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ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Pancreatic Quantitative Sensory Testing to Predict Treatment Response of Endoscopic Therapy or Surgery for Painful Chronic Pancreatitis with Pancreatic Duct Obstruction: Study Protocol for an Observational Clinical Trial</th>
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</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Phillips, Anna; Afghani, Elham; Akshintala, Venkata; Benos, Panayiotis; Das, Rohit; Drewes, Asbjørn; Easler, Jeffrey; Faghih, Mahya; Gabbert, Charles; Halappa, Vivek; Khashab, Mouen; Olesen, Søren; Saloman, Jami L.; Sholosh, Biatta; Slivka, Adam; Wang, Tianxiu; Yadav, D; Singh, Vikesh</td>
</tr>
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VERSION 1 – REVIEW

| REVIEWER                         | Strum, Williamson B  
|                                  | Scripps Health, Medicine |
| REVIEW RETURNED                  | 19-Nov-2023       |

| GENERAL COMMENTS                                                                 | 1. The age appears open-ended from age 18 and upward. Since a comparison of a 20 yo with no comorbidities may not compare well to a 55 yo with co-morbidities, a consideration of an upper age limit may be useful.  
|                                                                                  | 2. There is no apparent classification of cause for the pancreatic disease. Again, this may be problematic for comparing response of a 20 yo with genetic mutations to a 45 yo with alcoholic pancreatitis.  
|                                                                                  | 3. The protocol does not appear to address whether or not a subject is avoiding continued use of provocative agents such as alcohol, smoking, marijuana, etc.  
|                                                                                  | 4. Although not stated, it is assumed that the evaluators of the P-QST and the persons performing the therapies are of equal experience and capability in doing so; this may be helpful to be stated if true. |

| REVIEWER                         | Udd, Marianne  
|                                  | University of Helsinki and Helsinki University Hospital |
| REVIEW RETURNED                  | 13-Dec-2023       |

| GENERAL COMMENTS                                                                 | Important study, well designed minor comments: what is definition of technical success of endoscopic therapy/surgery, or clinical success of endotherapy/surgery  
|                                                                                  | Is treatment modalities standardised in this multicenter study, stenting time, diameter of the stents placed, stent exchange protocol, invasive procedures has risk of complication, how complications might affect on the treatment result and how are they handled in the analysis? |
some flow chart of study protocol would be informative
author contributions: AEP is probably Anna Phillips, the middle
name letter should be also in the author list or remove from this
author contribution paragraph.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Williamson B Strum, Scripps Health
Comments to the Author:
1. The age appears open-ended from age 18 and upward. Since a comparison of a 20
yo with no comorbidities may not compare well to a 55 yo with co-morbidities, a
consideration of an upper age limit may be useful.
Response:
Response: We thank the reviewer for this insightful comment. An upper age limit is not included
in an effort to allow these data to be as generalizable as possible to the population of interest.
This point is well taken, however, and age, etiology, and comorbidities will be included as
covariates in the analysis of our data. Furthermore, we highlight again that the unifying factor
for all participants included in the study is obstruction of the main pancreatic duct which is the
target for therapy regardless of age or etiology.
2. There is no apparent classification of cause for the pancreatic disease. Again,
this may be problematic for comparing response of a 20 yo with genetic
mutations to a 45 yo with alcoholic pancreatitis.
Response: We thank the reviewer for raising this concern. Although included within ‘CP
characteristics’ in our protocol, this has now been explicitly named in order to clarify the point
for readers.
3. The protocol does not appear to address whether or not a subject is avoiding
continued use of provocative agents such as alcohol, smoking, marijuana, etc.
Response: We also thank the reviewer for raising this point. While these details were included
within the phrase ‘risk factors’ in the prior version of the manuscript, this has now been
explicitly stated to clarify for readers.
4. Although not stated, it is assumed that the evaluators of the P-QST and the
persons performing the therapies are of equal experience and capability in doing
so; this may be helpful to be stated if true.
Response: We thank the reviewer for this point. In addition to the statements regarding testing
standards for P-QST evaluators, we have also included the statement that minimum standards
will be met for P-QST testing prior to inclusion of data from any tester into the study. While
experience levels of endoscopic and surgical operators vary among individuals, all individuals
performing therapies are qualified to do so, and the therapies being administered are standard
among these experts. We have included our definitions of technical success of each intervention
in the manuscript and will be tracking this throughout the study.

Reviewer: 2
Dr. Marianne Udd, University of Helsinki and Helsinki University Hospital
Comments to the Author:
Important study, well designed
minor comments: what is definition of technical success of endoscopic
therapy/surgery, or clinical success of endotherapy/surgery
Response: We thank the reviewer for this comment. We have now included the definitions of
technical success of endoscopic and surgical therapy in this revision to clarify for the audience.
Because there is no standard definition of clinical success of endotherapy or surgery (i.e., a universally accepted percentage of reduction in pain) and prior studies have used varying definitions, we have powered this study to detect even the smallest possible change (a one-point change) in numeric rating scale, using the follow-up pain score with covariate adjustment for baseline pain score. This will also allow us to additionally detect larger (and likely more meaningful) changes in pain score for these participants accordingly.

Is treatment modalities standardised in this multicenter study, stenting time, diameter of the stents placed, stent exchange protocol, invasive procedures has risk of complication, how complications might affect on the treatment result and how are they handled in the analysis?

Response: We thank the reviewer for this comment as well. Because this is an observational study designed to look at the predictive value of P-QST for outcome to invasive therapy, the clinical interventions for these participants are determined by their pancreatology providers and not prescribed by the study protocol. We are, however, tracking in detail the technical details of each initial and subsequent intervention including the length and diameter of stents placed, the tools used for lithotripsy or stone removal, the success rate of intervention (see above) and adverse events or complications. Each of these will be incorporated into analyses of the study outcomes once all data is collected.

Some flow chart of study protocol would be informative.

Response: We thank the reviewer for this feedback: A simple study flowsheet has now been submitted as a Figure 2.

Author contributions: AEP is probably Anna Phillips, the middle name letter should be also in the author list or remove from this author contribution paragraph.

Response: We thank the reviewer for noting this: The middle name letter has now been included in the author list in Scholar One.

**VERSION 2 – REVIEW**

**REVIEWER**
Strum, Williamson B  
Scripps Health, Medicine

**REVIEW RETURNED**
20-Feb-2024

**GENERAL COMMENTS**

Second Review:

(I am responding to a review of a re-submission of this MS dated Feb 06, 2024. The MS has changes highlighted in red. Most of my original concerns were addressed, including the addition of etiology of CP, assessment of use of EtOH, smoking, marijuana, etc, and certification of examiners of P-QST. A modification of the broad age-range was not addressed, but perhaps that could be done in the analysis.

My remaining concern centers around the above-mentioned known Risk Factors and whether a trial period of cessation is planned before treatment, as well as a monitoring of same during the f/up. This is in recognition of evidence that cessation can be beneficial in reducing pain by itself and this would be of further help in assuring that abstinence is maintained after treatment. This takes into account that a patient who cannot control these addictions is less likely to have a favorable outcome.)