AP (MAP). Nevertheless, approximately 70% of hospital admissions for AP are mild cases, if savings in health cost are to be achieved, it would be by lowering the cost of managing patients with MAP without affecting patient's safety and satisfaction.

Patients in the PADI_1 study from 2017 to 2019 were analysed, and the following observations were noted:

1. immediate oral low-fat solid diet to patients with mild and moderate AP is safe and feasible;
2. Immediate oral refeeding was associated with a significant reduction in hospital length-of-stay (LOS) (3.4 vs 8.8 days, \( P < 0.001 \));
3. and hospital costs (health costs were twice as low, with a savings of 1325.7€/patient in the immediate oral refeeding than conventional oral refeeding group);
4. Comparing the outcome of this treatment protocol with the nil per os protocol used in most hospitals showed that patients enjoyed benefits with no increasing the risk of complications.

PADI_1 study confirm the benefits of an early diet, the rapid recovery of patients with MAP and the reduction of hospital costs (1). The present study seeks to prospectively evaluate a new scope in the care of patients with mild AP and is justified on the following three points: 1) patients with MAP usually achieve a complete recovery of their symptoms in less than a week with conservative management, consisting primarily of intravenous hydration, analgesia, and diet; 2) clinical prognostic scoring systems, although criticized for their poor positive predictive value for severe AP, it is true that they have an excellent negative predictive value to determine which patients will have MAP early in the course of their hospitalisation; and 3) factors that predict hospital readmission within 30 days in AP have been studied and can be applied and include continued gastrointestinal symptoms or abdominal pain, discharge on diet, pancreatic necrosis, excessive alcohol consumption, and antibiotic treatment.

Therefore, to carry out this study in which outpatient and homecare treatment are compared versus hospitalisation for patients with MAP is proposed, fulfilling strict criteria for predicting severity. The main
objective of this trial is to determine whether in cases of MAP, outpatient treatment or home care is similar to usual treatment with hospital admission in terms of diet tolerance, pain control, risk of severity, complications, patient’s satisfaction and health cost.

METHODS

Design

This is a randomised controlled three-arms multicentre trial. Patients with MAP will be randomly in three groups: group A: outpatient treatment, group B: medical homecare and group C: hospitalisation.

Study population

All patients diagnosed with MAP will be informed of the possibility of participating in the PADI_2 study. After the consent form is signed, a computer using a block randomisation protocol will randomise the patients. Previously, by using severity scores, the patients will be in emergency room for 24 hours, in order to confirm that it is a MAP (Figure 1).

Inclusion criteria

The inclusion criteria are: (1) patient older than 18 years of age; (2) diagnosed of AP by at least two of these three criteria: compatible abdominal pain, amylase or lipase level superior in three-fold respective laboratory baseline levels, and suitable findings in imaging techniques (CT, ultrasound or MRI)¹; (3) MAP; (4) signed written informed consent form; (5) compliance with outpatient or homecare criteria; (6) randomization at 24 hours of stay in the emergency room.

Exclusion criteria

The exclusion criteria are: (1) pregnant or breastfeeding women; (2) abdominal pain >96 hours (4 days); (3) the possibility of poor oral intake or unable to eat for reasons other than AP; (4) Pancreatic neoplasm, endoscopic retrograde cholangiopancreatography or trauma etiology, biliar obstruction; (5) Chronic pancreatitis; (6) ASA ≥3; (7) moderate or severe acute pancreatitis.
Sample size

In a study with the same objective, an outpatient treatment failure rate of 4% was observed. Using calculations for a noninferiority study with an estimated 95% success rate, 80% power, 5% significance level, and 10% inferiority limit, a sample size of 75 patients per study group treatment (total 225 patients).

Randomisation

In each centre participants will be divided into three groups receiving one of the three study treatments. The allocation of participants to the different groups will be carried using a computer-generated random and stratified by center. The randomisation lists will be prepared in REDCap/PADI_2, and will be assigned when the register start and the patient completed criteria. after obtaining informed consent, physician on call at the different centers, will be responsible for enrollment and treatment allocation according to REDCap registry. Enrollment will be unblinded for patients and physicians due to the type of intervention.

Duration

The planned starting date of the study is November 1, 2022 and the planned finishing date of the study is November 1, 2024. Each patient in the control group will be followed-up at 1 week and 3 months after hospital discharge. In the experimental groups, patients will be contacted daily during 4 days after discharge from the emergency room by called in the outpatient group, and in the homecare group by nurse or doctor visit. In all groups will be a subsequent control between one month and 3 months after clinical discharge.

Intervention

Based on our last study, oral refeeding can be started immediately in emergency room with medical control symptoms. In addition, low fat diet has been described.

Patients will be randomised to group A, B or C (Table 1).

Table 1. Schedule of enrollment, interventions, and assessments according to the SPIRIT 2013 statement (16).

Patients will be randomised to group A (outpatient) or B (home care) or C (hospital admission). The REDCap/PADI_2 program contains the parameter collected on admission, 24h parameter at emergency room, parameters collected during the first days and 3 month after discharge.
<table>
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<tr>
<th>TIMEPOINT**</th>
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<th>Allocation</th>
<th>Post-allocation</th>
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<td>24h</td>
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<td>Day1</td>
<td>Day2</td>
<td>Day3</td>
</tr>
<tr>
<td>Discharge</td>
<td>3 month after discharge</td>
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</table>

**ENROLMENT:**
- Eligibility screen: X
- Informed consent: X
- Allocation: X

**INTERVENTIONS:**
- Group A: outpatient: X X X X X
- Group B: home care: X X X X X
- Group C: hospital admission: X X X X X

**ASSESSMENTS:**
- Questionnaire admission: X X
- Questionnaire 24h: X
- Questionnaire 48-72h: X X
- Questionnaire 3m: X

**Groups**
After a 24-hour stay in the emergency department, the predictive factors of severity evaluation and the diagnosis of MAP is confirmed and signed informed consent form, the patients will be randomized in:
Group A, Outpatient: the patient is discharged and contacted by phone daily for 4 consecutive days by the study investigators in each center.

Group B, Medical homecare: the patient is discharged and contacted by phone/visits by nurse/doctor daily for 4 consecutive days by the medical home care department in each center.

Group C, Hospital admission: the patient is hospitalised with usual treatment (PADI_1) in each center.

**General treatment**

General treatment indicated by the IAP/APA guidelines⁴.

**Predictors of severity**

Predictors of severity will be considered when: (1) SIRS ≥2 criteria; (2) BISAP>2 score; (3) organ failure.

**Discharge of patients**

Patients will be counted as discharged from hospital/from the study when: (1) oral feeding is tolerated (≥50% of plates); (2) Absence of nausea and vomiting with treatment; (3) Controlled pain with oral analgesia (VAS≤2); (4) Clinical characteristics without predictors of severity.

Hospital readmission within 1 week has to be considered as failure treatment PADI_2.

**Primary endpoint**

The primary end point of the trial was the treatment failure rate of the outpatient/home care PADI_2 management for patients with MAP compared with that of hospitalised patients.

**Failure treatment PADI_2, definition:**

It will be considered failure treatment when: (1) diet intolerance (<50% of plates); (2) uncontrolled nausea or vomiting; (3) uncontrolled pain despite oral painkillers; (4) predictors of severity are present.

**Another endpoints**
Secondary endpoints that will be analysed: (1) pain relapse; (2) diet intolerance; (3) causes of intolerance diet; (4) need from enteral/parenteral nutrition; (5) hospital readmission; (6) use of antibiotics; (7) amylase our lipase; (8) white blood cells; (9) creatinine/urea; (10) Bilirubine; (11) infection; (12) length of hospital stay; (13) need for ICU admission; (14) length of ICU therapy; (15) organ failure; (16) complications; (17) costs calculation; (18) patient satisfaction (15). Notably, only direct costs will be calculated that include all medications, services, salaries of healthcare professionals, equipment and day care costs.

Monitored parameters during hospitalisation

There will be a large assortment of parameters monitored during the study (medical history, physical examination, laboratory tests, diagnostic imaging, therapy, interventions, cost, satisfaction survey). Data collection on the electronic patient report form (ePRF) will be done electronically in REDCap/PADI_2 (see data management).

Trial organization

PADI_2 is coordinate by the Joan XXIII University Hospital of Tarragona, Spain. This group has published the PADI_1 study that it permitted an advanced in the treatment of AP.

Coordinating Committee (CC)

The CC will be led by ERM, RJM, MRR, RM (Surgeon, University Hospital of Tarragona Joan XXIII, Rovira i Virgili University, Tarragona, Spain); CF (Surgeon, IdiPAZ, CIBERehd, La Paz University Hospital, Madrid, Spain); SLG (Surgeon, Health Consortium Maresme, Mataró, Spain); AS (Gastroenterologist, Barcelona Clinic Hospital, IDIBAPS, CIBEREHD, University of Barcelona, Barcelona, Spain); SG (Surgeon, Moise’s Broggi Hospital, CSI, Barcelona, Spain).

Independent Data Monitoring Committee (IDMC)

Data will be managed by the Independent Data Manager Committee. Data security and monitoring.

Data Review Meeting (DRM)

Members of DRM are a delegated investigator, biostatistician, and data manager.

Data management and statistical analyses

Data management
Data will be managed by the IDMC. ePRF will be used at REDCap/PADI_2. The Investigator will ensure that the data in the ePRF are complete and accurate. Detailed data flow will be described in a Data Management Plan (DMP) reflected in a user manual of REDCap/PADI_2. Data from completed ePRFs will be accepted under the direction of the Data Manager at IDMC. Any incongruous or missing recordings in the ePRFs will be referred back to the Investigator using a Data Query Form (DQF), and be documented for each individual subject before clean file status is declared. All changes to ePRFs will be recorded. Before Data Base Lock the DRM will decide and document necessary steps related to any issue in the database and define the analysis sets. DRM will be responsible for protecting confidentially of patients before, during and after the trial.

Study populations

Three analysis populations will be defined:

Safety Analysis Population (SAP): all patients enrolled in the study.

Per Protocol population (PPP): the set of all enrolled patients who completing the study followed the rules of the study.

Intention to Treat (ITT): the set of all randomised participants who start on a treatment, excluding consent withdrawals.

Withdrawal of a subject from PPS

Any investigator and the IDMC can submit recommendations for dropouts from the PPP group with reasons given to the CC. All recommendations will be archived. The CC will discuss all the information and, if the change in the protocol would be expected to have any relation to the interventions and results of the study, the case will not be included in the final per-protocol analysis. Immediate dropout from the per-protocol group will be ordered if: (1) any of the exclusion criteria are diagnosed during the course of AP; (2) any predictor of severity is present; (3) parameters required for answering the primary endpoints are missing; or (4) serious medical reasons not related to AP occur (eg, heart attack, accidents, etc.).

Applied software

Data collection on the ePRF form and randomization will be done electronically in Research Electronic Data Capture 9.8.0 (REDCap/PADI_2). Statistical analysis will be performed using Statistical Analysis System -
SAS 9.4 or Statistical Package for the Social Sciences - SPSS 21 (or later) statistical packages; Microsoft MS Word will be used for reporting.

Statistical methods

In a first phase, the descriptive analysis will be carried out for each of the continuous variables with the calculation of measures of central tendency (mean or median) and dispersion (standard deviation and range), and of the qualitative variables according to their percentage.

In the univariate analysis, for the comparison of the quantitative variables that follow a normal distribution, the student's t test and ANOVA were used. For quantitative variables that do not follow a normal distribution, the Mann-Whitney and Kruskal-Wallis U tests will be used. For qualitative variables, the chi-square test ($\chi^2$) will be used, applying Fisher's exact test when deemed necessary. Actuarial survivals will be calculated using the Kaplan-Meier method and their comparison between groups will be carried out by applying the Log-Rank test. In all cases, the confidence level will be 95%, considering that there is statistical significance when $p < 0.05$.

In the multivariate survival analysis, the Cox regression method will be used, while for the multivariate analysis of risk factors, the logistic regression method will be used; introducing in the statistical model those variables that show statistical significance in the univariate analysis and/or those that in the bibliography and theoretical framework are prognostic factors.

Early quality assessment

An early quality assessment check will be performed on the first 70 patients. The IDMC will perform an independent review of the trial-related documents and activities, with the aim of ensuring the rights, safety and welfare of subjects are respected, and the clinical data is credible. The similarity of the groups will also be checked at the beginning of the study. The IDMC will inform to the CC. The CC will discuss all the information and, if the differences would be expected to have any relation on the interventions and results of the study or the overall dropout rate from PPP is $>20\%$ of all participants who were randomised or allocated into each group or the differential dropout rate is $>15\%$ between groups, the study should be reassessed and the IDMC
will make recommendations regarding reassessment of power calculation, extension of recruitment period, extension of number of study centres or trial completion.

**Interim analyses and premature termination of the study**

The IDMC may also recommend stopping the trial early for ethical reasons if one of the groups clearly shows evidence of significant benefit. An interim analysis on the primary endpoint will be performed when 50% of patients have been randomised and discharged from hospital. The interim analysis will be carried out by the IDMC, who will report to the CC.

The Haybittle–Peto boundary method will be used, and it states that if the interim analysis shows a probability of $\leq 0.001$ that a difference as extreme or more between the treatments is found, given that the null hypothesis is true, then the trial should be stopped early.

**Centers**

The trial will start in four centres, the participants in the PADI_1: Joan XXIII University Hospital of Tarragona, Barcelona Clinic Hospital, Health Consortium Maresme, and Moise’s Broggi Hospital after which the study is open for other centres. In all cases the IDMC will make an audit of the centre and will report to the CC. The CC has the right to decide whether the centre meets the required quality to join the study. Compulsory requirements for a centre are: (1) it needs to treat at least 30 patients with AP a year; (2) it needs to have a home care department; (3) besides the regular medical team, the centre has to appoint at least one doctor and one nurse available for the trial; (4) all persons need to attend a preliminary meeting where all the details concerning the studies are discussed fully and have qualified as investigators in a course on-line or face-to-face.

**Authorship aspects**

Authorships are based on international guidelines: all authors have to fulfill the International Committee of Medical Journal of Editors criteria (see [www.icmje.org/journals.html](http://www.icmje.org/journals.html)). All collaborating centres providing more than 25 patients can afford two authors. Every additional 20 patients will give the opportunity to propose an additional author. Every centre can also include formal ‘collaborators’ on the project for which the journal will be asked to list in PubMed at final publication. The first three authorship are reserved for the study.
coordinators (ERM, MRR, SLG) and the last authorship positions are reserved for the senior investigators (RJM, CF). All other authors will be listed in alphabetical order. Collaborators will be listed in alphabetical order in the ‘Catalan Pancreatitis Collaborative Group’.

**Feasibility**

As a general protocol for the treatment of AP at the Joan XXIII University Hospital, patients with AP receive PADI_1 treatment that is adjusted to the guidelines IAP/APA\(^4\). Patients in PADI_1 receive diet immediately when they arrive to the ward from the Emergency Department and their symptoms have been controlled. Comparing the outcome of this treatment protocol with the nil per os protocol used in most hospitals showed that patients enjoyed benefits with no increasing the risk of complications. About 100 patients at the PADI_1 hospitals are admitted annually. Therefore, if no other institution joins the study, it can be completed within 3 years.

**Safety**

Since no unknown drugs/therapy are used in the study, no adverse or serious adverse events are expected/interpretable that would be attributable to the intervention during the trial. In this trial the IDMS will examine safety variables after every 20 patients have completed. Moreover, investigators will report adverse or serious adverse events on a separate form which has to be sent to the IDMS and SC. The SC will discuss and, if the adverse effect is confirmed, it will be reported to the relevant institutional ethical committee (http://www.iispv.cat).

**Patient and public involvement**

None

**DISCUSSION**

Here we report the protocol of a prospective randomised controlled trial to study the safety and effectiveness of outpatient treatment of MAP patients. We have only been able to find one study in the literature that shows that home care treatment of MAP patients is safe and can represent a significant reduction in hospital costs (9). They found that only 3.6% of patients required hospital readmission. PADI_1 study demonstrated that
immediate diet was safe and effective in MAP patients, leading to a significant reduction in hospital stay. With this experience, we want to take a forward step in the treatment of this type of patient and that’s why we dare to propose a study such as the PADI_2. Our main hypothesis is that Outpatient / home care management of MAP patients is as safe and effective as hospital treatment, with savings in health cost and without affect patient’s satisfaction. Concerning ethical issues, this study has very low risk for patients. Therefore no adverse events are expected during the trial, there will be a close follow-up and if the patient presents some initial treatment failure, they will be re-admitted to the hospital.

ETHICS AND DISSEMINATION

The trial is registered at the ClinicalTrials.gov registry (NCT05360797) and received relevant ethical approval with the reference number 093/2022 issued by the Scientific and Research Ethics Committee of the Institut d’Investigació Sanitaria Pere Virgili - IISPV. At the end of the project we will disseminate our results to the medical community and will publish in open access way.

CONCLUSION

This study will provide type A evidence to establish the feasibility and safety of out-of-hospital treatment for patients with MAP. This protocol is the first version of the trial completed on May 4, 2022.

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de Manresa, Sant Joan de Déu Hospital, Manresa, Spain; General and Digestive Surgery Department, IdiPAZ, CIBERehd, La Paz University Hospital, Madrid, Spain; Investigators and Co-investigators from participant Hospitals.

ACKNOWLEDGEMENTS

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List of Abbreviations

AP Acute Pancreatitis
ASA American Society of Anesthesiologist
BISAP Bedside Index of Severity in Acute Pancreatitis
CC Coordinating Committed
CT Computed Tomography
DMP Data Management Plan
DQF Data Query Form
DRM Data Review Meeting
eRPF electronic Patient Report Form
IAP/APA International Association of Pancreatology / American Pancreatic Association
ICU Intensive Care Unit
IDMC Independent Data Monitoring Committee
ITT Intention to Treat
MAP Mild Acute Pancreatitis
MRI Magnetic Resonance Imaging
PPP Per Protocol population
SAP Safety Analysis Population
FUNDING

This work will be supported by Research grant award from the ‘Catalan society of surgeons ‘and ‘Spanish Association of Surgeons’.

AUTHOR CONTRIBUTION

Elena Ramírez-Maldonado and Rosa Jorba participated in all phases of the study with the help other authors in the different parts.

Conception and design: Elena Ramírez-Maldonado, Rosa Jorba-Martín, Sandra López Gordo, Ariadna Sánchez and, Constantino Fondevila.

Administrative, technical, or logistic support: Elena Ramírez-Maldonado, Rosa Jorba-Martín, Sandra López Gordo, Ariadna Sánchez, Sergio González, Robert Memba, Constantino Fondevila and, Marta Rodrigo-Rodrigo.

Drafting of the article: Elena Ramírez-Maldonado, Rosa Jorba, Robert Memba, Marta Rodrigo-Rodrigo, Constantino Fondevila and, Catalan Pancreatitis Collaborative Group.

Critical revision of the article for important intellectual content: Elena Ramírez-Maldonado, Rosa Jorba, Sandra López Gordo, Ariadna Sánchez, Sergio González, Robert Memba, Constantino Fondevila and, Marta Rodrigo-Rodrigo.

All author read and approved the final manuscript.

