## PEER REVIEW HISTORY

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## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | The SmartPill® as an objective parameter for determination of severity and duration of postoperative ileus – study protocol of a prospective, two-arm open-label trial (the PIDuSA-study) |
| **AUTHORS** | Vilz, Tim; Pantelis, Dimitrios; Lingohr, Philipp; Fimmers, Rolf; Esmann, Anke; Randau, Thomas; Kalff, Jörg; Coenen, Martin; Wehner, Sven |

## VERSION 1 - REVIEW

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| **REVIEWER** | Ian Bissett<br>University of Auckland<br>Auckland NZ<br><br>My only competing interests relate to the fact that we have a research group investigating prolonged postoperative ileus also. |
| **REVIEW RETURNED** | 11-Jan-2016 |

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| **GENERAL COMMENTS** | This study is seeking to answer an important question. I consider the approach novel and potentially offering important insights into post operative ileus.<br><br>There are several areas in which the methods could be improved to offer a better chance of success.<br>1. The objective is to assess the safety of the Smart pill but exactly how this will be measured is not clear and the independence of the person assessing safety is not outlined.<br>2. There is no attempt to provide any power calculation for the study and the patient numbers in each group are arbitrary. The likely occurrence of prolonged postoperative ileus is 20-25% in open surgery and lower in laparoscopic surgery. To show a difference between a control group of 10 and an experimental group of 50 with only 10 actually likely to have a PPOI may be unrealistic.<br>3. It would be appropriate to have a clear protocol for the treatment of all the patients and I would suggest that there is less variation in surgical procedures. Only including those with a colonic resection may be the best way to do this.<br>4. The time and method of introduction of the smart pill needs to be consistent across both groups and in all patients. It would seem to me that the smart pill should be introduced orally in the immediate postoperative period in all patients to ensure as much uniformity as possible.<br>5. There needs to be more detail as to how a prolonged postoperative Ileus is going to be defined clinically. I would recommend the consensus paper by Ryash Vather (VATHER R, TRIVEDI S, BISSETT I. Defining Postoperative Ileus: Results of a Systematic Review and Global Survey. Journal of Gastrointestinal Surgery. 2013;17(5):962-72.) |

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| | 6. There is no indication as to whether there is any involvement of the manufacturer of the Smart pill in the trial either as a sponsor or in any other way.<br>7. the use of different prokinetic and antiemetic medication is at the discretion of the clinician but this needs to be protocolised so that there might possibly be enough patients to demonstrate a difference between medications. |

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| **REVIEWER** | David I Soybel<br>Penn State Hershey College of Medicine, Hershey, PA |
| **REVIEW RETURNED** | 18-Jan-2016 |

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| **GENERAL COMMENTS** | The utility of reporting a trial design prior to publication is based on concerns that trials with negative results will not find a home in publication, resulting in reader and policy biases favoring trials that have positive results. An additional concern is other investigators will design and execute such trials, resulting in inappropriate use of resources and exposing experimental subjects to needless risks. This latter concern is addressed by registration of the trial per se: to be effective, there should be requirements by institutional review boards that investigators proposing any trial first check to see if others are underway that will address the same question and, if so, to show how the proposed design improves on trials underway. I mention these components of the rationale for publishing a trial proposal, in order to ask the authors to more explicitly discuss how publication of this proposal will contribute value to the research community and be of interest to the readership-- before any results are known?<br><br>An additional concern is that the study group is quite heterogeneous. It could include people undergoing all kinds of operations, with anastomoses in the colon, small intestine and upper GI tract, or a major abdominal wall reconstruction. Moreover, it may include-- at the discretion of the authors-- patients undergoing laparoscopic procedures. Implicit in the broad inclusion criteria is an assumption that the patterns of resolution and recovery will be similar in all patients. This assumption, which is really an hypothesis, should be tested in a patient cohort that is more homogeneous-- for example patients undergoing standard right or left colectomies, or patients undergoing open ventral hernia repair with >1 hr lysis of adhesions. Otherwise the diversity of procedures and manipulations may well obscure the correlations the authors are hoping to obtain.<br><br>A third consideration is that while gradients in pH may serve, under baseline conditions, to distinguish passage of the smartpill into different segments, it may be imagined that these boundaries in pH may be blurred in the presence of antibiotic therapy and the presence of ileus itself. Both conditions could alter the pH generated in the colon, where acidity depends on bacterial transformation of organic substrates, and may alter pH in the small bowel where there may be susceptibility to bacterial overgrowth until peristalsis is restored. At the very least the authors should be considering a means of independent verification of the location of the pill as it travels down the alimentary tract.<br><br>The ability to mathematically manage the periodic waveforms of intraluminal pressure and even pH should not be underestimated. The authors have not provided much detail about their methods for |

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| | managing the data and the statistical methods that may be required when they find a lot of noise and try to understand and quantify the periodicity underneath. |

## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Ian Bissett

1. The objective is to assess the safety of the Smart pill but exactly how this will be measured is not clear and the independence of the person assessing safety is not outlined.

