BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Home care/outpatient vs hospital admission in mild acute pancreatitis: protocol of a multicenter, randomized controlled trial (PADI_2 trial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Ramirez-Maldonado, Elena; Rodrigo-Rodrigo, Marta; Lopez Gordo, Sandra; Sanchez, Ariadna; Coronado Llanos, Daniel; Sanchez, Raquel; Vaz, Joao; Fondevila, Constantino; Jorba-Martin, Rosa; The Catalan Pancreatitis Collaborative Group, The Catalan Pancreatitis</td>
</tr>
</tbody>
</table>

GENERAL COMMENTS

Ramírez-Maldonado et al. exposed a very interesting trial comparing 3 types of interventions (home care, outpatient and hospital admission) for management of mild acute pancreatitis. In our opinion, the possibility of managing patients at home for non-severe acute pancreatitis is a major issue and we agree that this study is suitable for clinical practice. The protocol is well written and the research question is well exposed and defined. However, we have some queries to answer before publication:

1) Page 7 (page 6 of the manuscript) Line 44. Can you precise in inclusion criteria what are the criteria for compliance with outpatient or homecare.

2) In Intervention paragraph Can you precise when will the biologic analysis be perform especially for outpatients? For example in table 1 And which kind of biological analysis?

3) Page 10 (page 9 of the manuscript) Line 21 Can you give some details about the general treatment because it could be now different from IAP/AAP guidelines that were published in 2013. For example, in IPA guidelines it was recommended to perform aggressive fluid therapy (> 5 mL/kg/h). That is not now the actual. Moreover, an infusion could be difficult to perform at home. It could be interesting to detail how the different care will be given at home. Patients should certainly be discharged without an infusion About the different treatment given to patient, what about management of alcohol withdrawal syndrome for alcoholic patient. Is it an exclusion criteria for homecare management?

4) In safety paragraph Even if there is not unknown drugs used in this study, the protocol can induce some adverse events due to difference of monitoring between homecare and hospitalized patients. We can imagine that outpatients develop some complications with a later diagnostic.
5) Expected severe pancreatitis
At admission, it is a real difficulty to predict which patient will develop a severe form of pancreatitis.
In exclusion criteria, we believe that it would more appropriate to write “(7) expected moderate or severe acute pancreatitis” instead of “(7) moderate or severe acute pancreatitis”.

Can you add some justifications that SIRS< 2 criteria; BISAP < 2; initial absence of organ failure are sufficient criteria to exclude the development of a moderate or severe form of pancreatitis. Because that is above all persistent SIRS that is correlated to development of a severe form (Singh, 2009) and BISAP is not an uncriticale predictive score for severe pancreatitis (Gao et al, 2015).

Minor points:
1) Page 6 (page 5 of the manuscript) Line 6: A space is missing between pancreatitis and (AP)
2) Page 7 (page 6 of the manuscript) Line 52: A “r” is missing in “or breastfeeding”
3) Page 8 (page 7 of the manuscript) line 21. A Capital letter is missing in “After obtaining” and not after obtaining

REVIEWER
Gluud, Lise
Copenhagen University Hospital, Gastro Unit Copenhagen University Hospital – Hvidovre