CONFLICTS OF INTERESTS

The authors declare that they have no conflicts of interest.
REFERENCES


Figure 1. Flow chart of participants according to the SPIRIT 2013 statement (16)
Adult patients with an episode of acute pancreatitis (AP)

Exclusions
Not meeting inclusion criteria
1. Patient above 18y
2. Diagnosed AP (2 out 3 criteria)
3. Signed written informed consent form
Meeting exclusion criteria
1. Pregnant or breastfeeding women
2. Abdominal pain >96h
3. The possibility of poor oral intake for reasons other than AP
4. Pancreatic neoplasm, endoscopic retrograde cholangiopancreatography or trauma etiology, biliary obstruction
5. Chronic pancreatitis
6. ASA ≥3
7. Moderate or severe acute pancreatitis;
8. The patient is considered unable to eat an oral diet for other reasons than AP

X patients to be randomized

Outpatient Home Care Hospital Admission

X analysed X analysed X analysed
<table>
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<th>Section/item</th>
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<td>Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym</td>
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<td>Trial registration</td>
<td>2a</td>
<td>Trial identifier and registry name. If not yet registered, name of intended registry</td>
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<td>Roles and responsibilities</td>
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<td>Names, affiliations, and roles of protocol contributors</td>
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<td>Name and contact information for the trial sponsor</td>
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<td>5c</td>
<td>Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities</td>
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<td>5d</td>
<td>Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
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<tr>
<td>Background and rationale</td>
<td>6a</td>
<td>Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention</td>
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<td>6b</td>
<td>Explanation for choice of comparators</td>
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<tr>
<td>Objectives</td>
<td>7</td>
<td>Specific objectives or hypotheses</td>
</tr>
<tr>
<td>Trial design</td>
<td>8</td>
<td>Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)</td>
</tr>
</tbody>
</table>
Methods: Participants, interventions, and outcomes

Study setting 9 Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)

Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

Participant timeline 13 Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

Recruitment 15 Strategies for achieving adequate participant enrollment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation 16a Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions
Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions

Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how

17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

20b Methods for any additional analyses (eg, subgroup and adjusted analyses)

20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)

Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial

Financial and other competing interests for principal investigators for the overall trial and each study site

Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions

Authorship eligibility guidelines and any intended use of professional writers

Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

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Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Informed consent materials 32 Model consent form and other related documentation given to participants and authorised surrogates

Biological specimens 33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.
<table>
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<td>Title and abstract</td>
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<td>Identification as a randomised trial in the title</td>
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<td>Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)</td>
<td>2</td>
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<tr>
<td>Introduction</td>
<td>2a</td>
<td>Scientific background and explanation of rationale</td>
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<td>Specific objectives or hypotheses</td>
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<tr>
<td>Methods</td>
<td>3a</td>
<td>Description of trial design (such as parallel, factorial) including allocation ratio</td>
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<td>3b</td>
<td>Important changes to methods after trial commencement (such as eligibility criteria), with reasons</td>
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<tr>
<td>Participants</td>
<td>4a</td>
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<td>Settings and locations where the data were collected</td>
<td>7</td>
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<tr>
<td>Interventions</td>
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<td>The interventions for each group with sufficient details to allow replication, including how and when they were actually administered</td>
<td>7-8</td>
</tr>
<tr>
<td>Outcomes</td>
<td>6a</td>
<td>Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed</td>
<td>8-9</td>
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<td></td>
<td>6b</td>
<td>Any changes to trial outcomes after the trial commenced, with reasons</td>
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<tr>
<td>Sample size</td>
<td>7a</td>
<td>How sample size was determined</td>
<td>7</td>
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<td></td>
<td>7b</td>
<td>When applicable, explanation of any interim analyses and stopping guidelines</td>
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Randomisation:

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<tr>
<th>Sequence generation</th>
<th>8a Method used to generate the random allocation sequence</th>
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<td>8b Type of randomisation; details of any restriction (such as blocking and block size)</td>
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<tr>
<td>Allocation concealment mechanism</td>
<td>9 Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned</td>
<td>7</td>
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</table>

Implementation

| 10 Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 7 |

Blinding

| 11a If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how | Not blinding |
| 11b If relevant, description of the similarity of interventions | Not blinding |

Statistical methods

| 12a Statistical methods used to compare groups for primary and secondary outcomes | 11 |
| 12b Methods for additional analyses, such as subgroup analyses and adjusted analyses | 11 |

Results

| 13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | Not started |
| 13b For each group, losses and exclusions after randomisation, together with reasons | Not started |
| 14a Dates defining the periods of recruitment and follow-up | Not started |
| 14b Why the trial ended or was stopped | Not started |
| 15 A table showing baseline demographic and clinical characteristics for each group | Not started |
Numbers analysed 16  For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups  
Outcomes and estimation 17a  For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)  
17b  For binary outcomes, presentation of both absolute and relative effect sizes is recommended  
Ancillary analyses 18  Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory  
Harms 19  All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)  

Discussion  
Limitations 20  Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses  
Generalisability 21  Generalisability (external validity, applicability) of the trial findings  
Interpretation 22  Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence  

Other information  
Registration 23  Registration number and name of trial registry  
Protocol 24  Where the full trial protocol can be accessed, if available  
Funding 25  Sources of funding and other support (such as supply of drugs), role of funders  

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.
**Home care/outpatient vs hospital admission in mild acute pancreatitis: protocol of a multicenter, randomized controlled trial (PADI_2 trial)**

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<td>04-Apr-2023</td>
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| **Complete List of Authors:** | Ramírez-Maldonado, Elena; Joan XXIII University Hospital in Tarragona, General and Digestive Surgery Department  
Rodrigo-Rodrigo, Marta; Joan XXIII University Hospital in Tarragona, General and Digestive Surgery Department  
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The Catalan Pancreatitis Collaborative Group, The Catalan Pancreatitis; Joan XXIII University Hospital in Tarragona, General and Digestive Surgery Department |
| **Primary Subject Heading:** | Gastroenterology and hepatology |
| **Secondary Subject Heading:** | Emergency medicine, General practice / Family practice, Medical management, Surgery |
| **Keywords:** | Pancreatic disease < GASTROENTEROLOGY, Pancreatic surgery < SURGERY, Clinical trials < THERAPEUTICS |
Title
Home care/outpatient vs hospital admission in mild acute pancreatitis: protocol of a multicenter, randomized controlled trial (PADI_2 trial)

Authors
Ramírez-Maldonado Elena¹, Rodrigo-Rodrigo Marta¹, López Gordo Sandra², Sánchez Ariadna³, Coronado Llanos Daniel⁴, Li Jiazhen⁵, Wu Pengyu⁶, Jara Jimmy⁷, Blanco Laia⁸, Sánchez Jiménez Raquel⁹, Vaz Joao¹⁰, Fondevila Constantino¹¹ and, Jorba-Martin Rosa¹, on behalf of The Catalan Pancreatitis Collaborative Group¹²

The Catalan Pancreatitis Collaborative Group (in alphabetical last name order, with permission): Sonia Babiloni, University Hospital of Tarragona Joan XXIII, Tarragona, Spain; Sandra M. Bacca, Maresme Health Consortium, Matarò, Spain; Joaquim Balsells, Vall d’Hebron University Hospital, Barcelona, Spain; Carme Boqué, University Hospital of Tarragona Joan XXIII, Rovira i Virgili University, Tarragona, Spain; Pablo Collera Ormazabal, Althaia University Hospital, Xarxa Asistencial Universitària de Manresa, Sant Joan de Déu Hospital, Manresa, Spain; Ignasi Elizalde, Barcelona Clinic Hospital, IDIBAPS, CIBEREHD, University of Barcelona, Barcelona, Spain; Laia Estalella, University Hospital of Tarragona Joan XXIII, Rovira i Virgili University, Tarragona, Spain; Maria Teresa Fernández Planas, Maresme Health Consortium, Matarò, Spain; Lidia Florit Serra, University Hospital of Tarragona Joan XXIII, Rovira i Virgili University, Tarragona, Spain; Inmaculada Fonoll, University Hospital of Tarragona Joan XXIII, Rovira i Virgili University, Tarragona, Spain; Nil Gómez Vallvé, University Hospital of Tarragona Joan XXIII, Rovira i Virgili University, Tarragona, Spain; Sergio González, Moise’s Broggi Hospital, CSI, Barcelona, Spain; Erik Llàcer-Millán, University Hospital of Tarragona Joan XXIII, Rovira i Virgili University, Tarragona, Spain; Rui Pedro Major Branco, Hospital Garcia de Orca EPE, Almada, Portugal; Robert Mamba, University Hospital of Tarragona Joan XXIII, Rovira i Virgili University, Tarragona, Spain; Carme Mias, Arnau de Vilanova University Hospital, Lleida, Spain; David Nicolas, Barcelona Clinic Hospital, IDIBAPS, CIBEREHD, University of Barcelona, Barcelona, Spain; Elizabeth Pando, Vall d’Hebron University Hospital, Barcelona, Spain; Mihai-Calin Pavel, University Hospital of Tarragona Joan XXIII, Rovira i Virgili University, Tarragona, Spain; Eva Pueyo-Pérez, University Hospital of Tarragona Joan XXIII, Rovira i Virgili University, Tarragona, Spain; Jing
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**Running head**

Outpatient in mild acute pancreatitis

**Keywords**

Acute pancreatitis; outpatient; homecare; early oral refeeding; length of hospital stay; pain relapse.
ABSTRACT

Introduction: Acute pancreatitis (AP) is the third most common gastrointestinal disease resulting in hospital admission, with over 70% of AP admissions being mild cases. In the United States, it costs of 2.5 billion dollars annually. The most common standard management of mild AP (MAP) still is hospital admission. Patients with MAP usually achieve complete recovery in less than a week and the severity predictor scales are reliable. The aim of this study will be to compare three different strategies for the management of MAP.

Methods/design: This is a randomized, controlled, three-arm multicenter trial. Patients with MAP will be randomly assigned to group A (outpatient), B (home care), or C (hospital admission). The primary end point of the trial will be the treatment failure rate of the outpatient/homecare management for patients with MAP compared to that of hospitalized patients. The secondary endpoints will be pain relapse, diet intolerance, hospital readmission, hospital length-of-stay, need for ICU admission, organ failure, complications, costs, and patient satisfaction. The general feasibility, safety, and quality checks required for high quality evidence will be adhered to.

Ethics and dissemination: The study (version 3.0, 10/2022) has been approved by the Scientific and Research Ethics Committee of the 'Institut d'Investigació Sanitaria Pere Virgili-IISPV' (093/2022). This study will provide evidence as to whether outpatient/homecare are similar to usual management of AP. The conclusions of this study will be published in an open access journal.

Trial registration: The trial is registered at the ClinicalTrials.gov (NCT05360797).
STRENGTHS AND LIMITATIONS

1. Strength 1: A multidisciplinary team wrote this protocol.

2. Strength 2: The established treatment is the standard in patients with mild acute pancreatitis.

3. Strength 3: An Independent Data Manager Committee will be ensuring security and monitoring data.

4. Limitation 1: The three-arm method of the study requires a multidisciplinary team on the project which may limit the number of centers that can join.

5. Limitation 2: Lack of blinding increases the risk of performance bias, since the participants will be aware of their group assignment.
BACKGROUND

Acute pancreatitis (AP) is one of the most common reasons for hospitalization among gastrointestinal diseases worldwide. The costs caused by severe AP are higher than those for mild AP (MAP). Nevertheless, approximately 70% of hospital admissions for AP are MAP so, if savings in healthcare costs are to be achieved, it would be by lowering the cost of managing patients with MAP without complication or affecting patient safety and satisfaction.[1-7]

Patients in the PADI_1 study[1] from 2017 to 2019 were analyzed, and these following observations noted: (1) immediate oral low-fat solid diet to patients with mild and moderate AP is safe and feasible; (2) Immediate oral refeeding was associated with a significant reduction in hospital length-of-stay (LOS) (3.4 vs 8.8 days, P < 0.001); (3) hospital costs were half as much, with a savings of 1325.7€/patient in the immediate oral compared to the conventional oral refeeding group, and (4) comparing the outcome of the groups showed no increased risk of complications.[1]

This proposed study seeks to prospectively evaluate a new scope in the care of patients with MAP and is justified based on these three points: 1) patients with MAP usually achieve a complete recovery of their symptoms in less than a week with conservative management (intravenous hydration, analgesia, and early diet); 2) clinical prognostic scoring systems, although criticized for their poor positive predictive value for severe AP, have an excellent negative predictive value to determine which patients will have MAP early in their hospitalization; and 3) factors that predict hospital readmission within 30 days in AP have been studied and can be applied.[8-15]

The International Association of Pancreatology/American Pancreatic Association (IAP/APA) guidelines[4] advise using the presence of systemic inflammatory response syndrome (SIRS) to predict severe AP at admission and persistent SIRS at 48h. The three dimensions recommended by the guidelines for risk approximation are: (1) host risk factors (age, co-morbidity, body mass index), (2) clinical risk stratification (persistent SIRS), (3) monitoring response (persistent SIRS, blood urea nitrogen, creatinine). There are many predictive scoring systems and serum markers none have been shown to be better or worse predictors of
severity than SIRS.[4] Thus, the bedside index of severity in acute pancreatitis (BISAP) score, which includes the SIRS in its parameters, provides one more tool to approximate the patient's risk in the aforementioned three dimensions.

Ince et al[10], showed that MAP can be safely treated at home with regular visits by a nurse under the supervision of a physician with large cost savings. A recent cohort study, which included 419 patients, showed that after appropriate triage MAP patients can safely discharged from the emergency room (ER) after a mean of 12h with improved outcomes and cost savings.[11]

Therefore, to carry out this study which proposes to compare outpatient and homecare treatment with hospitalization for patients with MAP, strict criteria for predicting severity will need to be fulfilled. The main objective of this trial is to determine whether, in MAP cases, outpatient treatment or homecare is similar to standard with hospital admission treatments in terms of diet tolerance, pain control, risk of severity, complications, patient’s satisfaction, and health cost.

METHODS

Design

This is a randomized controlled three-arms multicenter trial. Patients with MAP will be randomly divided into three groups. Group A: outpatient treatment, group B: medical homecare, and group C: hospitalization.

Study population

All patients diagnosed with MAP (after 24h in the ER) will be informed of the possibility of participating in the PADI_2 study. After the informed consent form (ICF) is signed, investigator will have access to the electronic patient report form (ePRF) and will generate random number that will be the treatment arm to follow (group A, B or C).

To confirm a MAP, severity scores (SIRS, BISAP) of patients who have been in the ER for 24 hours will be used, (Figure 1, Appendix 1).
Inclusion criteria

The inclusion criteria are: (1) patient older than 18 years of age; (2) diagnosed with AP using at least two of these three criteria: compatible abdominal pain, amylase or lipase level superior in three-fold respective laboratory baseline levels, and suitable findings in imaging techniques (CT, ultrasound or MRI)[4]; (3) MAP; (4) signed written ICF; (5) compliance with outpatient or homecare criteria; and (6) randomization at 24 hours of stay in the ER.

Outpatient or homecare criteria

1. A companion who understands and accepts the process and who will cooperate with the patient's recovery at home.
2. A mobile or telephone to communicate with the patient or her family member.
3. The distance to the hospital should be a maximum of 45-60 minutes.

Exclusion criteria

The exclusion criteria are: (1) pregnant or breastfeeding women; (2) abdominal pain >96 hours (4 days); (3) the possibility of poor oral intake or unable to eat for reasons other than AP; (4) pancreatic neoplasm, endoscopic retrograde cholangiopancreatography, or trauma etiology; (5) Choldedocholithiasis and/or cholangitis; (6) chronic or recurrent pancreatitis; (7) ASA ≥3; (8) expected moderate or severe acute pancreatitis; and (9) alcohol withdrawal syndrome for patients with alcoholism.

Sample size

Only two studies with a similar objective have ever been reported,[10,11] and a treatment failure rate of 4-12% was observed in the home monitoring (outpatient/homecare) group. Using calculations for a non-inferiority study with an estimated 95% success rate, 80% power, 5% significance level, and 10% inferiority limit, a sample size of 75 patients per study group was calculated (total = 225 patients).

Randomization

Randomization will use a computer-generated random number based on predefined randomization lists created separately for each recruiting center. The ePRF will implement a block randomization method with a sequence of 1:1:1. After confirming a MAP and obtaining ICF, physicians on call at the different centers will have access
to the ePRF and generate the randomization sequence according to the REDCap registry. Enrollment will be unblinded for patients and physicians due to the nature of the intervention.

**Duration**

The planned starting date of the study is November 1, 2022, and the planned finishing date of the study is November 30, 2024.

**Intervention**

After a 24-hour stay in the ER, the predictive factors of severity evaluation and the diagnosis of MAP will be confirmed, the patient will sign ICF and be randomized into group A, B or C (Table 1). The experimental groups are A or B and the control group is C. For all the groups, the first follow-up will be at week 1, and the subsequent follow-up will be at 1-3 months after hospital discharge (Table 1). The patients will be asked to complete the security/satisfaction survey[16] at the last follow-up.

**Groups**

Group A, outpatient: the patient is discharged and contacted by phone daily for 4 consecutive days by the investigators in the corresponding center.

Group B, medical homecare: the patient is discharged and contacted by phone/visits by a nurse/doctor daily for 4 consecutive days by the medical home care department in the corresponding center.

Group C, hospital admission: the patient is hospitalized in the corresponding center.

**General treatment**

General treatment, indicated by the IAP/APA guidelines,[4] - fluid therapy, symptom control and dietary support - will be performed for the first 24h, in the ER for all patients with AP. The early diet is PADI_1[1] (Low-fat-diet immediately). After 24h, the treatment will be oral intake (antiemetics, painkillers, diet) by all three groups. Blood sample will be obtained 48-72h after discharge from the hospital.
or nearly primary care provider, B homecare team, and C in the hospital. The patients will be asked to complete the security/satisfaction survey\cite{16} at the last follow-up.

**Table 1.** Schedule of enrollment, interventions, and assessments according to the SPIRIT 2013 statement\cite{17}

Patients will be randomized to group A (outpatient), B (home care), C (hospital admission). Online supplementary contains the User Manual of the REDCap/PADI_2 that contains the parameters collected on admission, 24h in ER, and during the first days and 3 months after discharge.

<table>
<thead>
<tr>
<th>STUDY PERIOD</th>
<th>Enrollment</th>
<th>Allocation</th>
<th>Post-allocation</th>
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<tr>
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<td>Day 3</td>
<td>Day 4</td>
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<td></td>
<td>Discharge</td>
<td>Control</td>
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<td></td>
<td>Week 1</td>
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<td></td>
<td>1-3 month</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>after discharge</td>
</tr>
</tbody>
</table>

**ENROLMENT**

- Eligibility screen: X
- Informed consent: X
- [List other procedures]: X
- Allocation: X

**INTERVENTIONS**

- Group A: outpatient
  - X
  - .
  - __
  - ___
  - ____
  - ___

- Group B: home care
  - X
  - .
  - __
  - ___
  - ____
  - ___

- Group C: hospital admission
  - X
  - .
  - __
  - ___
  - ____
  - ___

**ASSESSMENTS**

- Questionnaire admission: X
Predictors of severity

Predictors of severity will be considered when: (1) SIRS $\geq 2$ criteria, (2) BISAP$\geq 2$ score, and (3) organ failure.

Discharge of patients

Patients will be counted as discharged from hospital/outpatient/home care, when: (1) oral feeding is tolerated ($\geq 50\%$ of plates), (2) absence of nausea and vomiting with treatment, (3) pain controlled with oral analgesia (VAS$\leq 2$), and (4) clinical characteristics without predictors of severity.

Failure to meet the abovementioned criteria within 1 week after ER discharge generates the need for hospital admission and must be considered as failed treatment in PADI_2.

Primary endpoint

The primary endpoint of the trial will be the treatment failure rate of the outpatient/homecare PADI_2 management for patients with MAP compared to hospitalized patients.

Failure of treatment PADI_2, definition:

The following will be considered failure of treatment: (1) diet intolerance (<50% of plates), (2) uncontrolled nausea or vomiting despite treatment, (3) uncontrolled pain despite oral painkillers, and (4) predictors of severity are present.

Secondary endpoints

BS: Blood Samples; SSS: Security-Satisfaction survey [17]
Secondary endpoints that will be analyzed: (1) pain relapse, (2) diet tolerance, (3) use enteral/parenteral nutrition, (4) hospital readmission, (5) LOS, (6) ICU admission, (7) organ failure, (8) complications, (9) health costs, (10) patient satisfaction/security, (11) SIRS, (12) BISAP, and (13) analytical parameters at hospital admission and 24h and 72h after discharge from ER. Only direct costs will be calculated (all medications, services, salaries of healthcare professionals, equipment, hospital bed cost) in the coordinating hospital.

**Monitored parameters**

There will be a large assortment of parameters monitored during the study (medical history, ASA score, physical examination, laboratory tests, diagnostic imaging, therapy, interventions, cost, satisfaction survey[16]). Data collection on the ePRF will be done electronically in REDCap/PADI_2 (see data management).

**Clinical parameters:** mean arterial pressure, heart rate, temperature, Glasgow scale, and abdominal pain.

**Analytical parameters:** white blood cells count, hematocrit, blood urea nitrogen, creatinine, amylase, lypase, glucose, and bilirubin.

**Trial organization**

PADI_2 is coordinated by the Joan XXIII University Hospital of Tarragona, Spain, the group that published the PADI_1 study that permitted advances in AP treatment.

