**Response to review on manuscript “The Abdominal Pain Unit (APU). Study protocol of a standardized and structured care pathway for patients with atraumatic abdominal pain in the emergency department: A stepped wedged cluster randomized controlled trial.” (PONE-D-21-28548)**

We would like to thank the reviewer for his/her thorough review of our manuscript and the constructive, relevant remarks and suggestions. In the following, we will try to explain how we solved remarks indicated by the reviewer. The remarks of the reviewer are depicted first, followed by our responses in italics.

**Reviewer's comments:**

**Reviewer #1:**

The fear of creating a standardized protocol for the emergency department may lead to less clinical judgement and more reliance on following a standardized practice that does not individualize the patient. It would be good to see a protocol that could help triage the severity of the diagnosis and how not to delay consultant involvement.

 *We thank the reviewer for his/her critical thoughts on the tested standardized APU-process and we agree that a standardized treatment process may have its benefits and limitations. The reviewer fears that a standardized treatment process, such as the APU-process could potentially lead to less clinical judgement and more reliance on the process. We argue that treatment guidelines or standardized processes do not lead to potential delay in consultation and/or treatment. Other standardized treatment processes, such as the chest pain unit (1, 2), show very promising indications that such processes can improve processes and patient-centered outcomes are also standardized processes within the clinical setting. Moreover, physicians follow clinical guidelines for certain diagnoses, which differ between hospital(s wards). Also, as mentioned in the manuscript on page 4 & 5, line 89 ff.: “[…] no standardized care pathway for patients with atraumatic abdominal pain exists, why finding a diagnosis for those patients depends on […] each physician’s qualifications and experience (3).” As described in our manuscript (page 5, line 96 f.), the APU-process was developed by a multidisciplinary team of experts in a Delphi process (4) and therefore, seems very promising in increasing patient safety, patient satisfaction with the care provided and subsequently reducing mortality.*

*It is important to note that there are no mandatory automatisms in the APU treatment process. The goal of the APU-process is to give guidance to physicians in a very complex field of emergency medicine. All final decisions in the treatment of atraumatic abdominal pain – even within the APU-process - are made by the physician. The APU-app guides-process can be seen as a checklist, which only supports physicians to not miss crucial aspects in treatment and diagnosis while being focused on clinical judgement.*

Severe pancreatitis was referenced in the paper, and it can be a very deadly disease. To diagnosis the diseases you need two of the following 1) Typical pain presentation 2) Elevated lipase greater than 3 times the upper limit of normal 3) imaging (CT or US) finding of pancreatic inflammation. Epigastric pain that radiates to the back may present in these patients, but is also found in ruptured aortic aneurysms (which is acutely more lethal). Would this protocol recognize this difference in severity? Early recognition of a diagnosis and resuscitation is what reduces mortality. This is done initially with a thorough history and physical. Imaging and labs only confirm diagnosis and should not be the leading factor in initial management of critical patients.

*We thank the reviewer for the attentive question whether the APU treatment process, may recognize the difference in severity, as for instance, between a ruptured aortic aneurism and a pancreatic inflammation. The APU treatment process is specifically designed to not miss crucial, time-critical diagnoses. This is ensured by various checks within the treatment process. The first step in the APU-process ensures that the attending physician recognizes signs of clinical instability, shock or sepsis based on vital parameters (like blood pressure, vigilance, heart rate) and clinical appearance. At the beginning of the APU-process, every patient receives an ECG to warrant that no ST-Elevation myocardial infarction is overlooked, which may present as upper abdominal pain. In a next and second step of the APU-process, a thorough history and physical examination, as well as pain management and abdominal lab will be executed. Then, as a result of the second step, a clinical evaluation of the patient’s condition will be done and again vital parameters will be checked. These steps have been designed to ensure that crucial diagnoses will be recognized as early as possible. As essential part of the APU-process, at many time points, physicians are reminded to watch out for “red flags” to guarantee, that they do not miss time-critical diagnoses, such as ruptured abdominal aortic aneurysm, incarcerated hernia, testicular torsion, hollow organ perforation, ileus, mesenteric ischemia, splenic rupture and myocardial infarction.*

*Opposed to the reviewer’s remark that imaging and labs might be leading factors in the initial management of critical patients, in the APU-process these two tools are only used to confirm or reject certain diagnoses.*

**Reviewer #2**:

The authors have embarked on a worthwhile albeit difficult journey. i am concerned that time in the ED is the primary endpoint. Time in the ed is dependent on so many variables, often not related directly to improved patient care or outcome. i would suggest the authors focus on a more patient centred outcome that is indicative of improved care, rather than a process measure.

*We thank the reviewer for this careful observation about potential concerns regarding the measurement and interpretation of the parameter time in the ED (i.e. we defined this parameter as “duration of treatment in the ED”). We agree with the reviewer that the parameter “duration of treatment in the ED” depends on various parameters, such as the triage level, chief complaint, and mode of arrival (5), and might therefore only partially illustrate improved care. However, a shortened duration of treatment can directly benefit patients regarding shorter waiting times for diagnostics and treatments. This is, because medical personal might be readily available and not engaged with other patients.*

*However, as suggested by the reviewer, we also do focus on patient-centered outcomes (see page 5, line 98 ff.), to have a primary, aggregated aim of our study (consisting of three hypotheses):*

*“1) Leading to a shorter duration of treatment in the ED while improving patient-reported outcomes (assessed as acute pain score or/and patient satisfaction) at discharge from the ED; or*

*2) Improving patient-reported outcomes (assessed as acute pain score or/and patient satisfaction) at discharge from the ED while measuring a constant duration of treatment in the ED; or*

*3) Leading to a shorter duration of treatment in the ED and unchanged patient-reported outcomes (assessed as acute pain score and patient satisfaction) at discharge from the ED.”*

*Thus, we can highlight that we also measure patient-centered outcomes as main/primary endpoints. Namely: Patient-reported outcomes: patient satisfaction and acute pain score.*

*Moreover, it is to be mentioned that by combining three different outcomes, it is possible that lower assesses pain score and higher patient satisfaction alone can be interpreted as an improvement of patient’s care, while the duration of treatment in the ED stays constant.*

Additionally there is little mention of how pain will be measured and controlled. Please describe

*With regards to the reviewer’s remark on the measurement of pain, we have now added a description of the measurement of pain with the NRS below Table 1 (page 8, line165 ff.): “*NRS = Numeric rating scale; subjective measure for rating the pain on an eleven-point numeric scale from 0 (no pain at all) to 10 (worst imaginable pain).”

**References**

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2. Keller T, Post F, Tzikas S, Schneider A, Arnolds S, Scheiba O, et al. Improved outcome in acute coronary syndrome by establishing a chest pain unit. Clin Res Cardiol. 2010;99(3):149-55.

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