REVIEW RETURNED
15-Feb-2023

GENERAL COMMENTS
The main objective of this non-inferiority, open, randomized trial is to compare in-patient versus outpatient versus medical homecare for the management of patients with mild acute pancreatitis. The objective is clearly clinically relevant, and the rationale is well described.
The sample size calculation is extremely important and should be clarified. There are three intervention groups, and the outpatient failure rate is described, but not the homecare failure rate. Also, the definition of failure and success should be made clear and the calculation should be adjusted for the three-arm design. The text lists hospital readmission as treatment failure (line 40 page 11) but also (line 53 page 11): (1) diet intolerance (<50% of plates); (2) uncontrolled nausea or vomiting; (3) uncontrolled pain despite oral painkillers; (4) predictors of severity are present. The online protocol registration in clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT05360797?term=outpatient&recr=ab&cond=Acute+Pancreatitis&draw=2&rank=1) lists “Primary objective Compare the results of 3 different strategies for the management of patients with mild acute pancreatitis (AP) and to analyze differences in satisfaction patients and economic costs” and “Treatment failure is defined as persistence, increase or recurrence of abdominal pain, or intolerance diet, hospital admission, and mortality”.
The comparison of three intervention groups means that the statistical analyses should be adjusted accordingly. A p-value of 5% is listed and the rationale for this should be clarified.
The description of the analyses should clearly state which of the three populations are used in the primary analyses. The trial is open, and investigators are given the opportunity to submit post-hoc information regarding, e.g., exclusion criteria. This can introduce bias in the per protocol analyses. The SAP population is listed first and includes all patients regardless of follow up or compliance. It also includes patients who withdraw their consent. It is not clear to me how patients who are withdrawn/lost to follow up are included in the analyses. What happens if, e.g., patients decline outpatient management but withdraw their consent and insist on in-patient treatment?
Some parts of the protocol were unclear to me. Considering the subsequent possible
external validity of the findings, I would recommend elaborating on the inclusion and exclusion criteria. For example, abdominal pain >96 hours (4 days) is listed under exclusion criteria. Is this pain before admission? If patients are randomized within 24 hours of admission, I would assume that this is the case. The criteria also list biliary obstruction. Does this mean that pancreatitis associated with gall stones are included unless there is evidence of biliary tract obstruction (I would assume so)? Are patients with external biliary tract obstruction eligible for inclusion? Are patients with recurrent acute pancreatitis eligible for inclusion?

The method of randomization is described as using a randomization sequence based on block-randomization. The allocation concealment was not clear to me. The text states that ‘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’. Does this mean that patients will be entered into the database by the investigator and after this is done the database will assign a randomisation number? What is the block size and what is done to avoid that this can cause a break in the allocation of patients (if the investigator knows that, e.g., the size is five, then it is possible to deduce the allocation of the last patients in the block)? I am surprised that there is no stratification for aetiology - only for centre?

The paragraph concerning duration and follow up does not explain why patients are followed at different intervals. Safety is very important so all patients should receive the same assessments during follow up. The text states that follow up visits could be planned between 1 and 3 months after the initial treatment for the experimental groups and three months for the control group (in-patient group). This can introduce bias which can be avoided by making sure that follow up is the same for all groups, e.g., by ensuring that all patients are followed according to table 3.

**VERSION 1 – AUTHOR RESPONSE**

Reviewer #1: Dr. Benoit Dupont, Centre Hospitalier Universitaire de Caen
Ramirez-Maldonado et al. exposed a very interesting trial comparing 3 types of interventions (home care, outpatient and hospital admission) for management of mild acute pancreatitis. In our opinion, the possibility of managing patients at home for non-severe acute pancreatitis is a major issue and we agree that this study is suitable for clinical practice. The protocol is well written and the research question is well exposed and defined. However, we have some queries to answer before publication:

Page 7 (page 6 of the manuscript) Line 44. Can you precise in inclusion criteria what are the criteria for compliance with outpatient or homecare?
Response: Thank you for this suggestion. Accordingly, the outpatient or homecare criteria have been added, at the end of the inclusion criteria.
Location: Methods, Inclusion criteria (Page 7, Paragraph 3)

In intervention paragraph. Can you precise when will the biologic analysis be perform especially for outpatients? For example in Table 1. And which kind of biological analysis?
Response: Thank you for this suggestion. Accordingly, the clinical and analytical parameters to be performed on all patients in all groups have been added.
Location: Methods, Monitored parameters (Page 11, Paragraph 4)

Page 10 (page 9 of the manuscript) Line 21. Can you give some details about general treatment because it could be now different from IAP / APA guidelines that were published in 2013. For example, in IPA guidelines it was recommended to perform aggressive fluid therapy (>5mL/kg/h). That is not actual. Moreover, an infusion could be difficult to perform at home. It could be interesting to detail how the different care will be given at home. Patients should certainly be discharged without
an infusion. About the different treatment given to patient, what about management of alcohol withdrawal syndrome for alcoholic patient. Is it an exclusion criteria for homecare management?
Response: Thank you for this feedback. We have added a better explanation of the general treatment of patients.
Location: Methods, General treatment (Page 9, Paragraph 3)
Response: Thank you for this feedback. We have added alcohol withdrawal syndrome for alcoholic patients as an exclusion criteria because this will lead to another type of treatment beyond the objectives of the study.
Location: Methods, exclusion criteria (Page 7, Paragraph 4)