**Coordinating Committee (CC)**

The CC will be led by ERM, RJM, MRR, and RM (Surgeons, University Hospital of Tarragona Joan XXIII, Rovira i Virgili University, Tarragona, Spain); CF (Surgeon, IdiPAZ, CIBERehd, La Paz University Hospital, Madrid, Spain); SLG (Surgeon, Health Consortium Maresme, Matarò, Spain); AS (Gastroenterologist, Barcelona Clinic Hospital, IDIBAPS, CIBEREHD, University of Barcelona, Barcelona, Spain); SG and DCLL (Surgeons, Moise’s Broggi Hospital, CSI, Barcelona, Spain).

**Independent data monitoring committee (IDMC)**

The Independent Data Manager Committee Data (IDMC) will manage data, data security, and monitoring.

**Data review meeting (DRM)**

Members are a delegated investigator, biostatistician, and data manager.
Data management and statistical analyses

Data management

Data will be managed by the IDMC, and ePRF will be used. The Investigator will ensure that the data in the ePRF are complete and accurate. Detailed data flow will be described in a Data Management Plan (DMP) reflected in a REDCap/PADI_2 user manual. Data from completed ePRFs will be accepted under the direction of the Data Manager at IDMC. Any incongruous or missing recordings in the ePRFs will be returned to the Investigator using a Data Query Form (DQF) and documented for each individual subject before clean file status is declared. All changes to ePRFs will be recorded. Before Data Base Lock the DRM will decide and document necessary steps related to any issue in the database and define the analysis sets. DRM will be responsible for protecting confidentially of patients before, during, and after the trial.

Study populations

Three populations will be defined:

Safety Analysis Population (SAP): all patients with confirmed MAP enrolled in the study.
Per-Protocol Population (PPP): all enrolled patients who completed the study following all the rules.
Intention to Treat (ITT): the set of all randomized participants who start a treatment, excluding consent withdrawals.

Withdrawal of a participant from PPP

Any investigator and the IDMC can submit recommendations for dropouts from the PPP group with reasons given to the CC. All recommendations will be archived. The CC will discuss all available information and, if the change in the protocol would be expected to have any relation to the interventions and results of the study, the case will not be included in the final per-protocol analysis. Immediate dropout from the per-protocol group will be ordered if: (1) any of the exclusion criteria are diagnosed during AP, (2) any predictor of severity is present, (3) parameters required for answering the primary endpoints are missing, or (4) for serious medical reasons not related to AP (e.g., heart attack, accidents, etc.).

Applied software
Data collection on the ePRF form and randomization will be done electronically in Research Electronic Data Capture 9.8.0 (REDCap/PADI_2). Statistical analysis will be performed using Statistical Analysis System - SAS 9.4 or Statistical Package for the Social Sciences - SPSS 21 (or later) statistical packages. Microsoft MS Word will be used for reporting.

**Statistical methods**

First, the descriptive analysis will be carried out for each variable. Central tendency (mean or median) and dispersion (standard deviation or IQR) measures will be provided for quantitative variables and absolute frequencies and percentages for qualitative variables.

Between group comparisons for quantitative variables under the assumption of normality will use a one-way ANOVA with Tukey's post hoc test to compare means of pairs of groups. In case of non-normality the Kruskal-Wallis test will be used and multiple comparisons carried out with Mann-Whitney tests, adjusting p-values by Bonferroni. For qualitative variables, the chi-square test ($\chi^2$) will be used, applying Fisher's exact test when deemed necessary. Actuarial survivals will be calculated using the Kaplan-Meier method and their comparison between groups will be carried out using the Log-Rank test. All the outcomes will be analyzed in intention-to-treat population (defined as participants randomized). The confidence level will always be 95% and p-values reported with sensible precision.

In the multivariate survival analysis, the Cox regression method will be used, while for the multivariate analysis of risk factors, the logistic regression method will be used. Variables that show statistical significance in the univariate analysis and/or those that are prognostic factors in the bibliography and theoretical framework will be introduced to the statistical model.

**Early quality assessment**

An early quality assessment check will be performed on the first 70 patients. The IDMC will independently review the trial-related documents and activities, to ensure the rights, safety, and welfare of participants are respected and the clinical data are credible. The similarity of the groups will also be checked at the beginning of the study. The IDMC will report these findings to the CC. The CC will discuss all the information and, if the differences would be expected to have any relation on the interventions and results of the study or the
overall dropout rate from PPP is >20% of all participants randomized or allocated into each group or the
differential dropout rate is >15% between groups, the study should be reassessed and the IDMC will make
recommendations regarding reassessment of power calculation, extension of recruitment period, extension of
number of study centers, or trial completion.

**Interim analyses and premature termination of the study**

The IDMC may also recommend stopping the trial early for ethical reasons if one group clearly shows evidence
of significant benefit. An interim analysis on the primary endpoint will be performed when 50% of patients
have been randomized and discharged. The interim analysis will be carried out by the IDMC, who will report
to the CC.

The Haybittle–Peto boundary method, which states that if the interim analysis shows a probability of $\leq 0.001$
that a difference as extreme or more between the treatments is found, given that the null hypothesis is true,
then the trial should be stopped early, will be used in this study.

**Centers**

The trial will start in four centers, who also participated in the PADI_1: Joan XXIII University Hospital of
Tarragona, Barcelona Clinic Hospital, Health Consortium Maresme and, Moise’s Broggi Hospital. After which
the study is open for other centers. The IDMC will always audit the center and report to the CC. The CC may
decide whether the center meets the requirements to join the study. Compulsory requirements for a center are:
(1) treats at least 30 patients with AP annually, (2) has a homecare department, (3) besides the regular medical
team, the center must appoint at least one doctor and one nurse specifically for the trial, and (4) all investigators
need to attend a preliminary meeting where all the details of the study is discussed fully and have qualified as
investigators by completing a course, either online or face-to-face.

**Authorship aspects**

Authorships are based on international guidelines: all authors must fulfill the International Committee of
Medical Journal of Editors criteria (see [www.icmje.org/journals.html](http://www.icmje.org/journals.html)). All collaborating centers providing
over 25 patients can be afforded one author. Every additional 20 patients will provide the center an additional
author. Every center can also include formal ‘collaborators’ on the project, which the journal will be asked to
list in PubMed at final publication. The first three authorship positions are reserved for the study coordinators (ERM, MRR, SLG) and the last two authorship positions are reserved for the senior investigators (RJM, CF). All other authors will be listed in numerical order according to the number of patients contributed to the study. Collaborators will be listed in alphabetical order as part of the ‘Catalan Pancreatitis Collaborative Group’.

**Feasibility**

As a general protocol to treat AP at the Joan XXIII University Hospital, patients with AP receive PADI treatment adjusted to the IAP/APA guidelines.[4] Patients in PADI receive diet immediately on their arrival in the ward from the ER once their symptoms have been controlled. Comparing the outcome of this treatment protocol with the nil per os protocol used in most hospitals showed that patients enjoyed benefits with no increasing the risk of complications. About 100 patients are admitted to the existing PADI hospitals annually. Therefore, if no other institution joins this study, it can be completed within 2-3 years.

**Safety**

Since no unknown drugs/therapy are used in the study, no adverse or serious adverse events are expected/interpretable that would be attributable to the intervention during the trial. As for the outpatient group, although it is a telephonic follow-up, it will be performed daily by the investigator team, asking for clear clinical parameters. Blood samples will also be obtained on the same day as in the other groups to identify predictors of severity that require the immediate hospital admission. In this trial the IDMS will examine safety variables after every 20 patients complete the program. Investigators will also report adverse or serious adverse events on a separate form which must be sent to the IDMS and CC. The CC will discuss and, if the adverse effect is confirmed, it will be reported to the relevant institutional ethical committee (http://www.iispv.cat).

**Patient and public involvement**

None

**DISCUSSION**

Here we report the protocol of a prospective multicenter, randomized, controlled, three-arm trial which provides the first type A evidence regarding a new safe and effective outpatient/homecare treatment
in selected patients with MAP. This study is suitable for clinical practice. We have only been able to find two studies in the literature that shows that home monitoring treatment of MAP patients is safe, with improved outcomes and hospital cost savings.[10,11] They found that only 3.6-12% of patients required hospital readmission. PADI_1 study demonstrated that immediate diet was safe and effective in MAP patients, leading to a significant reduction in LOS. With this experience, we want to take a step forward in the treatment of these patients and that is why we dare to propose the PADI_2. Our main hypothesis is that Outpatient/homecare management of patients with MAP is just as safe and effective as hospital treatment, without complications and with savings in health care cost and no effect on patient satisfaction. Concerning ethical issues, this study is very low risk for patients. Therefore, although no adverse events are expected, there will be a close follow-up and if a patient presents some initial treatment failure, they will immediately be re-admitted to the hospital.

ETHICS AND DISSEMINATION

The trial is registered at the ClinicalTrials.gov registry (NCT05360797) and received relevant ethical approval with the reference number 093/2022 issued by the Scientific and Research Ethics Committee of the Institut d’Investigació Sanitaria Pere Virgili-IISPV. At the end of the project we will disseminate our results to the medical community and publish it as open access.

Authors affiliations

1General and Digestive Surgery Department, University Hospital of Tarragona Joan XXIII, Rovira i Virgili University, Tarragona, Spain; 2General and Digestive Surgery Department, Maresme Health Consortium, Matarò, Spain; 3Gastroenterology Department, Barcelona Clinic Hospital, IDIBAPS, CIBEREHD, University of Barcelona, Barcelona, Spain; 4General and Digestive Surgery Department, Moïse’s Broggi Hospital, CSI, Barcelona, Spain; 5Clinical Nutrition Department, 6Gastroenterology Department, The Third People’s Hospital of Chengdu, Affiliated Hospital of Southwest Jiaotong University, Chengdu, China; 7Arnau de Vilanova University Hospital, Lleida, Spain; 8Hepato-pancreato-biliary and Transplant Surgery Department, Vall d’Hebron University Hospital, Barcelona, Spain; 9Althaia University Hospital, Xarxa Asistencial Universitària de Manresa, Sant Joan de Déu Hospital, Manresa, Spain; 10 Hospital Garcia de Orca EPE, Almada, Portugal;
11 General and Digestive Surgery Department, IdiPAZ, CIBERehd, La Paz University Hospital, Madrid, Spain;
12 Investigators and Co-investigators from participant hospitals.

ACKNOWLEDGEMENTS

The principal investigator wish to thank Dr. Péter Hegyi and the Hungary Pancreatic Study group for everything they have contributed to my process as researcher. This work will be supported by research grants award from the ‘Catalan society of surgeons’ and ‘Spanish Association of Surgeons’. Finally, the authors to thank Editage (www.editage.com) for their assistance in editing and improving this manuscript.

List of Abbreviations

AP Acute Pancreatitis
ASA American Society of Anesthesiologist
BISAP Bedside Index of Severity in Acute Pancreatitis
CC Coordinating Committed
CT Computed Tomography
DMP Data Management Plan
DQF Data Query Form
DRM Data Review Meeting
ER Emergency Room
eRPF electronic Patient Report Form
IAP/APA International Association of Pancreatoloy/American Pancreatic Association
ICF Informed Consent Form
ICU Intensive Care Unit
IDMC Independent Data Monitoring Committee
ITT Intention to Treat
MAP Mild Acute Pancreatitis
MRI Magnetic Resonance Imaging
PPP Per-Protocol population
SAP Safety Analysis Population
SIRS Systemic Inflammatory Response Syndrome
VAS Visual Analog Scale

FUNDING

This work will be supported by research grants awarded from the ‘Catalan society of surgeons’ and ‘Spanish Association of Surgeons’.

AUTHOR CONTRIBUTIONS

ERM, SLG, and RJM participated in all phases of the study with the help other authors in the different parts. Conception and design: ERM, RJM, SLG, AS, and CF.

Administrative, technical, or logistic support: ERM, RJM, SLG, AS, CF, DCLL, JL, PW, JJ, LB, RSJ, JV, and MRR.

Drafting of the article: RM, RJM, SLG, AS, CF, DCLL, JL, PW, JJ, LB, RSJ, JV, MRR, and the Catalan Pancreatitis Collaborative Group.

Critical revision of the article for important intelectual content: RM, RJM, SLG, AS, CF, DCLL, JL, PW, JJ, LB, RSJ, JV, MRR.

All authors read and approved the final manuscript.

CONFLICTS OF INTERESTS

The authors declare that they have no conflicts of interest.

REFERENCES


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   10.1002/jhbp.260.

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   Randomized Trial of Clear Liquids vs. Low-fat Solid Diet as the Initial Meal in Mild Acute Pancreatitis. 

   possible? observational prospective study in a tertiary-level hospital. *Pancreatology* 2017;**17**:669-74. doi: 

9. Kumar VV, Treacy PJ, Li M, Dharmawardane A. Early discharge of patients with acute pancreatitis to 

    home monitoring versus hospitalization for mild non-alcoholic acute interstitial pancreatitis: A pilot study. 

    prevent hospitalization in mild acute pancreatitis: outcomes and predictors of discharge. *Pancreatology* 

12. Pando E, Alberti P, Mata R, et al. Early changes in blood urea nitrogen (BUN) can predict mortality in 
    acute pancreatitis: comparative study between BISAP score, APACHE-II, and other laboratory markers. 


Figure 1. Flow chart of participants according to the SPIRIT 2013 statement[17]
Adult patients with an episode of acute pancreatitis (AP)

Exclusions
Not meeting inclusion criteria
(1) Patient above 18y
(2) Diagnosed AP (2 out 3 criteria)
(3) Signed written informed consent form

Meeting exclusion criteria
(1) Pregnant or breastfeeding women
(2) Abdominal pain >96h
(3) The possibility of poor oral intake for reasons other than AP
(4) Pancreatic neoplasm, endoscopic retrograde cholangiopancreatography or trauma etiology, biliar obstruction
(5) Chronic pancreatitis
(6) ASA ≥3
(7) Moderate or severe acute pancreatitis;
(8) the patient is considered unable to eat an oral diet for other reasons than AP

Stay in the emergency room for 24 h

Mild acute pancreatitis confirmed

X patients to be randomized

Outpatient

Home Care

Hospital Admission

X analysed

X analysed

X analysed
Acute pancreatitis (AP)
compliance with diagnostic criteria

Emergency stay for 24 hours

Intravenous fluids, analgesia and antiemetics for 24 hours

Diagnosis of MILD AP
Analytics at 24 hours
Pain scale VAS≤2
Diet tolerance >50%

Compliance with the inclusion criteria and none of the exclusion criteria
NO PREDICTIVE FACTORS OF SEVERITY
Mild exit criteria
Sign the informed consent

Randomization

Home hospitalization
Phone call in the afternoon
Diary visit
Blood sample 24-48 hours

Outpatient treatment
Phone call in the afternoon
Daily call phone
Blood sample 24-48 hours

Hospitalization
Evolution during admission
Admission
Blood sample 24-48 hours

AP Severity Predictors
- BUN on admission >23 mg/dl
- BUN increase at 24 h >1.87mg/dl
- SIRS ≥ 2 criteria
- BISAP ≥2 score
- organ failure

Emergency/hospital discharge criteria
- Tolerance ≥50% of fat-free diet
- Absence of nausea and vomiting with or without treatment
- Controlled pain with oral analgesia VAS≤2
- Analysis without gravity predictive factors

After discharge: visit in surgery consultations
1 week after discharge and 3 months
Fill out satisfaction survey.

Failure of the PADI2 treatment protocol
- No tolerance to diet
- Nausea or vomiting
- Uncontrolled pain with prescribed analgesia
- Any severity predictive factors

Hospitalization
Discharge at 72-96 hours

Discharge home
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<tr>
<th>Section/item</th>
<th>Item No</th>
<th>Description</th>
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<tr>
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<td>4</td>
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<td>Sources and types of financial, material, and other support</td>
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<td>Roles and responsibilities</td>
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<td>Names, affiliations, and roles of protocol contributors</td>
<td>1, 19</td>
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<td>Name and contact information for the trial sponsor</td>
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<tr>
<td></td>
<td>5c</td>
<td>Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities</td>
<td>-</td>
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<tr>
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<td>5d</td>
<td>Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see item 21a for data monitoring committee)</td>
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<td>Introduction</td>
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<tr>
<td>Background and rationale</td>
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<td>Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention</td>
<td>6-7</td>
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<tr>
<td></td>
<td>6b</td>
<td>Explanation for choice of comparators</td>
<td>6-7</td>
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<tr>
<td>Objectives</td>
<td>7</td>
<td>Specific objectives or hypotheses</td>
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</tr>
<tr>
<td>Trial design</td>
<td>8</td>
<td>Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)</td>
<td>7</td>
</tr>
</tbody>
</table>

**Methods: Participants, interventions, and outcomes**
Study setting

Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained.

Eligibility criteria

Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists).

Interventions

11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered.

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease).

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests).

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial.

Outcomes

12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended.

Participant timeline

13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure).

Sample size

14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations.

Recruitment

15 Strategies for achieving adequate participant enrolment to reach target sample size.

Methods: Assignment of interventions (for controlled trials)

Allocation:

16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions.

16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned.
Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions

Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how

If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

Methods: Data collection, management, and analysis

Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known.

Reference to where data collection forms can be found, if not in the protocol

Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values).

Reference to where details of data management procedures can be found, if not in the protocol

Statistical methods

Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

Methods for any additional analyses (e.g., subgroup and adjusted analyses)

Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)

Methods: Monitoring

Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination
<table>
<thead>
<tr>
<th>Research ethics approval</th>
<th>24</th>
<th>Plans for seeking research ethics committee/institutional review board (REC/IRB) approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol amendments</td>
<td>25</td>
<td>Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)</td>
</tr>
<tr>
<td>Consent or assent</td>
<td>26a</td>
<td>Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)</td>
</tr>
<tr>
<td></td>
<td>26b</td>
<td>Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable</td>
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<tr>
<td>Confidentiality</td>
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<td>Authorship eligibility guidelines and any intended use of professional writers</td>
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<td>Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code</td>
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**Appendices**

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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license."
Home care/outpatient vs hospital admission in mild acute pancreatitis: protocol of a multicenter, randomized controlled trial (PADI_2 trial)

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| Complete List of Authors: | Ramirez-Maldonado, Elena; Joan XXIII University Hospital in Tarragona, General and Digestive Surgery Department
Rodrigo-Rodrigo, Marta; Joan XXIII University Hospital in Tarragona, General and Digestive Surgery Department
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The Catalan Pancreatitis Collaborative Group, The Catalan Pancreatitis; Joan XXIII University Hospital in Tarragona, General and Digestive Surgery Department |
| Primary Subject Heading: | Gastroenterology and hepatology |
| Secondary Subject Heading: | Emergency medicine, General practice / Family practice, Medical management, Surgery |
| Keywords: | Pancreatic disease < GASTROENTEROLOGY, Pancreatic surgery < SURGERY, Clinical trials < THERAPEUTICS |
Title

Home care/outpatient vs hospital admission in mild acute pancreatitis: protocol of a multicenter, randomized controlled trial (PADI_2 trial)

Authors

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**Running head**

Outpatient in mild acute pancreatitis

**Keywords**

Acute pancreatitis; outpatient; homecare; early oral refeeding; length of hospital stay; pain relapse.
ABSTRACT

Introduction: Acute pancreatitis (AP) is the third most common gastrointestinal disease resulting in hospital admission, with over 70% of AP admissions being mild cases. In the United States, it costs 2.5 billion dollars annually. The most common standard management of mild AP (MAP) still is hospital admission. Patients with MAP usually achieve complete recovery in less than a week and the severity predictor scales are reliable. The aim of this study will be to compare three different strategies for the management of MAP.

Methods/design: This is a randomized, controlled, three-arm multicenter trial. Patients with MAP will be randomly assigned to group A (outpatient), B (home care), or C (hospital admission). The primary end point of the trial will be the treatment failure rate of the outpatient/homecare management for patients with MAP compared to that of hospitalized patients. The secondary endpoints will be pain relapse, diet intolerance, hospital readmission, hospital length-of-stay, need for ICU admission, organ failure, complications, costs, and patient satisfaction. The general feasibility, safety, and quality checks required for high quality evidence will be adhered to.

Ethics and dissemination: The study (version 3.0, 10/2022) has been approved by the Scientific and Research Ethics Committee of the `Institut d'Investigació Sanitaria Pere Virgili-IISPV’ (093/2022). This study will provide evidence as to whether outpatient/homecare are similar to usual management of AP. The conclusions of this study will be published in an open access journal.

Trial registration: The trial is registered at the ClinicalTrials.gov (NCT05360797).
STRENGTHS AND LIMITATIONS

1. Strength 1: A multidisciplinary team wrote this protocol.

2. Strength 2: The established treatment is the standard in patients with mild acute pancreatitis.

3. Strength 3: An Independent Data Manager Committee will be ensuring security and monitoring data.

4. Limitation 1: The three-arm method of the study requires a multidisciplinary team on the project which may limit the number of centers that can join.

5. Limitation 2: Lack of blinding increases the risk of performance bias, since the participants will be aware of their group assignment.
BACKGROUND

Acute pancreatitis (AP) is one of the most common reasons for hospitalization among gastrointestinal diseases worldwide. The costs caused by severe AP are higher than those for mild AP (MAP). Nevertheless, approximately 70% of hospital admissions for AP are MAP so, if savings in healthcare costs are to be achieved, it would be by lowering the cost of managing patients with MAP without complication or affecting patient safety and satisfaction.[1-7]

Patients in the PADI_1 study[1] from 2017 to 2019 were analyzed, and these following observations noted: (1) immediate oral low-fat solid diet to patients with mild and moderate AP is safe and feasible; (2) Immediate oral refeeding was associated with a significant reduction in hospital length-of-stay (LOS) (3.4 vs 8.8 days, P < 0.001); (3) hospital costs were half as much, with a savings of 1325.7€/patient in the immediate oral compared to the convencional oral refeeding group, and (4) comparing the outcome of the groups showed no increased risk of complications.[1]

This proposed study seeks to prospectively evaluate a new scope in the care of patients with MAP and is justified based on these three points: 1) patients with MAP usually achieve a complete recovery of their symptoms in less than a week with conservative management (intravenous hydration, analgesia, and early diet); 2) clinical prognostic scoring systems, although criticized for their poor positive predictive value for severe AP, have an excellent negative predictive value to determine which patients will have MAP early in their hospitalization; and 3) factors that predict hospital readmission within 30 days in AP have been studied and can be applied.[8-16]

The International Association of Pancreatology/American Pancreatic Association (IAP/APA) guidelines[4] advise using the presence of systemic inflammatory response syndrome (SIRS) to predict severe AP at admission and persistent SIRS at 48h. The three dimensions recommended by the guidelines for risk approximation are: (1) host risk factors (age, co-morbidity, body mass index), (2) clinical risk stratification (persistent SIRS), (3) monitoring response (persistent SIRS, blood urea nitrogen, creatinine). There are many predictive scoring systems and serum markers none have been shown to be better or worse predictors of...
severity than SIRS.[4] Thus, the bedside index of severity in acute pancreatitis (BISAP) score, which includes the SIRS in its parameters, provides one more tool to approximate the patient's risk in the aforementioned three dimensions.

Ince et al[10], showed that MAP can be safely treated at home with regular visits by a nurse under the supervision of a physician with large cost savings. A recent cohort study, which included 419 patients, showed that after appropriate triage MAP patients can safely discharged from the emergency room (ER) after a mean of 12h with improved outcomes and cost savings.[11]

Therefore, to carry out this study which proposes to compare outpatient and homecare treatment with hospitalization for patients with MAP, strict criteria for predicting severity will need to be fulfilled. The main objective of this trial is to determine whether, in MAP cases, outpatient treatment or homecare is similar to standard with hospital admission treatments in terms of diet tolerance, pain control, risk of severity, complications, patient’s satisfaction, and health cost.

METHODS

Diagnosis and classification of AP

According to the Revised Atlanta criteria 2012 [12], the diagnosis of AP requires two of the following three features: (1) onset of upper abdominal pain often radiating to the back; (2) serum lipase or amylase level at least three times higher than the normal upper limit; (3) characteristics findings of AP on imaging techniques such as contrast-enhanced CT, ultrasonography (US) and/or magnetic resonance imaging. Severity of AP was classified as Mild (no organ failure, local or systemic complications), Moderately severe (presence of transient organ failure, local complications or exacerbation of comorbid disease), Severe (persistent organ failure (>48 hours) affecting respiration, renal function or the cardiovascular system). [12]

Design

This is a randomized controlled three-arms multicenter trial. Patients with MAP will be randomly divided into three groups. Group A: outpatient treatment, group B: medical homecare, and group C: hospitalization.
Study population

All patients diagnosed with MAP (after 24h in the ER) will be informed of the possibility of participating in the PADI_2 study. After the informed consent form (ICF) is signed, investigator will have access to the electronic patient report form (ePRF) and will generate random number that will be the treatment arm to follow (group A, B or C).

To confirm a MAP, severity scores (SIRS, BISAP) of patients who have been in the ER for 24 hours will be used, (Figure 1, Appendix 1).

Inclusion criteria

The inclusion criteria are: (1) patient older than 18 years of age; (2) diagnosed with AP using at least two of these three criteria: compatible abdominal pain, amylase or lipase level superior in three-fold respective laboratory baseline levels, and suitable findings in imaging techniques (CT, ultrasound or MRI)[4]; (3) MAP; (4) signed written ICF; (5) compliance with outpatient or homecare criteria; and (6) randomization at 24 hours of stay in the ER.

Outpatient or homecare criteria

1. A companion who understands and accepts the process and who will cooperate with the patient's recovery at home.
2. A mobile or telephone to communicate with the patient or her family member.
3. The distance to the hospital should be a maximum of 45-60 minutes.

Exclusion criteria

The exclusion criteria are: (1) pregnant or breastfeeding women; (2) abdominal pain >96 hours (4 days); (3) the possibility of poor oral intake or unable to eat for reasons other than AP; (4) pancreatic neoplasm, endoscopic retrograde cholangiopancreatography, or trauma etiology; (5) Choldedocholithiasis and/or cholangitis; (6) chronic or recurrent pancreatitis; (7) ASA ≥3; (8) expected moderate or severe acute pancreatitis; and (9) alcohol withdrawal syndrome for patients with alcoholism.

Sample size
Only two studies with a similar objective have ever been reported,[10,11] and a treatment failure rate of 4-12% was observed in the home monitoring (outpatient/homecare) group. Using calculations for a non-inferiority study with an estimated 95% success rate, 80% power, 5% significance level, and 10% inferiority limit, a sample size of 75 patients per study group was calculated (total = 225 patients).

**Randomization**

Randomization will use a computer-generated random number based on predefined randomization lists created separately for each recruiting center. The ePRF will implement a block randomization method with a sequence of 1:1:1. After confirming a MAP and obtaining ICF, physicians on call at the different centers will have access to the ePRF and generate the randomization sequence according to the REDCap registry. Enrollment will be unblinded for patients and physicians due to the nature of the intervention.

**Duration**

The planned starting date of the study is November 1, 2022, and the planned finishing date of the study is November 30, 2024.

**Intervention**

After a 24-hour stay in the ER, the predictive factors of severity evaluation and the diagnosis of MAP will be confirmed, the patient will sign ICF and be randomized into group A, B or C (Table 1). The experimental groups are A or B and the control group is C. For all the groups, the first follow-up will be at week 1, and the subsequent follow-up will be at 1-3 months after hospital discharge (Table 1). The patients will be asked to complete the security/satisfaction survey [17] at the last follow-up.

**Groups**

Group A, outpatient: the patient is discharged and contacted by phone daily for 4 consecutive days by the investigators in the corresponding center.

Group B, medical homecare: the patient is discharged and contacted by phone/visits by a nurse/doctor daily for 4 consecutive days by the medical home care department in the corresponding center.
Group C, hospital admission: the patient is hospitalized in the corresponding center.

**General treatment**

General treatment, indicated by the IAP/APA guidelines,[4] - fluid therapy, symptom control and dietary support - will be performed for the first 24h, in the ER for all patients with AP. The early diet is PADI_1[1] (Low-fat-diet immediately). After 24h, the treatment will be oral intake (antiemetics, painkillers, diet) by all three groups. Blood sample will be obtained 48-72h after discharge from the as follows, group A in the hospital or nearly primary care provider, B homecare team, and C in the hospital. The patients will be asked to complete the security / satisfaction survey [17] at the last follow-up.

**Table 1.** Schedule of enrollment, interventions, and assessments according to the SPIRIT 2013 statement.[18] Patients will be randomized to group A (outpatient), B (home care), C (hospital admission). Online supplementary contains the User Manual of the REDCap/PADI_2 that contains the parameters collected on admission, 24h in ER, and during the first days and 3 months after discharge.
### INTERVENTIONS

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### ASSESSMENTS

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**BS**: Blood Samples; **SSS**: Security-Satisfaction survey [17]

### Predictors of severity

Predictors of severity will be considered when: (1) SIRS ≥2 criteria, (2) BISAP≥2 score, and (3) organ failure.

### Discharge of patients

Patients will be counted as discharged from hospital/outpatient/home care, when: (1) oral feeding is tolerated (≥50% of plates), (2) absence of nausea and vomiting with treatment, (3) pain controlled with oral analgesia (VAS≤2), and (4) clinical characteristics without predictors of severity.

Failure to meet the abovementioned criteria within 1 week after ER discharge generates the need for hospital admission and must be considered as failed treatment in PADI_2.
Primary endpoint

The primary endpoint of the trial will be the treatment failure rate of the outpatient/homecare management for patients with MAP compared to hospitalized patients.

Failure of treatment definition:

The following will be considered failure of treatment: (1) diet intolerance (<50% of plates), (2) uncontrolled nausea or vomiting despite treatment, (3) uncontrolled pain despite oral painkillers, and (4) predictors of severity are present.

Secondary endpoints

Secondary endpoints that will be analyzed: (1) pain relapse, (2) diet tolerance, (3) use enteral/parenteral nutrition, (4) hospital readmission, (5) LOS, (6) ICU admission, (7) organ failure, (8) complications, (9) health costs, (10) patient satisfaction/security, (11) SIRS, (12) BISAP, and (13) analytical parameters at hospital admission and 24h and 72h after discharge from ER. Only direct costs will be calculated (all medications, services, salaries of healthcare professionals, equipment, hospital bed cost) in the coordinating hospital.

Monitored parameters

There will be a large assortment of parameters monitored during the study (medical history, ASA score, physical examination, laboratory tests, diagnostic imaging, therapy, interventions, cost, satisfaction survey[17]). Data collection on the ePRF will be done electronically in REDCap/PADI_2 (see data management).

Clinical parameters: mean arterial pressure, heart rate, temperature, Glasgow scale, and abdominal pain.

Analytical parameters: white blood cells count, hematocrit, blood urea nitrogen, creatinine, amylase, lypase, glucose, and bilirubin.

Trial organization

PADI_2 is coordinated by the Joan XXIII University Hospital of Tarragona, Spain, the group that published the PADI_1 study that permitted advances in AP treatment.

Coordinating Committee (CC)
The CC will be led by ERM, RJM, MRR, and RM (Surgeons, University Hospital of Tarragona Joan XXIII, Rovira i Virgili University, Tarragona, Spain); CF (Surgeon, IdiPAZ, CIBERehd, La Paz University Hospital, Madrid, Spain); SLG (Surgeon, Health Consortium Maresme, Matarò, Spain); AS (Gastroenterologist, Barcelona Clinic Hospital, IDIBAPS, CIBEREHD, University of Barcelona, Barcelona, Spain); SG and DCLL (Surgeons, Moisè’s Broggi Hospital, CSI, Barcelona, Spain).

Independent data monitoring committee (IDMC)

The Independent Data Manager Committee Data (IDMC) will manage data, data security, and monitoring.

Data review meeting (DRM)

Members are a delegated investigator, biostatistician, and data manager.

Data management and statistical analyses

Data management

Data will be managed by the IDMC, and ePRF will be used. The Investigator will ensure that the data in the ePRF are complete and accurate. Detailed data flow will be described in a Data Management Plan (DMP) reflected in a REDCap/PADI_platform user manual. Data from completed ePRFs will be accepted under the direction of the Data Manager at IDMC. Any incongruous or missing recordings in the ePRFs will be returned to the Investigator using a Data Query Form (DQF) and documented for each individual subject before clean file status is declared. All changes to ePRFs will be recorded. Before Data Base Lock the DRM will decide and document necessary steps related to any issue in the database and define the analysis sets. DRM will be responsible for protecting confidentially of patients before, during, and after the trial.

Study populations

Three populations will be defined:

Safety Analysis Population (SAP): all patients with confirmed MAP enrolled in the study.

Per-Protocol Population (PPP): all enrolled patients who completed the study following all the rules.

Intention to Treat (ITT): the set of all randomized participants who start a treatment, excluding consent withdrawals.

Withdrawal of a participant from PPP
Any investigator and the IDMC can submit recommendations for dropouts from the PPP group with reasons given to the CC. All recommendations will be archived. The CC will discuss all available information and, if the change in the protocol would be expected to have any relation to the interventions and results of the study, the case will not be included in the final per-protocol analysis. Immediate dropout from the per-protocol group will be ordered if: (1) any of the exclusion criteria are diagnosed during AP, (2) any predictor of severity is present, (3) parameters required for answering the primary endpoints are missing, or (4) for serious medical reasons not related to AP (e.g., heart attack, accidents, etc.).

**Applied software**

Data collection on the ePRF form and randomization will be done electronically in Research Electronic Data Capture 9.8.0 (REDCap/PADI_2). Statistical analysis will be performed using Statistical Analysis System - SAS 9.4 or Statistical Package for the Social Sciences - SPSS 21 (or later) statistical packages. Microsoft MS Word will be used for reporting.

**Statistical methods**

First, the descriptive analysis will be carried out for each variable. Central tendency (mean or median) and dispersion (standard deviation or IQR) measures will be provided for quantitative variables and absolute frequencies and percentages for qualitative variables.

Between group comparisons for quantitative variables under the assumption of normality will use a one-way ANOVA with Tukey’s post hoc test to compare means of pairs of groups. In case of non-normality the Kruskal-Wallis test will be used and multiple comparisons carried out with Mann-Whitney tests, adjusting p-values by Bonferroni. For qualitative variables, the chi-square test ($\chi^2$) will be used, applying Fisher's exact test when deemed necessary. Actuarial survivals will be calculated using the Kaplan-Meier method and their comparison between groups will be carried out using the Log-Rank test. All the outcomes will be analyzed in intention-to-treat population (defined as participants randomized). The confidence level will always be 95% and p-values reported with sensible precision.

In the multivariate survival analysis, the Cox regression method will be used, while for the multivariate analysis of risk factors, the logistic regression method will be used. Variables that show statistical significance
in the univariate analysis and/or those that are prognostic factors in the bibliography and theoretical framework will be introduced to the statistical model.

**Early quality assessment**

An early quality assessment check will be performed on the first 70 patients. The IDMC will independently review the trial-related documents and activities, to ensure the rights, safety, and welfare of participants are respected and the clinical data are credible. The similarity of the groups will also be checked at the beginning of the study. The IDMC will report these findings to the CC. The CC will discuss all the information and, if the differences would be expected to have any relation on the interventions and results of the study or the overall dropout rate from PPP is >20% of all participants randomized or allocated into each group or the differential dropout rate is >15% between groups, the study should be reassessed and the IDMC will make recommendations regarding reassessment of power calculation, extension of recruitment period, extension of number of study centers, or trial completion.

**Interim analyses and premature termination of the study**

The IDMC may also recommend stopping the trial early for ethical reasons if one group clearly shows evidence of significant benefit. An interim analysis on the primary endpoint will be performed when 50% of patients have been randomized and discharged. The interim analysis will be carried out by the IDMC, who will report to the CC.

The Haybittle–Peto boundary method, which states that if the interim analysis shows a probability of $\leq 0.001$ that a difference as extreme or more between the treatments is found, given that the null hypothesis is true, then the trial should be stopped early, will be used in this study.

**Centers**

The trial will start in four centers, who also participated in the PADI_1: Joan XXIII University Hospital of Tarragona, Barcelona Clinic Hospital, Health Consortium Maresme and, Moise’s Broggi Hospital. After which the study is open for other centers. The IDMC will always audit the center and report to the CC. The CC may decide whether the center meets the requirements to join the study. Compulsory requirements for a center are: (1) treats at least 30 patients with AP annually, (2) has a homecare department, (3) besides the regular medical
team, the center must appoint at least one doctor and one nurse specifically for the trial, and (4) all investigators need to attend a preliminary meeting where all the details of the study is discussed fully and have qualified as investigators by completing a course, either online or face-to-face.

**Authorship aspects**

Authorships are based on international guidelines: all authors must fulfill the International Committee of Medical Journal of Editors criteria (see [www.icmje.org/journals.html](http://www.icmje.org/journals.html)). All collaborating centers providing over 25 patients can be afforded one author. Every additional 20 patients will provide the center an additional author. Every center can also include formal ‘collaborators’ on the project, which the journal will be asked to list in PubMed at final publication. The first three authorship positions are reserved for the study coordinators (ERM, MRR, SLG) and the last two authorship positions are reserved for the senior investigators (RJM, CF). All other authors will be listed in numerical order according to the number of patients contributed to the study. Collaborators will be listed in alphabetical order as part of the ‘Catalan Pancreatitis Collaborative Group’.

**Feasibility**

As a general protocol to treat AP at the Joan XXIII University Hospital, patients with AP receive PADI_1 treatment adjusted to the IAP/APA guidelines.[4] Patients in PADI_1 receive diet immediately on their arrival in the ward from the ER once their symptoms have been controlled. Comparing the outcome of this treatment protocol with the nil per os protocol used in most hospitals showed that patients enjoyed benefits with no increasing the risk of complications. About 100 patients are admitted to the existing PADI_1 hospitals annually. Therefore, if no other institution joins this study, it can be completed within 2-3 years.

**Safety**

Since no unknown drugs/therapy are used in the study, no adverse or serious adverse events are expected/interpretable that would be attributable to the intervention during the trial. As for the outpatient group, although it is a telephonic follow-up, it will be performed daily by the investigator team, asking for clear clinical parameters. Blood samples will also be obtained on the same day as in the other groups to identify predictors of severity that require the immediate hospital admission. In this trial the IDMS will examine safety variables after every 20 patients complete the program. Investigators will also report adverse or serious adverse
events on a separate form which must be sent to the IDMS and CC. The CC will discuss and, if the adverse
effect is confirmed, it will be reported to the relevant institutional ethical committee (http://www.iispv.cat).

**Patient and public involvement**

None

**ETHICS AND DISSEMINATION**

The trial is registered at the ClinicalTrials.gov registry (NCT05360797) and received relevant ethical approval
with the reference number 093/2022 issued by the Scientific and Research Ethics Committee of the Institut
d’Investigació Sanitaria Pere Virgili-IISPV. At the end of the project we will disseminate our results to the
medical community and publish it as open access.

**Authors affiliations**

1 General and Digestive Surgery Department, University Hospital of Tarragona Joan XXIII, Rovira i Virgili
University, Tarragona, Spain; 2 General and Digestive Surgery Department, Maresme Health Consortium,
Matarò, Spain; 3 Gastroenterology Department, Barcelona Clinic Hospital, IDIBAPS, CIBEREHD, University
of Barcelona, Barcelona, Spain; 4 General and Digestive Surgery Department, Moise’s Broggi Hospital, CSI,
Barcelona, Spain; 5 Althaia University Hospital, Xarxa Asistencial Universitària de Manresa, Sant Joan de Dèu
Hospital, Manresa, Spain; 6 Hospital Garcia de Orca EPE, Almada, Portugal; 7 General and Digestive Surgery
Department, IdiPAZ, CIBERehd, La Paz University Hospital, Madrid, Spain; 8 Investigators and Co-
investigators from study group.