In safety paragraph. Even is there is not unknown drugs used in this study, the protocol can induce some adverse events due to difference of monitoring between homecare and hospitalized patients. We can imagine that outpatients develop some complications with a later diagnostic.
Response: Thank you for this comment. Accordingly, we have explained the safety strategy for outpatients.
Location: Methods, Safety (Page 16, Paragraph 3)

Expected severe pancreatitis. At admission, it is a real difficulty to predict which patient develop a severe form of pancreatitis. In exclusion criteria, we believe that it would more appropriate to write ‘(7) expected moderate or severe acute pancreatitis’ instead of ‘(7) moderate or severe acute pancreatitis’.
Response: Thank you for this valuable suggestion. Accordingly, the term ‘expected’ has been added.
Location: Methods, Exclusion criteria (Page 7, Paragraph 4)

Can you add some justifications that SIRS<2 criteria; BISAP<2; initial absence of organs failure are sufficient criteria to exclude the development of a moderate or severe form pancreatitis. Because that is above all persistent SIRS that is correlated development of a severe form (Singh, 2009) and BISAP is not an uncritical predictive score for severe pancreatitis (Gap et al, 2015).
Response: Thank you for this comment. Accordingly, we added an explanation for the SIRS and BISP parameters.
Location: Background, (Page 5, paragraph 4)

Minor points

Page 6 (Page 5 of the manuscript Line 6: A space is missing between pancreatitis an (AP).
Response: Thank you for pointing this out. We have included that space.
Location: described location

Page 7 (Page 6 of the manuscript Line 52: A ‘r’ is missing in ‘or breastfeeding’.
Response: Thank you for pointing this out. We have included this ‘r’.
Location: described location

Page 8 (Page 7 of the manuscript Line 21: A capital letter is missing in ‘After obtaining’ and not after obtaining.
Response: Thank you for pointing this out. We have changed this capital letter.
Location: described location

Reviewer #2: Dr. Lise Glued, Copenhagen University Hospital
The main objective of this non-inferiority, open, randomized trial is to compare in-patient versus outpatient versus medical homecare for the management of patients with mild acute pancreatitis. The objective is clearly clinically relevant, and the rationale is well described.

The sample size calculation is extremely important and should be clarified. There are three intervention groups, and the outpatient failure rate is described, but not the homecare failure rate. Also, the definition of failure and success should be made clear and the calculation should be adjusted for the three-arm design.
Response: Thank you for this insightful comment, which we agree with. Accordingly, we have clarified that the treatment failure rate is for a home monitoring group (outpatient or homecare). There are two only published studies on homecare/outpatient. We have based the calculation of the sample for the
three branches on these studies and added it to the protocol.
Location: Methods, Sample size (Page 7, Paragraph 5)

The text lists hospital readmission as treatment failure (line 40 page 11) but also (line 53 page 11): (1) diet intolerance (<50% of plates); (2) uncontrolled nausea or vomiting; (3) uncontrolled pain despite oral painkillers; (4) predictors of severity are present. The online protocol registration in clinicaltrials.gov
(https://clinicaltrials.gov/ct2/show/NCT05360797?term=outpatient&recrs=ab&cond=Acute+Pancreatitis&s&draw=2&rank=1) lists “Primary objective Compare the results of 3 different strategies for the management of patients with mild acute pancreatitis (AP) and to analyze differences in satisfaction patients and economic costs” and “Treatment failure is defined as persistence, increase or recurrence of abdominal pain, and or intolerance diet, hospital admission, and mortality”.
Response: Thank you for this valuable suggestion. Accordingly, we have clarified the methods in this manuscript and the online protocol registration at www.clinicaltrials.gov.
Response: Thank you for this suggestion. Hospital readmission or admission results from failure of treatment. Failure of treatment is defined in our manuscript.
Location: Methods, Secondary endpoints (Page 11, Paragraph 3).