**ACKNOWLEDGEMENTS**

The principal investigator wish to thank Dr. Péter Hegyi and the Hungary Pancreatic Study group for
everything they have contributed to my process as researcher. This work will be supported by research grants
award from the ‘Catalan society of surgeons ’ and ‘Spanish Association of Surgeons’. Finally, the authors to
thank Editage (www.editage.com) for their assistance in editing and improving this manuscript.
List of Abbreviations

AP       Acute Pancreatitis
ASA      American Society of Anesthesiologist
BISAP    Bedside Index of Severity in Acute Pancreatitis
CC       Coordinating Committed
CT       Computed Tomography
DMP      Data Management Plan
DQF      Data Query Form
DRM      Data Review Meeting
ER       Emergency Room
eRPF     electronic Patient Report Form
IAP/APA  International Association of Pancreatology/American Pancreatic Association
ICF      Informed Consent Form
ICU      Intensive Care Unit
IDMC     Independent Data Monitoring Committee
ITT      Intention to Treat
MAP      Mild Acute Pancreatitis
MRI      Magnetic Resonance Imaging
PPP      Per-Protocol population
SAP      Safety Analysis Population
SIRS     Systemic Inflammatory Response Syndrome
VAS      Visual Analog Scale

FUNDING

Catalan society of surgeons
Spanish Association of Surgeons

AUTHOR CONTRIBUTIONS
ERM, SLG, CF and RJM participated in all phases of the study with the help other authors in the different parts.

Conception and design: ERM, RJM, SLG, AS, and CF.

Administrative, technical, or logistic support: ERM, RJM, SLG, AS, CF, DCLL, RSJ, JV, and MRR.

Drafting of the article: ERM, RJM, SLG, AS, CF, DCLL, RSJ, JV, MRR and the Catalan Pancreatitis Collaborative Group.

Critical revision of the article for important intellectual content: ERM, RJM, SLG, AS, CF, DCLL, RSJ, JV, and MRR.

All authors read and approved the final manuscript.

CONFLICTS OF INTERESTS

The authors declare that they have no conflicts of interest.
DICTAMEN COMITÉ ÉTICO DE INVESTIGACIÓN CON MEDICAMENTOS

Josep Mª Alegret Colomé, Vicepresidente del Comité Ético de Investigación con Medicamentos del IISPV preside la reunión.

HACE CONSTAR QUE
Este Comité, en su reunión de fecha 15/12/2022 acta número 011/2022 se ha evaluado la enmienda presentada y decidido emitir Informe Favorable para que se realice el estudio titulado:

"ENSAYO CLÍNICO MULTICÉNTRICO, PROSPECTIVO ALEATORIZADO, PARA COMPARAR LA EFICACIA Y SEGURIDAD DEL TRATAMIENTO MÉDICO AMBULATORIO Y CON HOSPITALIZACIÓN DOMICILIARIA DE LA PANCREATITIS AGUDA LEVE (Protocolo de estudio PADI_2)"

Código: PADI_2
Versión Protocolo: Versión 3 Mayo 2022
Versión H.I.P. y Consentimiento Informado: Versión 2 Mayo 2022
Promotor: Dra. Ruby Elena Ramírez Maldonado - Servicio Cirugía General y Aparato Digestivo - Hospital Universitari de Tarragona Joan XXIII
Ref. CEIm: 093/2022

CONSIDERA QUE:
- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.
- La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio.
- Son adecuados tanto el procedimiento para obtener el consentimiento informado como la compensación prevista para los sujetos por daños que pudieran derivarse de su participación en el estudio.
- El alcance de las compensaciones económicas previstas no interfiera con el respeto a los postulados éticos.

Este comité acepta que dicho estudio sea realizado en el Hospital Universitari Joan XXIII de Tarragona por la Dra. Ruby Elena Ramírez Maldonado, del Servicio de Cirugía General y Aparato Digestivo.

En el caso que se evalúe algún proyecto en el que participe como investigador/colaborador algún miembro de este comité, se ausentará de la reunión durante la discusión del estudio.

La composición actual del CEIm del Instituto d’Investigació Sanitària Pere Virgili es la siguiente:

Presidente
Dra. Maria Teresa Auguet Quintilla
Servicio de Medicina Interna. Hospital Universitari Joan XXIII. Representante de la Comisión de Investigación.

Vicepresidente
Dr. Josep Mª Alegret Colomé
Cardiólogo. Salut Sant Joan de Reus-Baix Camp.

www.iispv.cat
Secretaria
Sra. Eliabet Galve Aixa
Secretaria CEIm IISPV

Vocales

Dr. Xavier Ruiz Plazas
Urologia. Hospital Universitari Joan XXIII.
Sra. Montserrat Boi Borbonés
Farmacia –Sant Joan de Reus-Baix Camp.
Sra. Mónica Cots Morenilla
Unidad de Atención Primaria. Hospital Universitari Joan XXIII.
Dr. Joaquín Escribano Súbias.
Médico del Servicio de Pediatría. Representante de la Comisión de Bioética Asistencial. Salut Sant Joan de Reus-Baix Camp.
Dra. M. Francisca Jiménez Herrera
Doctora en Antropología Social y Cultural. Profesora Titular Universitaria Departamento Enfermería. Universitat Rovira i Virgili
Sra. M. Mar Granell Barceló
Abogada i Atesora Jurídic del Comité.
Dr. Jesús Miguel López-Dupla
Servicio de Medicina Interna. Hospital Universitari Joan XXIII

Firma

Sr. Jordi Mallol Miró
Catedrático de Farmacología. Facultad de Medicina, Universitat Rovira i Virgili.
Dra. Montserrat Olona Cabezas
Medicina Preventiva i Epidemiología. Hospital Universitari Joan XXIII
Dra. Mª Angéls Roch Ventura
Farmacia Hospitalaria Hospital Universitari Joan XXIII
Sra. Isabel Rosich Martí
Farmacéutica Atención Primaria
Sr. Francesc Xavier Sureda Batlle
Profesor Titular de Farmacología. Universitat Rovira i Virgili.
Dr. Donis Mas Rosell
Medicina Psiquiatria - Institut Pere Mata.
Sra. Mercè Vilella Papaedt
Representante de la Sociedad Civil

Dr. Josep Mª Alegret Colomé,
Vicepresidente CEIm IISPV
Reus, 15 de diciembre 2022
INFORME DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN SOBRE PROYECTOS DE INVESTIGACIÓN BIOMÉDICA

El Dr. Enric Sospeda Martínez, responsable de la Secretaría Técnica del Comité de Ética de la Investigación del Hospital Universitari de Bellvitge,

CERTIFICA

Que el Comité de Ética de la Investigación, en su reunión de fecha 10 de noviembre de 2022 (Acta 24/22), tras examinar toda la documentación presentada sobre el proyecto de investigación con nuestra Ref. PR273/22 (CSI 22/66) titulado:

"ENSENDO CLÍNICO MULTICÉNTRICO, PROSPECTIVO ALEATORIZADO, PARA COMPARAR LA EFICACIA Y SEGURIDAD DEL TRATAMIENTO MÉDICO AMBULATORIO Y CON HOSPITALIZACIÓN DOMICILIARIA VS INGRESO HOSPITALARIO DE LA PANCREATITIS AGUDA LEVE (Protocolo PADI_2).", código: PADI_2

Documentos con versiones:

<table>
<thead>
<tr>
<th>Protocolo</th>
<th>Versión 3 Mayo 2022</th>
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</thead>
<tbody>
<tr>
<td>Hoja de Información al Paciente y Consentimiento Informato</td>
<td>Versión 2 Mayo 2022</td>
</tr>
</tbody>
</table>

Presentado por el Dr. Sergio González Martínez, del Servicio de Cirugía General y Aparato Digestivo del Hospital de Sant Joan Despí Moisés Broggi - Consorci Sanitari Integral (CSI), como investigador principal y promovido por la Dra. Ruby Elena Ramírez Maldonado, del Servicio de Cirugía General y Aparato Digestivo del Hospital Universitari Joan XXIII de Tarragona, ha acordado emitir INFORME FAVORABLE al mencionado proyecto.

Que la composición actual del Comité de Ética de la Investigación es la siguiente:

Presidente: Dr. Francesc Esteve Urbano
Vicepresidente: Dra. Pilar Hereu Boher
Secretario: Dr. Enric Sospeda Martínez
Vocales:
- Dr. Jordi Adamuz Tomás
- Sra. Anna Boix Traserra
- Dra. Concepción Cañete Ramos
- Dra. Sara Cobo Sacristán

Médico - Medicina Intensiva
Médico - Farmacología Clínica
Farmacéutico - Farmacia Hospitalaria
Enfermero – Enfermería
Derecho - DPD
Médico - Neurológia
Farmacéutica – Farmacia Hospitalaria
Dr. José Luis Ferreiro Gutiérrez  
Dra. Ana María Ferrer Arjola  
Sra. Esther Ferrer Canals  
Dr. Xavier Fulladosa Oliveras  
Dr. Carles Lladó i Carbonell  
Dra. Sara Larriba Bartolomé  
Sra. Sonia López Ortega  
Dr. Juan Jesús Martín Liberal  
Dr. Sergio Merchón Ramos  
Dr. Miguel Ángel Pavón Ribas  
Dr. Joan Josep Queralt Jiménez  
Dra. Gemma Rodríguez Palomar  
Dr. Petru Cristian Simon  

Médico - Cardiología  
Farmacéutica - Miembro sanitario  
Representante de los pacientes  
Médico - Nefrología  
Médico - Urología  
Farmacía - Sanitario  
Graduado Social - Atención a la Ciudadanía  
Médico - Oncología Médica  
Médico - Medicina Preventiva  
Biólogo- Miembro no sanitario  
Jurista  
Farmacéutica – Atención Primaria  
Médico - Farmacología Clínica

Que este Comité cumple la legislación española vigente para este tipo de proyectos, así como las normas ICH y las Normas de Buena Práctica Clínica.

Que en dicha reunión del Comité de Ética de la Investigación se cumplió el quórum preceptivo legalmente.

Lo que firmo en L’Hospitalet de Llobregat, a 30 de noviembre de 2022

Signat digitalment per

SOPEDRA MARTINEZ
ENRIQUE - 36986426B

DN: c=ES,  
serialNumber=IDCES-36986  
426B, givenName=ENRIQUE,  
sn=SOPEDRA MARTINEZ,  
 cn=SOPEDRA MARTINEZ  
ENRIQUE - 36986426B  
Date: 2022.11.30 14:21:26  
+01’00’

Dr. Enric Sospedra Martínez
INFORME DEL COMITÉ DE ÉTICA D’INVESTIGACIÓN CLÍNICA

Mireia Bolivar Prados, en calidad de secretaria técnica del Comité d’Ética d’Investigación Clínica amb Medicaments de l’Hospital de Mataró, Consorci Sanitari del Maresme,

CERTIFICA

Que aquest Comitè ha avaluat la proposta presentada per Hospital Universitari Tarragona Joan XXIII per a que sigui realitzat a l’Hospital de Mataró l’estudi titulat:

Ensayo clínico multicéntrico, prospectivo aleatorizado, para comparar la eficacia y seguridad del tratamiento médico ambulatorio y con hospitalización domiciliaria de la pancreatitis aguda leve

<table>
<thead>
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<td>Protocol</td>
<td>Versión 2</td>
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<tr>
<td>Full d’informació al Pacient / Consentiment Informat</td>
<td>Versión 2</td>
</tr>
<tr>
<td>Procediments i material utilitzat pel reclutament dels subjectes (anuncis publicitaris, informació web, etc.)</td>
<td>NA</td>
</tr>
</tbody>
</table>

I considera que:

- Es compleixen els requisits necessaris d’idoneitat del protocol en relació amb els objectius de l’estudi i es troben justificats els riscos i molèsties previsibles pel subjecte
- La capacitat de l’Investigador i els mitjans disponibles són apropisats per a dur a terme l’estudi
- El procediment per a obtenir el consentiment informat és adequat
- Les compensacions econòmiques previstes no interfereixen amb el respecte dels postulats ètics

I que aquest Comitè emet informe favorable per a que l’esmenat estudi sigui realitzat a l’Hospital de Mataró per López, S com Investigadora Principal.

El que firmo a Mataró a 12 de juliol de 2022,
BOLIVAR PRADOS MIREIA - 45985345L
Mireia Bolivar Prados
Secretaria Técnica del CEIm del CSdM,
Hospital de Mataró
Mireia Bolívar Prados, en qualitat de secretaria tècnica del Comitè d’Ètica d’Investigació Clínica amb Medicaments de l’Hospital de Mataró, Consorci Sanitàri del Maresme,

FA CONSTAR QUE:

1. En la reunió celebrada a dia 22/06/2022, acta 06 – 22.06.2022 es decideix emetre informe condicionat a l’estudi de referència
2. Que a dia 12/07/2022, s’emete informe favorable amb les modificacions pertinents suggerides pel Comitè.
3. En l’esmentada reunió, es compleixen els requisits establerts en la legislació vigent per a que la decisió de l’anomenat CEIm sigui vàlida.
4. El CEIm del CSDM, tant en la seva composició com als PNT compleix amb les normes de BPC (CPMP/ICH/135/95)
5. La composició actual del CEIm és la següent:

<table>
<thead>
<tr>
<th>Pere Clavé Civit</th>
<th>Metge. Especialista en cirurgia. Director Acadèmic, d’Investigació i Innovació del Consorci Sanitàri del Maresme. President de la Comissió d’Investigació del CSDM.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberto Zamora Cervantes</td>
<td>Metge. Servei de Medicina Interna. Hospital de Blanes. Coordinador Comissió Recerca i Innovació, Corporació Salut Maresme i la Selva.</td>
</tr>
<tr>
<td>Mireia Bolívar Prados</td>
<td>Farmacèutica. Unitat de Fisiologia Digestiva del Consorci Sanitàri del Maresme.</td>
</tr>
<tr>
<td>Mateu Serra Prat</td>
<td>Metge. Epidemiòleg. Cap de la Unitat de Recerca. Membre de la Comissió d’Investigació del CSDM. Membre del Comitè d’Ètica Assistencial del CSDM.</td>
</tr>
<tr>
<td>Itziar Flores Aliri</td>
<td>Advocada. Membre no sanitari i alliè al centre.</td>
</tr>
<tr>
<td>Maria Bartolomé Regué</td>
<td>Metge especialista en MFCIC. CAP Mataró-Centre del CSDM.</td>
</tr>
<tr>
<td>Lluís Campins Barnadas</td>
<td>Farmacèutic Hospitalari. Cap de Servei de Farmàcia de l’Hospital de Mataró.</td>
</tr>
<tr>
<td>Rubén Sánchez Borrego</td>
<td>Administratiu. Cap de la Unitat d’Atenció a l’Usuari del CSDM.</td>
</tr>
<tr>
<td>David López Faixó</td>
<td>Farmacèutic Atenció Primària. Servei de Farmàcia del CSDM.</td>
</tr>
<tr>
<td>Azahara Sánchez Ulayar</td>
<td>Farmacèutica Hospitalària. Servei de Farmàcia del CSDM.</td>
</tr>
<tr>
<td>Omar Ortega Fernández</td>
<td>Biòleg. Investigador CIBEREHD del CSDM.</td>
</tr>
<tr>
<td>Isabel Lorenzo Sánchez</td>
<td>Biòloga. Responsable econòmica. Direcció Acadèmica, de Recerca i d’Innovació del CSDM.</td>
</tr>
<tr>
<td>Vanessa Vicente Arcúa</td>
<td>Infermera. Hospital de Mataró, CSDM.</td>
</tr>
<tr>
<td>Francesc Moya Olvera</td>
<td>Informàtic. Director de sistemes d’Informació i Coordinador Protecció de Dades del CSDM.</td>
</tr>
<tr>
<td>Carme Pascual González</td>
<td>Metge especialista en MFCIC. ABS Calella.</td>
</tr>
</tbody>
</table>

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PARA E AUTORIZAÇÃO PARA REALIZAÇÃO DE ESTUDO

Hospital Garcia de Orta EPE
Centro de Investigação Hospital Garcia de Orta

Título: Participação no Estudo clínico multicêntrico, prospectivo e randomizado, para comparar a eficácia e segurança do tratamento médico em ambulatório e com hospitalização domiciliária vs internamento hospitalar na pancreatite aguda ligeira - Protocolo PADI_2.

Investigador Principal: Dr Rui Branco

A Comissão de Ética para a Saúde do Hospital Garcia de Orta informa que o trabalho em epígrafe obteve parecer positivo por unanimidade ☑ maioria ☐ em reunião do dia 27/02/2023.

Estiveram presentes:
☐ Nome: Dra Natália Dias (Presidente)
☐ Nome: Dra Ana Soares
☐ Nome: Dra Aurora Tomaz
☐ Nome: Dra Benedita Nunes
☐ Nome: Dra Cátia Gradil
☐ Nome: Dra Eunice Teixeira
☐ Nome: Dra Isabel Pereirinha
☐ Nome: Dr. José Luis Metello
☐ Nome: Dr. Manuel Quintaños
☐ Nome: Dr. Miguel Rodrigues
☐ Nome: Enfª Teresa Chambel

A CES solicita ao Investigador Principal que quando da conclusão deste estudo, lhe seja enviada uma síntese dos resultados e conclusões do mesmo.

Dra. Natália Dias
Presidente da Comissão de Ética

O Estudo em epígrafe foi aprovado pelo Conselho de Administração em reunião do dia 27/03/2023.

Dra. Paula Breia
Presidente do Centro Garcia de Orta

Almada, 06 / 03/2023
COMITÉ ÉTICO DE LA INVESTIGACIÓN CON MEDICAMENTOS

Dra. Ana Lucía Arellano Andino, Secretaria del Comité Ético de Investigación Clínica del Hospital Clínic de Barcelona

CERTIFICA

Que este Comité ha recibido el proyecto:

Título: Ensayo clínico multicéntrico prospectivo aleatorizado, para comparar la eficacia y seguridad del tratamiento medico ambulatorio y con hospitalización domiciliaria vs ingreso hospitalario de la pancreatitis aguda leve (Protocolo PADI_2).
Investigador/es principal/es: ARIADNA SANCHEZ GARCIA

Y acepta el Dictamen favorable del CEIm del INSTITUT D’INVESTIGACIÓ SANITÀRIA PERE VIRGILI

Barcelona, a 21 de julio de 2022

Reg. HCB/2022/0812

Mod._28 [V1 de 9/05/2017] Aceptación CEIm
INFORME DEL COMITÈ D’ÈTICA D’INVESTIGACIÓ

Dr. Miquel Nolla, com a President del Comitè d’Ètica d’Investigació de la FUNDACIÓ UNIO CATALANA HOSPITALS

CERTIFICA:
Que aquest Comitè en la seva reunió del dimarts 20 de desembre, ha avaluat la proposta presentada, per que es realitzi l’estudi que porta per títol “Ensayo clínico multicéntrico, prospectivo aleatorizado, para comparar la eficacia y seguridad del tratamiento médico ambulatorio y con hospitalización domiciliaria vs ingreso hospitalario de la pancreatitis aguda leve (PADL_2).”, amb codi CEI 22/111, i considera que:

Es compleixen els requisits necessaris d’idoneitat del protocol en relació amb els objectius de l’estudi i que estan justificats els riscos i les molesties previsibles per al subjecte. La capacitació de l’investigador i els mitjans disponibles són apropriats per portar a terme l’estudi. Són adequats tant el procediment per obtenir el consentiment informat com la compensació prevista per als subjectes per danys que es puguin derivar de la seva participació a l’estudi.

Que aquest Comitè decideix emetre INFORME FAVORABLE, a la resolució dels aclariments.

Que aquest comitè accepta que aquest estudi es digui a terme a Althaia, Xarxa Assistencial Universitària de Manresa, amb Raquel Sánchez Jiménez com a investigadora principal, i que la investigadora principal no ha estat present en les deliberacions i aprovació d’aquest estudi.

En aquesta reunió s’han complert els requisits establerts en la legislació vigent. El CEIm tant en la seva composició, com en els PNT compleix amb les normes de BPC (CPMP/ICH/135/95).

MEMBRES DEL CEIm DE LA FUNDACIÓ UNIO CATALANA D’HOSPITALS

<table>
<thead>
<tr>
<th>Nomi del membre</th>
<th>Cargo</th>
<th>Institution</th>
</tr>
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<tbody>
<tr>
<td>Miquel Nolla Salas</td>
<td>President</td>
<td>Metge</td>
</tr>
<tr>
<td>Anna Altés Cais</td>
<td>Vicepresidenta</td>
<td>Metge</td>
</tr>
<tr>
<td>Vanessa Massó Marigot</td>
<td>Secretaria tècnica</td>
<td>C. Empresarials</td>
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<tr>
<td>Ainhoa Gómez Lumbreras</td>
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<td>Farmacòlega Clínica</td>
</tr>
<tr>
<td>Iitzar Alíri Flores</td>
<td>Vocal</td>
<td>Advocadessa, experta protecció de dades</td>
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<td>Ana Barajas Vélez</td>
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<td>Josep M Tornos Muñoz</td>
<td>Vocal</td>
<td>Metge</td>
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</table>

Barcelona, 24 de gener de 2023

Dr. Miquel Nolla
President del CEIm
TÍTULO: ENSAYO CLÍNICO MULTICÉNTRICO, PROSPECTIVO ALEATORIZADO, PARA COMPARAR LA EFICACIA Y SEGURIDAD DEL TRATAMIENTO MÉDICO AMBULATORIO Y CON HOSPITALIZACIÓN DOMICILIARIA VS INGRESO HOSPITALARIO DE LA PANCREATITIS AGUDA LEVE

INVESTIGADOR PRINCIPAL: CONSTANTINO FONDEVILA CAMPO del Servicio de CIRUGÍA GENERAL Y APARATO DIGESTIVO del HOSPITAL UNIVERSITARIO LA PAZ
CEIm: INSTITUT D'INVESTIGACIÓ SANITARIA PERE VIRIGLI Tipo de Estudio: EECC
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Código Promotor: PADI2 Promotor: FONDEVILA CAMPO CONSTANTINO

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RESOLUCIÓN: Ratificación

OBSERVACIONES: Madrid, a 12/01/2023

Fdo. EMMA FERNÁNDEZ DE UZQUIANO
Secretario técnico del CEIm

Firmado digitalmente por: FERNÁNDEZ DE UZQUIANO MARIA EMMA
Fecha: 2023.01.12 15:38
REFERENCES


Figure 1. Flow chart of participants according to the SPIRIT 2013 statement [18]
Adult patients with an episode of acute pancreatitis (AP)

Exclusions
Not meeting inclusion criteria
(1) Patient above 18y
(2) Diagnosed AP (2 out 3 criteria)
(3) Signed written informed consent form
Meeting exclusion criteria
(1) Pregnant or breastfeeding women
(2) Abdominal pain >96h
(3) The possibility of poor oral intake for reasons other than AP
(4) Pancreatic neoplasm, endoscopic retrograde cholangiopancreatography or trauma etiology, biliar obstruction
(5) Chronic pancreatitis
(6) ASA ≥3
(7) Moderate or severe acute pancreatitis;
(8) The patient is considered unable to eat an oral diet for other reasons than AP

Stay in the emergency room for 24 h

Mild acute pancreatitis confirmed

X patients to be randomized

Outpatient
Home Care
Hospital Admission

X analysed
X analysed
X analysed
Acute pancreatitis (AP)

**Compliance with diagnostic criteria**

- Emergency stay for 24 hours
- Intravenous fluids, analgesia and antiemetics for 24 hours
- Diagnosis of MILD AP
  - Analytics at 24 hours
  - Pain scale VAS≤2
  - Diet tolerance >50%
- Randomization
- Home hospitalization
  - Phone call in the afternoon
  - Diary visit
    - Blood sample 24-48 hours
  - Treatment Failure
    - YES: Hospitalization
    - NO: Discharge at 72-96 hours
- Outpatient treatment
  - Phone call in the afternoon
  - Daily call phone
    - Blood sample 24-48 hours
  - Admission
    - Blood sample 24-48 hours
  - Hospital discharge criteria

**Non-compliance with inclusion criteria**

- Hospitalization

**NO PREDICTIVE FACTORS OF SEVERITY**

- Emergency discharge criteria
  - Tolerance ≥50% of fat-free diet
  - Absence of nausea and vomiting with or without treatment
  - Controlled pain with oral analgesia VAS≤2

- Analysis without gravity predictive factors

- After discharge: visit in surgery consultations 1 week after discharge and 3 months
  - Fill out satisfaction survey.

**AP Severity Predictors**

- SIRS ≥ 2 criteria
- BISAP ≥2 score
- Organ failure

**Emergency/hospital discharge criteria**

- Tolerance ≥50% of fat-free diet
- Absence of nausea and vomiting with or without treatment
- Controlled pain with oral analgesia VAS≤2
- Analysis without gravity predictive factors

**Failure of the PADI2 treatment protocol**

- No tolerance to diet
- Nausea or vomiting
- Uncontrolled pain with prescribed analgesia
- Any severity predictive factors
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<td>Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym</td>
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<td>Trial registration 2a</td>
<td>Trial identifier and registry name. If not yet registered, name of intended registry</td>
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<td>Roles and responsibilities 5b</td>
<td>Name and contact information for the trial sponsor</td>
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<td>Roles and responsibilities 5c</td>
<td>Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities</td>
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<tr>
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<td>Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)</td>
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<td>Methods: Participants, interventions, and outcomes</td>
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Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequencing 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation

Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions

Blinding (masking)

Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how

If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection methods

Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known.

Reference to where data collection forms can be found, if not in the protocol

Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

Data management

Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values).

Reference to where details of data management procedures can be found, if not in the protocol

Statistical methods

Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

Methods for any additional analyses (e.g., subgroup and adjusted analyses)

Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)

Methods: Monitoring

Data monitoring

Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms

Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing

Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination
<table>
<thead>
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<td>26a</td>
<td>Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)</td>
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<td>Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable</td>
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<tr>
<td>Confidentiality</td>
<td>27</td>
<td>How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial</td>
</tr>
<tr>
<td>Declaration of interests</td>
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<td>Financial and other competing interests for principal investigators for the overall trial and each study site</td>
</tr>
<tr>
<td>Access to data</td>
<td>29</td>
<td>Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators</td>
</tr>
<tr>
<td>Ancillary and post-trial care</td>
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<td>Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation</td>
</tr>
<tr>
<td>Dissemination policy</td>
<td>31a</td>
<td>Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions</td>
</tr>
<tr>
<td></td>
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<td>Authorship eligibility guidelines and any intended use of professional writers</td>
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<tr>
<td></td>
<td>31c</td>
<td>Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code</td>
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**Appendices**

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<tr>
<td>Biological specimens</td>
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.*
# Home care/outpatient vs hospital admission in mild acute pancreatitis: protocol of a multicenter, randomized controlled trial (PADI_2 trial)

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<td>15-May-2023</td>
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<td>Complete List of Authors:</td>
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Title

Home care/outpatient vs hospital admission in mild acute pancreatitis: protocol of a multicenter, randomized controlled trial (PADI_2 trial)

Authors

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Running head

Outpatient in mild acute pancreatitis

Keywords

Acute pancreatitis; outpatient; homecare; early oral refeeding; length of hospital stay; pain relapse.
ABSTRACT

Introduction: Acute pancreatitis (AP) is the third most common gastrointestinal disease resulting in hospital admission, with over 70% of AP admissions being mild cases. In the United States, it costs $2.5 billion dollars annually. The most common standard management of mild AP (MAP) still is hospital admission. Patients with MAP usually achieve complete recovery in less than a week and the severity predictor scales are reliable. The aim of this study will be to compare three different strategies for the management of MAP.

Methods/design: This is a randomized, controlled, three-arm multicenter trial. Patients with MAP will be randomly assigned to group A (outpatient), B (home care), or C (hospital admission). The primary end point of the trial will be the treatment failure rate of the outpatient/homecare management for patients with MAP compared to that of hospitalized patients. The secondary endpoints will be pain relapse, diet intolerance, hospital readmission, hospital length-of-stay, need for ICU admission, organ failure, complications, costs, and patient satisfaction. The general feasibility, safety, and quality checks required for high quality evidence will be adhered to.

Ethics and dissemination: The study (version 3.0, 10/2022) has been approved by the Scientific and Research Ethics Committee of the 'Institut d'Investigació Sanitaria Pere Virgili-IISPV' (093/2022). This study will provide evidence as to whether outpatient/homecare are similar to usual management of AP. The conclusions of this study will be published in an open access journal.

Trial registration: The trial is registered at the ClinicalTrials.gov (NCT05360797).
STRENGTHS AND LIMITATIONS

1. Strength 1: A multidisciplinary team wrote this protocol.

2. Strength 2: The established treatment is the standard in patients with mild acute pancreatitis.

3. Strength 3: An Independent Data Manager Committee will be ensuring security and monitoring data.

4. Limitation 1: The three-arm method of the study requires a multidisciplinary team on the project which may limit the number of centers that can join.

5. Limitation 2: Lack of blinding increases the risk of performance bias, since the participants will be aware of their group assignment.
BACKGROUND

Acute pancreatitis (AP) is one of the most common reasons for hospitalization among gastrointestinal diseases worldwide. The costs caused by severe AP are higher than those for mild AP (MAP). Nevertheless, approximately 70% of hospital admissions for AP are MAP so, if savings in healthcare costs are to be achieved, it would be by lowering the cost of managing patients with MAP without complication or affecting patient safety and satisfaction.[1-7]

Patients in the PADI_1 study[1] from 2017 to 2019 were analyzed, and these following observations noted: (1) immediate oral low-fat solid diet to patients with mild and moderate AP is safe and feasible; (2) Immediate oral refeeding was associated with a significant reduction in hospital length-of-stay (LOS) (3.4 vs 8.8 days, P < 0.001); (3) hospital costs were half as much, with a savings of 1325.7€/patient in the immediate oral compared to the convencional oral refeeding group, and (4) comparing the outcome of the groups showed no increased risk of complications.[1]

This proposed study seeks to prospectively evaluate a new scope in the care of patients with MAP and is justified based on these three points: 1) patients with MAP usually achieve a complete recovery of their symptoms in less than a week with conservative management (intravenous hydration, analgesia, and early diet); 2) clinical prognostic scoring systems, although criticized for their poor positive predictive value for severe AP, have an excellent negative predictive value to determine which patients will have MAP early in their hospitalization; and 3) factors that predict hospital readmission within 30 days in AP have been studied and can be applied.[8-16]

The International Association of Pancreatology/American Pancreatic Association (IAP/APA) guidelines[4] advise using the presence of systemic inflammatory response syndrome (SIRS) to predict severe AP at admission and persistent SIRS at 48h. The three dimensions recommended by the guidelines for risk approximation are: (1) host risk factors (age, co-morbidity, body mass index), (2) clinical risk stratification (persistent SIRS), (3) monitoring response (persistent SIRS, blood urea nitrogen, creatinine). There are many predictive scoring systems and serum markers none have been shown to be better or worse predictors of
severity than SIRS. [4] Thus, the bedside index of severity in acute pancreatitis (BISAP) score, which includes the SIRS in its parameters, provides one more tool to approximate the patient's risk in the aforementioned three dimensions.

Ince et al [10], showed that MAP can be safely treated at home with regular visits by a nurse under the supervision of a physician with large cost savings. A recent cohort study, which included 419 patients, showed that after appropriate triage MAP patients can safely discharged from the emergency room (ER) after a mean of 12h with improved outcomes and cost savings. [11]

Therefore, to carry out this study which proposes to compare outpatient and homecare treatment with hospitalization for patients with MAP, strict criteria for predicting severity will need to be fulfilled. The main objective of this trial is to determine whether, in MAP cases, outpatient treatment or homecare is similar to standard with hospital admission treatments in terms of diet tolerance, pain control, risk of severity, complications, patient’s satisfaction, and health cost.

METHODS

Diagnosis and classification of AP

According to the Revised Atlanta criteria 2012 [12], the diagnosis of AP requires two of the following three features: (1) onset of upper abdominal pain often radiating to the back; (2) serum lipase or amylase level at least three times higher than the normal upper limit; (3) characteristics findings of AP on imaging techniques such as contrast-enhanced CT, ultrasonography (US) and/or magnetic resonance imaging. Severity of AP was classified as Mild (no organ failure, local or systemic complications), Moderately severe (presence of transient organ failure, local complications or exacerbation of comorbid disease), Severe (persistent organ failure (>48 hours) affecting respiration, renal function or the cardiovascular system). [12]

Design

This is a randomized controlled three-arms multicenter trial. Patients with MAP will be randomly divided into three groups. Group A: outpatient treatment, group B: medical homecare, and group C: hospitalization.
Study population

All patients diagnosed with MAP (after 24h in the ER) will be informed of the possibility of participating in the PADI_2 study. After the informed consent form (ICF) is signed, investigator will have access to the electronic patient report form (ePRF) and will generate random number that will be the treatment arm to follow (group A, B or C).

To confirm a MAP, severity scores (SIRS, BISAP) of patients who have been in the ER for 24 hours will be used, (Figure 1, Appendix 1).

Inclusion criteria

The inclusion criteria are: (1) patient older than 18 years of age; (2) diagnosed with AP using at least two of these three criteria: compatible abdominal pain, amylase or lipase level superior in three-fold respective laboratory baseline levels, and suitable findings in imaging techniques (CT, ultrasound or MRI)[4]; (3) MAP; (4) signed written ICF; (5) compliance with outpatient or homecare criteria; and (6) randomization at 24 hours of stay in the ER.

Outpatient or homecare criteria

1. A companion who understands and accepts the process and who will cooperate with the patient's recovery at home.

2. A mobile or telephone to communicate with the patient or her family member.

3. The distance to the hospital should be a maximum of 45-60 minutes.

Exclusion criteria

The exclusion criteria are: (1) pregnant or breastfeeding women; (2) abdominal pain >96 hours (4 days); (3) the possibility of poor oral intake or unable to eat for reasons other than AP; (4) pancreatic neoplasm, endoscopic retrograde cholangiopancreatography, or trauma etiology; (5) Choldeocholithiasis and/or cholangitis; (6) chronic or recurrent pancreatitis; (7) ASA ≥3; (8) expected moderate or severe acute pancreatitis; and (9) alcohol withdrawal syndrome for patients with alcoholism.

Sample size
Only two studies with a similar objective have ever been reported,[10,11] and a treatment failure rate of 4-12% was observed in the home monitoring (outpatient/homecare) group. Using calculations for a non-inferiority study with an estimated 95% success rate, 80% power, 5% significance level, and 10% inferiority limit, a sample size of 75 patients per study group was calculated (total = 225 patients).

Randomization
Randomization will use a computer-generated random number based on predefined randomization lists created separately for each recruiting center. The ePRF will implement a block randomization method with a sequence of 1:1:1. After confirming a MAP and obtaining ICF, physicians on call at the different centers will have access to the ePRF and generate the randomization sequence according to the REDCap registry. Enrollment will be unblinded for patients and physicians due to the nature of the intervention.

Duration
The planned starting date of the study is November 1, 2022, and the planned finishing date of the study is November 30, 2024.

Intervention
After a 24-hour stay in the ER, the predictive factors of severity evaluation and the diagnosis of MAP will be confirmed, the patient will sign ICF and be randomized into group A, B or C (Table 1). The experimental groups are A or B and the control group is C. For all the groups, the first follow-up will be at week 1, and the subsequent follow-up will be at 1-3 months after hospital discharge (Table 1). The patients will be asked to complete the security / satisfaction survey [17] at the last follow-up.

Groups
Group A, outpatient: the patient is discharged and contacted by phone daily for 4 consecutive days by the investigators in the corresponding center.

Group B, medical homecare: the patient is discharged and contacted by phone/visits by a nurse/doctor daily for 4 consecutive days by the medical home care department in the corresponding center.
Group C, hospital admission: the patient is hospitalized in the corresponding center.

**General treatment**

General treatment, indicated by the IAP/APA guidelines,[4] - fluid therapy, symptom control and dietary support - will be performed for the first 24h, in the ER for all patients with AP. The early diet is PADI_1[1] (Low-fat-diet immediately). After 24h, the treatment will be oral intake (antiemetics, painkillers, diet) by all three groups. Blood sample will be obtained 48-72h after discharge from the as follows, group A in the hospital or nearly primary care provider, B homecare team, and C in the hospital. The patients will be asked to complete the security / satisfaction survey [17] at the last follow-up.

**Table 1.** Schedule of enrollment, interventions, and assessments according to the SPIRIT 2013 statement.[18] Patients will be randomized to group A (outpatient), B (home care), C (hospital admission). Online supplementary contains the User Manual of the REDCap/PADI_2 that contains the parameters collected on admission, 24h in ER, and during the first days and 3 months after discharge.
| INTERVENTIONS | Group A: outpatient | X |   |   |   | X |
|              | Group B: home care  | X |   |   |   | X |
|              | Group C: hospital admission | X |   |   |   | X |

| ASSESSMENTS | Questionnaire admission | X |
|             | Questionnaire 24h       | X |
|             | Questionnaire 2-3d      |   | X |
|             | Questionnaire 1 w       |   | X |
|             | Questionnaire and SSS 1-3m |   |   | X |

BS: Blood Samples; SSS: Security-Satisfaction survey [17]

Predictors of severity

Predictors of severity will be considered when: (1) SIRS ≥2 criteria, (2) BISAP≥2 score, and (3) organ failure.

Discharge of patients

Patients will be counted as discharged from hospital/outpatient/home care, when: (1) oral feeding is tolerated (≥50% of plates), (2) absence of nausea and vomiting with treatment, (3) pain controlled with oral analgesia (VAS≤2), and (4) clinical characteristics without predictors of severity.

Failure to meet the abovementioned criteria within 1 week after ER discharge generates the need for hospital admission and must be considered as failed treatment in PADI_2.
Primary endpoint

The primary endpoint of the trial will be the treatment failure rate of the outpatient/homecare management for patients with MAP compared to hospitalized patients.

Failure of treatment definition:

The following will be considered failure of treatment: (1) diet intolerance (<50% of plates), (2) uncontrolled nausea or vomiting despite treatment, (3) uncontrolled pain despite oral painkillers, and (4) predictors of severity are present.

Secondary endpoints.

Secondary endpoints that will be analyzed: (1) Abdominal pain relapse, (2) Diet tolerance, (3) BISAP, (4) SIRS, (5) Organ failure, (6) complications, (7) hospital readmission, (8) ICU admission, (9) health costs, (10) patient satisfaction/security, (11) LOS, and (12) analytical parameters (white blood cells count, hematocrit, blood urea nitrogen, creatinine, amylase, lypase, glucose, and bilirubin) at hospital admission and 24h and 72h after discharge from ER. Only direct costs will be calculated (all medications, services, salaries of healthcare professionals, equipment, hospital bed cost) in the coordinating hospital.

Monitored parameters

There will be a large assortment of parameters monitored during the study (medical history, ASA score, physical examination, laboratory tests, diagnostic imaging, therapy, interventions, cost, satisfaction survey[17]). Data collection on the ePRF will be done electronically in REDCap/PADI_2 (see data management).

Clinical parameters: mean arterial pressure, heart rate, temperature, Glasgow scale, and abdominal pain.

Analytical parameters: white blood cells count, hematocrit, blood urea nitrogen, creatinine, amylase, lypase, glucose, and bilirubin.

Trial organization

PADI_2 is coordinated by the Joan XXIII University Hospital of Tarragona, Spain, the group that published the PADI_1 study that permitted advances in AP treatment.
Coordinating Committee (CC)

The CC will be led by ERM, RJM, MRR, and RM (Surgeons, University Hospital of Tarragona Joan XXIII, Rovira i Virgili University, Tarragona, Spain); CF (Surgeon, IdiPAZ, CIBERehd, La Paz University Hospital, Madrid, Spain); SLG (Surgeon, Health Consortium Maresme, Matarò, Spain); AS (Gastroenterologist, Barcelona Clinic Hospital, IDIBAPS, CIBEREHD, University of Barcelona, Barcelona, Spain); SG and DCLL (Surgeons, Moise’s Broggi Hospital, CSI, Barcelona, Spain).

Independent data monitoring committee (IDMC)

The Independent Data Manager Committee Data (IDMC) will manage data, data security, and monitoring.

Data review meeting (DRM)

Members are a delegated investigator, biostatistician, and data manager.

Data management and statistical analyses

Data management

Data will be managed by the IDMC, and ePRF will be used. The Investigator will ensure that the data in the ePRF are complete and accurate. Detailed data flow will be described in a Data Management Plan (DMP) reflected in a REDCap/PADI_2 user manual. Data from completed ePRFs will be accepted under the direction of the Data Manager at IDMC. Any incongruous or missing recordings in the ePRFs will be returned to the Investigator using a Data Query Form (DQF) and documented for each individual subject before clean file status is declared. All changes to ePRFs will be recorded. Before Data Base Lock the DRM will decide and document necessary steps related to any issue in the database and define the analysis sets. DRM will be responsible for protecting confidentially of patients before, during, and after the trial.

Study populations

Three populations will be defined:

Safety Analysis Population (SAP): all patients with confirmed MAP enrolled in the study.