The comparison of three intervention groups means that the statistical analyses should be adjusted accordingly. A p-value of 5% is listed and the rationale for this should be clarified.
Response: We clarified the statistical method for the three treatment groups, as the reviewer suggested.
Location: Methods, Statistical method (Page 13, Paragraph 6)

The description of the analyses should clearly state which of the three populations are used in the primary analyses. The trial is open, and investigators are given the opportunity to submit post-hoc information regarding, e.g., exclusion criteria. This can introduce bias in the per protocol analyses. The SAP population is listed first and includes all patients regardless of follow up or compliance. It also includes patients who withdraw their consent. It is not clear to me how patients who are withdrawn/lost to follow up are included in the analyses. What happens if, e.g., patients decline outpatient management but withdraw their consent and insist on in-patient treatment?
Response: Thank you for this excellent feedback. This study will us Per-protocol (PPP) as well as intention-to-treat (ITT) analyses. In the section 'Withdrawal of a participant from PPP' The process to be followed if any of the described situations occurs is described. But as in all studies, researchers must meet the inclusion and exclusion criteria as reflected in the annex to the treatment scheme.
Location: Methods, Withdrawal of a participant from PPP (Page 13, Paragraph 4)

Some parts of the protocol were unclear to me. Considering the subsequent possible external validity of the findings, I would recommend elaborating on the inclusion and exclusion criteria. For example, abdominal pain >96 hours (4 days) is listed under exclusion criteria. Is this pain before admission? If patients are randomized within 24 hours of admission, I would assume that this is the case. The criteria also list biliary obstruction. Does this mean that pancreatitis associated with gall stones are included unless there is evidence of biliary tract obstruction (I would assume so)? Are patients with external biliary tract obstruction eligible for inclusion? Are patients with recurrent acute pancreatitis eligible for inclusion?
Response: Thank you for this valuable feedback. Accordingly, we have clarified the exclusion criteria.
Location: Methods, Exclusion criteria (Page 7, Paragraph 5)

The method of randomization is described as using a randomization sequence based on block-randomization. The allocation concealment was not clear to me. The text states that ‘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’. Does this mean that patients will be entered into the database by the investigator and after this is done the database will assign a randomisation number? What is the block size and what is done to avoid that this can cause a break in the allocation of patients (if the investigator knows that, e.g., the size is five, then it is possible to deduce the allocation of the last patients in the block? I am surprised that there is no stratification for a etiology - only for centre?
Response: Thank you for this insightful feedback. Accordingly, we have clarified the randomization method.
The paragraph concerning duration and follow up does not explain why patients are followed at different intervals. Safety is very important so all patients should receive the same assessments during follow up. The text states that follow up visits could be planned between 1 and 3 months after the initial treatment for the experimental groups and three months for the control group (in-patient group). This can introduce bias which can be avoided by making sure that follow up is the same for all groups, e.g., by ensuring that all patients are followed according to table 3.

Response: Thank you for this suggestion. We have improved the wording of this point and corrected the Table 1 for greater clarity. The only difference in the three groups is the place of treatment, the follow-up is the same for all patients.

Location: Methods, Duration (Page 8, Paragraph 3 and Page 9, Table 1)

## VERSION 2 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Dupont, Benoit</th>
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<td>REVIEW RETURNED</td>
<td>17-Apr-2023</td>
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| GENERAL COMMENTS          | The authors responded to requests made after the first reviewing. In my opinion, the article can be published. |

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Gluud, Lise</th>
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<td>24-Apr-2023</td>
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</table>

| GENERAL COMMENTS          | Thank you for the opportunity to read this clinically highly relevant protocol. I only have one minor comment, which you may consider: The inclusion criteria are listed in the protocol as (SIRS, BISAP) and in the appendix as BUN on admission >23 mg/dl, BUN increase at 24 h >1.87 mg/dl, SIRS ≥ 2 criteria, BISAP ≥2 score, organ failure. The BISAP also includes SIRS and a different value for BUN (>23 mg/dl). I would suggest writing the specific list of items that will be used to avoid any confusion. I assume that a list will be generated for the CRF and the criteria will include the specific items that will be assessed and these may be included to ensure that any subsequent readers will now how patients were selected. |

Location: Methods, Randomization (Page 8, Paragraph 2)