Per-Protocol Population (PPP): all enrolled patients who completed the study following all the rules.

Intention to Treat (ITT): the set of all randomized participants who start a treatment, excluding consent withdrawals.
Withdrawal of a participant from PPP

Any investigator and the IDMC can submit recommendations for dropouts from the PPP group with reasons given to the CC. All recommendations will be archived. The CC will discuss all available information and, if the change in the protocol would be expected to have any relation to the interventions and results of the study, the case will not be included in the final per-protocol analysis. Immediate dropout from the per-protocol group will be ordered if: (1) any of the exclusion criteria are diagnosed during AP, (2) any predictor of severity is present, (3) parameters required for answering the primary endpoints are missing, or (4) for serious medical reasons not related to AP (e.g., heart attack, accidents, etc.).

Applied software

Data collection on the ePRF form and randomization will be done electronically in Research Electronic Data Capture 9.8.0 (REDCap/PADI_2). Statistical analysis will be performed using Statistical Analysis System - SAS 9.4 or Statistical Package for the Social Sciences - SPSS 21 (or later) statistical packages. Microsoft MS Word will be used for reporting.

Statistical methods

First, the descriptive analysis will be carried out for each variable. Central tendency (mean or median) and dispersion (standard deviation or IQR) measures will be provided for quantitative variables and absolute frequencies and percentages for qualitative variables.

Between group comparisons for quantitative variables under the assumption of normality will use a one-way ANOVA with Tukey's post hoc test to compare means of pairs of groups. In case of non-normality the Kruskal-Wallis test will be used and multiple comparisons carried out with Mann-Whitney tests, adjusting p-values by Bonferroni. For qualitative variables, the chi-square test ($\chi^2$) will be used, applying Fisher's exact test when deemed necessary. Actuarial survivals will be calculated using the Kaplan-Meier method and their comparison between groups will be carried out using the Log-Rank test. All the outcomes will be analyzed in intention-to-treat population (defined as participants randomized). The confidence level will always be 95% and p-values reported with sensible precision.
In the multivariate survival analysis, the Cox regression method will be used, while for the multivariate analysis of risk factors, the logistic regression method will be used. Variables that show statistical significance in the univariate analysis and/or those that are prognostic factors in the bibliography and theoretical framework will be introduced to the statistical model.

**Early quality assessment**

An early quality assessment check will be performed on the first 70 patients. The IDMC will independently review the trial-related documents and activities, to ensure the rights, safety, and welfare of participants are respected and the clinical data are credible. The similarity of the groups will also be checked at the beginning of the study. The IDMC will report these findings to the CC. The CC will discuss all the information and, if the differences would be expected to have any relation on the interventions and results of the study or the overall dropout rate from PPP is \( >20\% \) of all participants randomized or allocated into each group or the differential dropout rate is \( >15\% \) between groups, the study should be reassessed and the IDMC will make recommendations regarding reassessment of power calculation, extension of recruitment period, extension of number of study centers, or trial completion.

**Interim analyses and premature termination of the study**

The IDMC may also recommend stopping the trial early for ethical reasons if one group clearly shows evidence of significant benefit. An interim analysis on the primary endpoint will be performed when 50\% of patients have been randomized and discharged. The interim analysis will be carried out by the IDMC, who will report to the CC.

The Haybittle–Peto boundary method, which states that if the interim analysis shows a probability of \( \leq 0.001 \) that a difference as extreme or more between the treatments is found, given that the null hypothesis is true, then the trial should be stopped early, will be used in this study.

**Centers**

The trial will start in four centers, who also participated in the PADI_1: Joan XXIII University Hospital of Tarragona, Barcelona Clinic Hospital, Health Consortium Maresme and, Moise’s Broggi Hospital. After which the study is open for other centers. The IDMC will always audit the center and report to the CC. The CC may
decide whether the center meets the requirements to join the study. Compulsory requirements for a center are:

1. treats at least 30 patients with AP annually,
2. has a homecare department,
3. besides the regular medical team, the center must appoint at least one doctor and one nurse specifically for the trial,
4. all investigators need to attend a preliminary meeting where all the details of the study is discussed fully and have qualified as investigators by completing a course, either online or face-to-face.

**Authorship aspects**

Authorships are based on international guidelines: all authors must fulfill the International Committee of Medical Journal of Editors criteria (see [www.icmje.org/journals.html](http://www.icmje.org/journals.html)). All collaborating centers providing over 25 patients can be afforded one author. Every additional 20 patients will provide the center an additional author. Every center can also include formal ‘collaborators’ on the project, which the journal will be asked to list in PubMed at final publication. The first three authorship positions are reserved for the study coordinators (ERM, MRR, SLG) and the last two authorship positions are reserved for the senior investigators (RJM, CF). All other authors will be listed in numerical order according to the number of patients contributed to the study. Collaborators will be listed in alphabetical order as part of the ‘Catalan Pancreatitis Collaborative Group’.

**Feasibility**

As a general protocol to treat AP at the Joan XXIII University Hospital, patients with AP receive PADI_1 treatment adjusted to the IAP/APA guidelines.[4] Patients in PADI_1 receive diet immediately on their arrival in the ward from the ER once their symptoms have been controlled. Comparing the outcome of this treatment protocol with the nil per os protocol used in most hospitals showed that patients enjoyed benefits with no increasing the risk of complications. About 100 patients are admitted to the existing PADI_1 hospitals annually. Therefore, if no other institution joins this study, it can be completed within 2-3 years.

**Safety**

Since no unknown drugs/therapy are used in the study, no adverse or serious adverse events are expected/interpretable that would be attributable to the intervention during the trial. As for the outpatient group, although it is a telephonic follow-up, it will be performed daily by the investigator team, asking for clear clinical parameters. Blood samples will also be obtained on the same day as in the other groups to identify
predictors of severity that require the immediate hospital admission. In this trial the IDMS will examine safety variables after every 20 patients complete the program. Investigators will also report adverse or serious adverse events on a separate form which must be sent to the IDMS and CC. The CC will discuss and, if the adverse effect is confirmed, it will be reported to the relevant institutional ethical committee (http://www.iispv.cat).

Patient and public involvement

None

ETHICS AND DISSEMINATION

The trial is registered at the ClinicalTrials.gov registry (NCT05360797) and received relevant ethical approval by each center:

• University Hospital of Tarragona Joan XXIII (Coordinating center), with the reference number 093/2022 issued by the Scientific and Research Ethics Committee of the Institut d’Investigació Sanitaria Pere Virgili-IISPV;

• Maresme Health Consortium, with the reference CEIm 34/22 issued by the Scientific and Research of the Mataró Hospital;

• Barcelona Clinic Hospital, with the reference HCB/2022/0812 issued by the Scientific and Research of the Barcelona Clinic Hospital;

• Moise’s Broggi Hospital, with the reference PR273/22 (CSI22/66) issued by the Scientific and Research of the Bellvitge Hospital University;

• Althaia University Hospital, with the reference CEI22-111 issued by the Scientific and Research of the Fundació Catalana d’Hospitals;

• Garcia de Orca EPE Hospital, with the date 27/02/2023 issued by the Scientific and Research of the Garcia de Orca EPE Hospital;

• La Paz University Hospital, with the reference HULP 6364 issued by the Scientific and Research of the La Paz University Hospital.

At the end of the project we will disseminate our results to the medical community and publish it as open access.
Authors affiliations

1 General and Digestive Surgery Department, University Hospital of Tarragona Joan XXIII, Rovira i Virgili University, Tarragona, Spain; 2 General and Digestive Surgery Department, Maresme Health Consortium, Matarò, Spain; 3 Gastroenterology Department, Barcelona Clinic Hospital, IDIBAPS, CIBEREHD, University of Barcelona, Barcelona, Spain; 4 General and Digestive Surgery Department, Moise’s Broggi Hospital, CSI, Barcelona, Spain; 5 Althaia University Hospital, Xarxa Asistencial Universitària de Manresa, Sant Joan de Déu Hospital, Manresa, Spain; 6 Hospital Garcia de Orca EPE, Almada, Portugal; 7 General and Digestive Surgery Department, IdiPAZ, CIBERehd, La Paz University Hospital, Madrid, Spain; 8 Investigators and Co-investigators from study group.

ACKNOWLEDGEMENTS

The principal investigator wish to thank Dr. Péter Hegyi and the Hungary Pancreatic Study group for everything they have contributed to my process as researcher. This work will be supported by research grants award from the ‘Catalan society of surgeons’ and ‘Spanish Association of Surgeons’. Finally, the authors to thank Editage (www.editage.com) for their assistance in editing and improving this manuscript.

List of Abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AP</td>
<td>Acute Pancreatitis</td>
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<tr>
<td>ASA</td>
<td>American Society of Anesthesiologist</td>
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<tr>
<td>BISAP</td>
<td>Bedside Index of Severity in Acute Pancreatitis</td>
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<tr>
<td>CC</td>
<td>Coordinating Committed</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>DMP</td>
<td>Data Management Plan</td>
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<tr>
<td>DQF</td>
<td>Data Query Form</td>
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<tr>
<td>DRM</td>
<td>Data Review Meeting</td>
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<tr>
<td>ER</td>
<td>Emergency Room</td>
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<tr>
<td>eRPF</td>
<td>electronic Patient Report Form</td>
</tr>
<tr>
<td>IAP/APA</td>
<td>International Association of Pancreatologists/American Pancreatic Association</td>
</tr>
</tbody>
</table>
FUNDING

Catalan society of surgeons

Spanish Association of Surgeons

AUTHOR CONTRIBUTIONS

ERM, SLG, CF and RJM participated in all phases of the study with the help other authors in the different parts.

Conception and design: ERM, RJM, SLG, AS, and CF.

Administrative, technical, or logistic support: ERM, RJM, SLG, AS, CF, DCLL, RSJ, JV, and MRR.

Drafting of the article: ERM, RJM, SLG, AS, CF, DCLL, RSJ, JV, MRR and the Catalan Pancreatitis Collaborative Group.

Critical revision of the article for important intellectual content: ERM, RJM, SLG, AS, CF, DCLL, RSJ, JV, and MRR.

All authors read and approved the final manuscript.

CONFLICTS OF INTERESTS

The authors declare that they have no conflicts of interest.
DICTAMEN COMITÉ ÉTICO DE INVESTIGACIÓN CON MEDICAMENTOS

Josep Mª Alegret Colomé, Vicepresidente del Comité Ético de Investigación con Medicamentos del IISPV preside la reunión.

HACE CONSTAR QUE
Este Comité, en su reunión de fecha 15/12/2022, ha evaluado la enmienda presentada y ha decidido emitir Informe Favorable para que se realice el estudio titulado:

"ENSEÑO CLÍNICO MULTICÉNTRICO, PROSPECTIVO ALEATORIZADO, PARA COMPARAR LA EFICACIA Y SEGURIDAD DEL TRATAMIENTO MÉDICO AMBULATORIO Y CON HOSPITALIZACIÓN DOMICILIARIA DE LA PANCREATITIS AGUDA LEVE (Protocolo de estudio PADI_2)"

Código: PADI_2
Versión Protocolo: Versión 3 Mayo 2022
Versión H.I.P. y Consentimiento Informatizado: Versión 2 Mayo 2022
Promotor: Dra. Elena Ramírez Maldonado - Servicio Cirugía General y Aparato Digestivo - Hospital Universitari de Tarragona Joan XXIII
Ref. CEIm: 093/2022

CONSIDERA QUE:
- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.
- La operación del investigador y el medio disponible son apropiados para llevar a cabo el estudio.
- Son adecuados tanto el procedimiento para obtener el consentimiento informado como la compensación prevista para los sujetos por daños que pudieran derivarse de su participación en el estudio.
- El alcance de las compensaciones económicas previstas no interfiera con el respeto a los postulados éticos.

Este comité acepta que dicho estudio se realice en el Hospital Universitari Joan XXIII de Tarragona por la Dra. Elena Ramírez Maldonado, del Servicio de Cirugía General y Aparato Digestivo.

En el caso de que se evalúe algún proyecto en el que participe como investigador/colaborador algún miembro de este comité, se ausentará de la reunión durante el debate del estudio.

La composición actual del CEIm del Instituto d'Investigación Sanitaria Pere Virgili es la siguiente:

Presidente
Dra. María Teresa Auguet Quintana
Servicio de Medicina Interna. Hospital Universitari Joan XXIII. Representante de la Comisión de Investigación.

Vicepresidente
Dr. Josep Mª Alegret Colomé
Cardiólogo. Salut Sant Joan de Reus-Baix Camp.

www.iispv.cat
Secretaria
Sra. Eliubet Galve Aixa
Secretaria CEIm IISPV

Vocales

Dr. Xavier Ruiz Plazas
Urología. Hospital Universitari Joan XXIII.

Sra. Montserrat Boj Borbonés
Farmacía – Salut Sant Joan de Reus-Baix Camp.

Sra. Mónica Cots Morenilla
Unidad de Atención Usuaria. Hospital Universitari Joan XXIII.

Dr. Joaquín Escrivan Súbias.
Médico del Servicio de Pediatría. Representante de la Comisión de Bioética Asistencial. Salut Sant Joan de Reus-Baix Camp.

Dra. M. Francisca Jiménez Herrera

Sra. M. Mar Granell Barceló
Abogada i Asesora Jurídica del Comité.

Dr. Jesús Miguel López-Dupla
Servicio de Medicina Interna. Hospital Universitari Joan XXIII.

Firma

Dr. Josep M. Alegret Colomé,
Vicepresidente CEIm IISPV
Reus, 15 de diciembre 2022

Sr. Jordi Mallol Mirón
Catedrático de Farmacología. Facultad de Medicina. Universitat Rovira i Virgili.

Dra. Montserrat Oloa Cabezas
Medicina Preventiva e Epidemiología. Hospital Universitari Joan XXIII.

Dra. M. Àngels Roch Ventura
Farmacia Hospitalaria Hospital Universitari Joan XXIII.

Sra. Isabel Rosich Martí
Farmacêutica. Atención Primaria.

Sr. Francesc Xavier Sureda Batlle
Profesor Titular de Farmacología. Universitat Rovira i Virgili.

Dr. Donis Mas Rosell
Medicina Psiquiatría – Institut Pere Mata.

Sra. Mercè Vilella Papaseit
Representante de la Sociedad Civil
INFORME DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN SOBRE PROYECTOS DE INVESTIGACIÓN BIOMÉDICA

El Dr. Enric Sospedra Martínez, responsable de la Secretaría Técnica del Comité de Ética de la Investigación del Hospital Universitari de Bellvitge,

CERTIFICA

Que el Comité de Ética de la Investigación, en su reunión de fecha 10 de noviembre de 2022 (Acta 24/22), tras examinar toda la documentación presentada sobre el proyecto de investigación con nuestra Ref. PR273/22 (CSI 22/66) titulado:

"ENSEYAO CLÍNICO MULTICÉNTRICO, PROSPECTIVO ALEATORIZADO, PARA COMPARAR LA EFICACIA Y SEGURIDAD DEL TRATAMIENTO MÉDICO AMBULATORIO Y CON HOSPITALIZACIÓN DOMICILIARIA VS INGRESO HOSPITALARIO DE LA PANCREATITIS AGUDA LEVE (Protocolo PADI_2).”, código PADI_2

Documentos con versiones:

<table>
<thead>
<tr>
<th>Protocolo</th>
<th>Versión 3 Mayo 2022</th>
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<tbody>
<tr>
<td>Hoja de Información al Paciente y Consentimiento Informato</td>
<td>Versión 2 Mayo 2022</td>
</tr>
</tbody>
</table>

Presentado por el Dr. Sergio González Martínez, del Servicio de Cirugía General y Aparato Digestivo del Hospital de Sant Joan Despí Molls Broggi - Consorci Sanitari Integral (CSI), como investigador principal y promovido por la Dra. Ruby Elena Ramírez Moldonado, del Servicio de Cirugía General y Aparato Digestivo del Hospital Universitari Joan XXIII de Tarragona, ha acordado emitir INFORME FAVORABLE al mencionado proyecto.

Que la composición actual del Comité de Ética de la Investigación es la siguiente:

Presidente: Dr. Francesc Esteve Urbano - Médico - Medicina Intensiva
Vicepresidenta: Dra. Pilar Hereu Boher - Médico - Farmacología Clínica
Secretario: Dr. Enric Sospedra Martínez - Farmacéutico - Farmacia Hospitalaria
Vocales:
- Dr. Jordi Adamuz Tomàs - Enfermero - Enfermería
- Sra. Anna Boix Traserra - Derecho - DPD
- Dra. Concepción Cañete Ramos - Médico - Neurología
- Dra. Sara Cobo Sacristán - Farmacéutica - Farmacia Hospitalaria

Generalitat de Catalunya
Dr. José Luis Ferreiro Gutiérrez  
Médico - Cardiología

Dra. Ana María Ferrer Artola  
Farmacéutica - Miembro sanitario

Sra. Esther Ferrer Canals  
Representante de los pacientes

Dr. Xavier Fuliadosa Oliveras  
Médico - Nefrología

Dr. Carles Liadó i Carbonell  
Médico - Urología

Dra. Sara Larriba Bartolomé  
Farmacía - Sanitario

Sra. Sonia López Ortega  
Graduado Social - Atención a la Ciudadanía

Dr. Juan Jesús Martín Liberal  
Médico - Oncología Médica

Dr. Sergio Marchón Ramos  
Médico - Medicina Preventiva

Dr. Miguel Ángel Pavón Ribas  
Biólogo- Miembro no sanitario

Dr. Joan Josep Queralt Jiménez  
Jurista

Dra. Gemma Rodríguez Palomar  
Farmacéutica – Atención Primaria

Dr. Petru Cristian Simon  
Médico - Farmacología Clínica

Que este Comité cumple la legislación española vigente para este tipo de proyectos, así como las normas ICH y las Normas de Buena Práctica Clínica.

Que en dicha reunión del Comité de Ética de la Investigación se cumplió el quórum preceptivo legalmente.

Lo que firme en L’Hospitalet de Llobregat, a 30 de noviembre de 2022

SOSPEDRA MARTÍNEZ
ENRIQUE - 36986426B

DN: c=ES,
serialNumber=IDCES-36986426B, givenName=ENRIQUE,
sn=SOSPEDRA MARTÍNEZ,

ENRIQUE - 36986426B
Data: 2022.11.30 14:21:26
+01’00’

Dr. Enric Sospedra Martínez

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
INFORME DEL COMITÈ DE ÈTICA D’INVESTIGACIÓ CLÍNICA

Mireia Bolívar Prados, en qualitat de secretaria tècnica del Comitè d’Ètica d’Investigació Clínica amb Medicaments de l’Hospital de Mataró, Consorci Sanitari del Maresme,

CERTIFICA

Que aquest Comitè ha avaluat la proposta presentada per Hospital Universitari Tarragona Joan XXIII per a que sigui realitzat a l’Hospital de Mataró l’estudi titulat:

Ensayo clínico multicéntrico, prospectivo aleatorizado, para comparar la eficacia y seguridad del tratamiento médico ambulatorio y con hospitalización domiciliaria de la pancreatitis aguda leve

<table>
<thead>
<tr>
<th>Tipus d’estudi</th>
<th>Observacional</th>
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<tbody>
<tr>
<td>Protocol</td>
<td>Versió 2</td>
</tr>
<tr>
<td>Data d’informació al Pacient / Consentiment Informat</td>
<td>Data: Juliol 2022</td>
</tr>
<tr>
<td>Procediments i material utilitzat pel reclutament dels subjectes (anuncis publicitaris, informació web, etc.)</td>
<td>NA</td>
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</tbody>
</table>

I considera que:

- Es compleixen els requisits necessaris d’idoneïtat del protocol en relació amb els objectius de l’estudi i es troben justificats els riscos i molèsties previsibles pel subjecte
- La capacitat de l’Investigador i els mitjans disponibles són apropisats per a dur a terme l’estudi
- El procediment per a obtenir el consentiment informat és adequat
- Les compensacions econòmiques previstes no interfereixen amb el respecte dels postulats ètics

I que aquest Comitè emet informe favorable per a que l’esmenat estudi sigui realitzat a l’Hospital de Mataró per López, S com Investigadora Principal.

El que firma a Mataró a 12 de juliol de 2022,

BOLÍVAR PRADOS
MIREIA -
45985345L
Firma: 28/06/2023

Mireia Bolívar Prados
Secretària Tècnica del CEIm del CSdM,
Hospital de Mataró
Mireia Bolívar Prados, en qualitat de secretaria tècnica del Comitè d'Ètica d'Investigació Clínica amb Medicaments de l'Hospital de Mataró, Consorci Sanitari del Maresme,

FA CONSTAR QUE:

1. En la reunió celebrada a dia 22/06/2022, acta 06 – 22.06.2022 es decideix emetre informe condicionat a l'estudi de referència.
2. Que a dia 12/07/2022, s'emet informe favorable amb les modificacions pertinents suggerides pel Comitè.
3. En l'esmentada reunió, es compleixen els requisits establets en la legislació vigent per a que la decisió del anomenat CEIm sigui vàlida.
4. El CEIm del CSdM, tant en la seva composició com als PNT compleix amb les normes de BPC (CPMP/ICH/135/95).
5. La composició actual del CEIm és la següent:

<table>
<thead>
<tr>
<th>Pere Clavé Civil (President)</th>
<th>Metge. Especialista en cirugía. Director Acadèmic, d'Investigació i Innovació del Consorci Sanitari del Maresme. President de la Comissió d'Investigació del CSdM.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mireia Bolívar Prados (Secretaria Tècnica)</td>
<td>Farmacèutica. Unitat de Fisiologia Digestiva del Consorci Sanitari del Maresme.</td>
</tr>
<tr>
<td>Mateu Serra Prat</td>
<td>Metge. Epidemiòleg. Cap de la Unitat de Recerca. Membre de la Comissió d'Investigació del CSdM. Membre del Comitè d'Ètica Assistencial del CSdM.</td>
</tr>
<tr>
<td>Alexis Rodríguez Gallego</td>
<td>Metge Farmacòleg Clínic. Hospital Vall d'Hebron. Membre alliè al centre.</td>
</tr>
<tr>
<td>Itziar Flores Aliri</td>
<td>Advocada. Membre no sanitari i alliè al centre.</td>
</tr>
<tr>
<td>Maria Bartolomé Regué</td>
<td>Metge especialista en MFiC. CAP Mataró-Centre del CSdM.</td>
</tr>
<tr>
<td>Lluís Campins Barnadas</td>
<td>Farmacèutic Hospitalari. Cap de Servei de Farmàcia de l'Hospital de Mataró.</td>
</tr>
<tr>
<td>Rubén Sánchez Borrego</td>
<td>Administratiu. Cap de la Unitat d'Atenció al Usuari del CSdM.</td>
</tr>
<tr>
<td>David López Faixó</td>
<td>Farmacèutic Atenció Primària. Servei de Farmàcia del CSdM.</td>
</tr>
<tr>
<td>Ainhoa Sánchez Ulzar</td>
<td>Farmacèutica Hospitalària. Servei de Farmàcia del CSdM.</td>
</tr>
<tr>
<td>Omar Ortega Fernández</td>
<td>Biòleg. Investigador CIBERehd del CSdM.</td>
</tr>
<tr>
<td>Isabel Lorenzo Sánchez</td>
<td>Biòloga. Responsable econòmica. Direcció Acadèmica, de Recerca i d'Innovació del CSdM.</td>
</tr>
<tr>
<td>Vanessa Vicente Arcús</td>
<td>Enfermera. Hospital de Mataró, CSdM.</td>
</tr>
<tr>
<td>Francesc Moya Olvera</td>
<td>Informàtic. Director de sistemes d'Informació i Coordinador Protecció de Dades del CSdM.</td>
</tr>
<tr>
<td>Carme Pascual González</td>
<td>Metge especialista en MFiC. ABS Calella.</td>
</tr>
</tbody>
</table>

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
PARECER E AUTORIZAÇÃO PARA REALIZAÇÃO DE ESTUDO

Hospital Garcia de Orta EPE
Centro de Investigação Hospital Garcia de Orta

**Título:** Participação no Estudo clínico multicêntrico, prospectivo e randomizado, para comparar a eficácia e segurança do tratamento médico em ambulatório e com hospitalização domiciliária vs internamento hospitalar na pancreatite aguda leve - Protocolo PADI_2.

**Investigador Principal:** Dr Rui Branco

A **Comissão de Ética** para a Saúde do Hospital Garcia de Orta informa que o trabalho em epígrafe obteve parecer positivo por unanimidade □ maioria ☑ em reunião do dia 27/02/2023.

**Estiveram presentes:**
☑ Nome: Dra Natália Dias (Presidente)
☑ Nome: Dra Ana Soares
☑ Nome: Dra Aurora Tomaz
☑ Nome: Dra Benedita Nunes
☑ Nome: Dra Cátia Gradil
☐ Nome: Dra Eunice Teixeira
☑ Nome: Dra Isabel Pereirinha
☐ Nome: Dr. José Luís Metello
☑ Nome: Dr. Manuel Quintâos
☑ Nome: Dr. Miguel Rodrigues
☐ Nome: Enfª Teresa Chambel

A CES solicita ao Investigador Principal que quando da conclusão deste estudo, lhe seja enviada uma síntese dos resultados e conclusões do mesmo.

---

O Estudo em epígrafe foi aprovado pelo **Conselho de Administração** em reunião do dia 02/03/2023.

---

Assinatura:

Dra. Natália Dias
Presidente da Comissão de Ética

Dra. Paula Breia
Presidente do Centro Garcia de Orta

Almada, 06/03/2023
COMITÉ ÉTICO DE LA INVESTIGACIÓN CON MEDICAMENTOS

Dra. Ana Lucía Arellano Andino, Secretaria del Comité Ético de Investigación Clínica del Hospital Clínic de Barcelona

CERTIFICA

Que este Comité ha recibido el proyecto:

Título: Ensayo clínico multicéntrico prospectivo aleatorizado, para comparar la eficacia y seguridad del tratamiento médico ambulatorio y con hospitalización domiciliaria vs ingreso hospitalario de la pancreatitis aguda leve (Protocolo PADI_2).

Investigador/es principal/es: ARIADNA SANCHEZ GARCIA

Y acepta el Dictamen favorable del CEIm del INSTITUT D’INVESTIGACIÓ SANITÀRIA PERE VIRGILI

Barcelona, a 21 de julio de 2022

Reg. HCB/2022/0812

Mod_28 (V1 de 9/05/2017)

Aceptación CEIm
INFORME DEL COMITÉ D’ÈTICA D’INVESTIGACIÓN

Dr. Miquel Nolla, com a President del Comité d’Ètica d’Investigació de la FUNDACIÓ UNIO CATALANA HOSPITALS

CERTIFICA:
Que aquest Comité en la seva reunió del dimarts 20 de desembre, ha avaluat la proposta presentada, per que es realitzi l’estudi que porta per títol “Ensayo clínico multicéntrico, prospectivo aleatorizado, para comparar la eficacia y seguridad del tratamiento médico ambulatorio y con hospitalización domiciliaria vs ingreso hospitalario de la pancreatitis aguda leve (PADI_2)”, amb codi CEI 22/111, i considera que:

Es compleixen els requisits necessaris d’idoneitat del protocol en relació amb els objectius de l’estudi i que estan justificats els riscos i les molesties previsibles per al subjecte. La capacitat de l’investigador i els mitjans disponibles són apropisats per portar a terme l’estudi. Són adequats tant el procediment per obtenir el consentiment informat com la compensació prevista per als subjectes per danys que es puguin derivar de la seva participació a l’estudi.

Que aquest Comité decideix emetre INFORME FAVORABLE, a la resolució dels aclariments.

Que aquest comitè accepta que aquest estudi es digui a terme a Althaia, Xarxa Assistencial Universitària de Manresa, amb Raquel Sánchez Jiménez com a investigadora principal. I que la investigadora principal no ha estat present en les deliberacions i aprovació d’aquest estudi.

En aquesta reunió s’han complert els requisits establerts en la legislació vigent. El CEIm tant en la seva composició, com en els PNT compleix amb les normes de BPC (CPMP/ICH/135/95).

MEMBRES DEL CEIm DE LA FUNDACIÓ UNIO CATALANA D’HOSPITALS

<table>
<thead>
<tr>
<th>Miquel Nolla Sala</th>
<th>President</th>
<th>Metge</th>
</tr>
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<tbody>
<tr>
<td>Anna Altés Cais</td>
<td>Vicepresidenta</td>
<td>Metge</td>
</tr>
<tr>
<td>Vanessa Massó Marigot</td>
<td>Secretaria tècnica</td>
<td>C. Empresarials</td>
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<tr>
<td>Anxo Gómez Lumbrañas</td>
<td>Vocal</td>
<td>Farmacòleg Clinica</td>
</tr>
<tr>
<td>Itziar Arí Flores</td>
<td>Vocal</td>
<td>Advocadessa, experta protecció de dades</td>
</tr>
<tr>
<td>Ana Barajas Vélez</td>
<td>Vocal</td>
<td>Psicòleg</td>
</tr>
<tr>
<td>Lucía García Valiño</td>
<td>Vocal</td>
<td>Psicòleg - Atenció Usuari</td>
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<tr>
<td>Núria López Matons</td>
<td>Vocal</td>
<td>Psicòleg</td>
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<tr>
<td>Conxita Malo Guíllet</td>
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<td>Encarna Martínez Navarro</td>
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<td>Ernesto Ezequiel Mónaco</td>
<td>Vocal</td>
<td>Metge</td>
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<tr>
<td>Queralt Moreno Gil</td>
<td>Vocal</td>
<td>Farmacèutica primària</td>
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<tr>
<td>Cristina Pérez Reche</td>
<td>Vocal</td>
<td>Farmacèutica hospitalària</td>
</tr>
<tr>
<td>Josep M Tormo Muñoz</td>
<td>Vocal</td>
<td>Metge</td>
</tr>
</tbody>
</table>

Barcelona, 24 de gener de 2023

Dr. Miquel Nolla
President del CEIm
PA Recer e autorizaçã o para realização de estudo
Hospital Garcia de Orta EPE
Centro de Investigação Hospital Garcia de Orta

Título: Participação no Estudo clínico multicêntrico, prospectivo e randomizado, para comparar a eficácia e segurança do tratamento médico em ambulatorio e com hospitalização domiciliária vs internamento hospitalar na pancreatite aguda ligeira - Protocolo PADI_2.

Investigador Principal: Dr Rui Branco

A Comissão de Ética para a Saúde do Hospital Garcia de Orta informa que o trabalho em epígrafe obteve parecer positivo por unanimidade ☑ maioria ☐ em reunião do dia 27/02/2023.

Estiveram presentes:
☑ Nome: Dra Natália Dias (Presidente)
☑ Nome: Dra Ana Soares
☑ Nome: Dra Aurora Tomaz
☑ Nome: Dra Benedita Nunes
☑ Nome: Dra Cátila Gradil
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☐ Nome: Dra Isabel Pereirinha
☐ Nome: Dr. José Luís Metello
☑ Nome: Dr. Manuel Quintãos
☑ Nome: Dr. Miguel Rodrigues
☐ Nome: Enfª Teresa Chambel

A CES solicita ao Investigador Principal que quando da conclusão deste estudo, lhe seja enviada uma síntese dos resultados e conclusões do mesmo.

O Estudo em epígrafe foi aprovado pelo Conselho de Administração em reunião do dia 02/03/2023.

Dra. Paula Breia
Presidente do Centro Garcia de Orta
Almada, 04/03/2023
RATIFICACIÓN

TÍTULO: ENSAYO CLÍNICO MULTICÉNTRICO, PROSPECTIVO ALEATORIZADO, PARA COMPARAR LA Eficacia y SEGURIDAD del TRATAMIENTO MÉDICO AMBULATORIO y CON HOSPITALIZACIÓN DOMICILIARIA VS INGRESO HOSPITALARIO DE LA PANCREATITIS AGUDA LEVE

<table>
<thead>
<tr>
<th>Protocolo</th>
<th>Versión 3 Mayo 2022</th>
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<tr>
<td>Hoja Información</td>
<td>Versión 2 Mayo 2022</td>
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</table>

INVESTIGADOR PRINCIPAL: CONSTANTINO FONDEVILA CAMPO del Servicio de CIRUGÍA GENERAL y APARATO DIGESTIVO del HOSPITAL UNIVERSITARIO LA PAZ
CEIm: INSTITUT D'INVESTIGACIÓ SANITÀRIA PERE VIRGILI TIPO DE ESTUDIO: EECC
CÓDIGO INTERNO: 2023,025 CÓDIGO HULP: 6364 ACTA: 01/2023
CÓDIGO PROMOTOR: PADI_2 PROMOTOR: FONDEVILA CAMPO CONSTANTINO

Presidente:
- ALMUDENA CASTRO CONDE - Médico Adjunto. Servicio de Cardiología

Vicepresidente:
- ROSA VILLANUEVA PEÑA - Médico Adjunto. Servicio de Psiquiatría

Secretario:
- EMMA FERNÁNDEZ DE UZQUIANO - Jefe de la Secretaría Técnica

Vocales:
- JOSE MANUEL AÑÓN ELIZALDE - Jefe de Sección. Servicio de Medicina Intensiva
- JOSÉ IGNACIO BERNARDINO DE LA SERNA - Médico Adjunto. 5º de Medicina Interna
- NORA VIVIANA BUTTA COLL - Jefe de Laboratorio de Enzimas Transaminasas. IMPAZ
- FERNANDO CABASAS GONZALEZ - Investigador IdiPaz
- MARIANA DIAZ ALMIRON - Investigador IdiPaz. Sección de Bioestadística
- MARÍA DOLORES DIESTRO TEJEDOR - Médico Adjunto. Servicio de Gastroenterología y Digestión Obstetricia
- JAIME FERNANDEZ BUJARRABAL - Médico Adjunto. Servicio de Nefrología
- MARÍA JUSTA GARCÍA-MATÍES Y CORTES - Médico Adjunto. Servicio de Urología
- PEDRO HERRANZ PINO - Jefe de Servicio. Servicio de Dermatología
- CARLOS LARIOZA RALLO - Médico Adjunto. Servicio de Medicina Interna
- EVA PRIETO UTIEL - Farmacéutico. At. Primaria del Área Norte. M. a la Institución
- NURIA DRODRIGUEZ SALAS - Médico Adjunto. Servicio de Oncología Médica
- MIRIAM ROMERO PORTALES - Médico Adjunto. Servicio de Aparato Digestivo
- PABLO TRONCOLI GONZALEZ - Enfermero. Servicio de Neurología
- ELENA VILLAMENA BUNO - Farmacéutica Adjunta. Servicio de Farmacia
- PALOMA OLIVER SAÁ - Farmacéutica Adjunta. Servicio de Análisis Clinicos
- MERCEDES GASIOR KABAT - Médico Adjunto de Hematología
- ALEJANDRA VILANOVA SANCHEZ - Médico Adjunto de Cirugía Pediátrica
- ANTONIO J. CARCAS SANZUAN - Jefe de Servicio. Farmacología Clínica
- IRENE GARCÍA GARCÍA - FEA Farmacología Clínica

RESOLUCIÓN:

Ratificación

OBSERVACIONES:

Madrid, a 12/01/2023

Fdo. EMMA FERNÁNDEZ DE UZQUIANO
Secretario técnico del CEIm

Firmado digitalmente por: FERNANDEZ DE UZQUIANO MARIA EMMA
Fecha: 2023.01.12 15:38
REFERENCES


Figure 1. Flow chart of participants according to the SPIRIT 2013 statement [18]
Adult patients with an episode of acute pancreatitis (AP)

Exclusions

Not meeting inclusion criteria
(1) Patient above 18y
(2) Diagnosed AP (2 out 3 criteria)
(3) Signed written informed consent form

Meeting exclusion criteria
(1) Pregnant or breastfeeding women
(2) Abdominal pain >96h
(3) The possibility of poor oral intake for reasons other than AP
(4) Pancreatic neoplasm, endoscopic retrograde cholangiopancreatography or trauma etiology, biliar obstruction
(5) Chronic pancreatitis
(6) ASA ≥3
(7) Moderate or severe acute pancreatitis;
(8) The patient is considered unable to eat an oral diet for other reasons than AP

X patients to be randomized

Outpatient

Stay in the emergency room for 24 h

Mild acute pancreatitis confirmed

Home Care

Hospital Admission

X analysed

X analysed

X analysed
<table>
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<tr>
<th>Section/item</th>
<th>Item number</th>
<th>Description</th>
<th>Pages</th>
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</thead>
<tbody>
<tr>
<td>Administrative info.</td>
<td>Title</td>
<td>Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym</td>
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<td>Trial registration 2a</td>
<td>Trial identifier and registry name. If not yet registered, name of intended registry</td>
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<tr>
<td></td>
<td>Protocol version 3</td>
<td>Date and version identifier</td>
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<tr>
<td></td>
<td>Funding 4</td>
<td>Sources and types of financial, material, and other support</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Roles and responsibilities 5a</td>
<td>Names, affiliations, and roles of protocol contributors</td>
<td>1, 19</td>
</tr>
<tr>
<td></td>
<td>Roles and responsibilities 5b</td>
<td>Name and contact information for the trial sponsor</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Roles and responsibilities 5c</td>
<td>Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities</td>
<td>-</td>
</tr>
<tr>
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<td>Roles and responsibilities 5d</td>
<td>Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)</td>
<td>12-13</td>
</tr>
<tr>
<td>Introduction</td>
<td>Background and rationale 6a</td>
<td>Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention</td>
<td>6-7</td>
</tr>
<tr>
<td></td>
<td>Objectives 7</td>
<td>Specific objectives or hypotheses</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Trial design 8</td>
<td>Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)</td>
<td>7</td>
</tr>
</tbody>
</table>

Methods: Participants, interventions, and outcomes
<table>
<thead>
<tr>
<th>Study Setting</th>
<th>9</th>
<th>Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility Criteria</td>
<td>10</td>
<td>Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)</td>
</tr>
<tr>
<td>Interventions</td>
<td>11a</td>
<td>Interventions for each group with sufficient detail to allow replication, including how and when they will be administered</td>
</tr>
<tr>
<td></td>
<td>11b</td>
<td>Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)</td>
</tr>
<tr>
<td></td>
<td>11c</td>
<td>Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)</td>
</tr>
<tr>
<td></td>
<td>11d</td>
<td>Relevant concomitant care and interventions that are permitted or prohibited during the trial</td>
</tr>
<tr>
<td>Outcomes</td>
<td>12</td>
<td>Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended</td>
</tr>
<tr>
<td>Participant Timeline</td>
<td>13</td>
<td>Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)</td>
</tr>
<tr>
<td>Sample Size</td>
<td>14</td>
<td>Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations</td>
</tr>
<tr>
<td>Recruitment</td>
<td>15</td>
<td>Strategies for achieving adequate participant enrolment to reach target sample size</td>
</tr>
<tr>
<td>Methods: Assignment of interventions (for controlled trials)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allocation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequence Generation</td>
<td>16a</td>
<td>Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions</td>
</tr>
<tr>
<td>Allocation Concealment</td>
<td>16b</td>
<td>Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned</td>
</tr>
</tbody>
</table>
Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions

Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how

If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial

Methods: Data collection, management, and analysis

Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.

Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).

Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

Methods for any additional analyses (eg, subgroup and adjusted analyses)

Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination
<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>Plans for seeking research ethics committee/institutional review board (REC/IRB) approval</td>
</tr>
<tr>
<td>25</td>
<td>Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)</td>
</tr>
<tr>
<td>26a</td>
<td>Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)</td>
</tr>
<tr>
<td>26b</td>
<td>Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable</td>
</tr>
<tr>
<td>27</td>
<td>How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial</td>
</tr>
<tr>
<td>28</td>
<td>Financial and other competing interests for principal investigators for the overall trial and each study site</td>
</tr>
<tr>
<td>29</td>
<td>Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators</td>
</tr>
<tr>
<td>30</td>
<td>Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation</td>
</tr>
<tr>
<td>31a</td>
<td>Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions</td>
</tr>
<tr>
<td>31b</td>
<td>Authorship eligibility guidelines and any intended use of professional writers</td>
</tr>
<tr>
<td>31c</td>
<td>Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code</td>
</tr>
</tbody>
</table>

**Appendices**

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>Model consent form and other related documentation given to participants and authorised surrogates</td>
</tr>
<tr>
<td>33</td>
<td>Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable</td>
</tr>
</tbody>
</table>

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.*