As pointed out correctly the primary objective of the study is the evaluation of the safety of the SmartPill which is based on the occurrence of adverse device effects and severe adverse device effects. Therefore patients will be visited and examined twice a day for adverse events (AEs) during the postoperative course. An independent monitor of the clinical study core unit will verify the proper conduct and assessments of the study procedures and particularly the documentation of AEs (added on page 6 of the manuscript)
Occurring serious AEs (SAEs) will additionally be evaluated with regard to a causal relationship with the SmartPill ("serious adverse device effect", SADE) by an independent and specially trained vigilance officer now described in more detail in a passage added to the discussion (added on page 8).

2. There is no attempt to provide any power calculation for the study and the patient numbers in each group are arbitrary. The likely occurrence of prolonged postoperative ileus is 20-25% in open surgery and lower in laparoscopic surgery. To show a difference between a control group of 10 and an experimental group of 55 with only 10 actually likely to have a PPOI may be unrealistic.

Dr. Bissett mentioned an important point demonstrating his expertise in POI research. We would like to comment on his annotations.
There are only a few trials investigating the SmartPill in patients with severe medical conditions, the patient numbers are very limited lying round about 10 patients (10 patients with decompensated liver cirrhosis[1], 10 patients with cystic fibrosis[2], 8 patients after severe trauma[3]). Therefore there are only limited experiences for using the SmartPill in patients with severe medical conditions all trials have a "proof of concept" character. Thus, the PIDuSA trial including 65 patients is by far the largest study investigating the opportunities and limitations of the SmartPill in people with serious illness. Nevertheless we tried to perform a power calculation before starting the trial, a statistician (Dr. R. Fimmers) calculated the patient number. But as we do not only want to investigate patients with prolonged POI (pPOI) the sample size is not based on the incidence of pPOI. The primary aim of the study is to evaluate the general safety in patients undergoing abdominal surgery. Therefore we do not depend on the occurrence of POI or pPOI. The sample size for the experimental group was based on the assumption that an event with a probability of occurrence of 3% could be seen with a certainty of 80% for at least once in the sample. The use of the SmartPill in patients after extraabdominal surgery is already approved by the marketing authorization, so that there is no need to investigate safety issues for the control group.
A secondary objective of the PIDuSA trial is to demonstrate, that the SmartPill is able to detect decelerated transit times or reduced peristaltic activity after abdominal surgery (as it has been shown for several other indications like liver cirrhosis[1], cystic fibrosis[2] or major trauma[3]). The aim of the trial is to establish an objective, reliable patient and investigator independent method for the determination of the severity of postoperative bowel motility disorders (including, but not exclusively its most severe form, the pPOI). Summarized, we want to analyse whether the SmartPill is able to

distinguish between the slightly reduced bowel function in the control group (due to opioids and narcotics), a significantly reduced bowel function after a laparotomy (due to opioids and intestinal manipulation) and a severe motility disorder with symptoms of POI/pPOI like abdominal distension, long lasting nausea and a lack of defecation.
By demonstrating a correlation between reduced bowel function (lack of peristaltic activity, decelerated transit times) and severity of POI symptoms we hope to introduce a new read-out parameter in order to abandon “soft” parameters like nausea, vomiting, abdominal distension etc.
We take the comments of the reviewer seriously and added some explanations for our study design in the discussion part of the manuscript (page 11 of the manuscript).

3. It would be appropriate to have a clear protocol for the treatment of all the patients and I would suggest that there is less variation in surgical procedures. Only including those with a colonic resection may be the best way to do this.

As the primary objective of the PIDuSA trial is the assessment of the general safety of the SmartPill in patients following abdominal surgery (for which it is not approved for marketing authorization), we consciously decided to include patients undergoing heterogeneous surgical procedures and not only patients after colorectal surgery. The study population should reflect the patients of the daily clinical routine and allow the study results to be transferred to a wider range of surgical procedures for possible future trials in patients after abdominal surgery.
Furthermore we want to analyse - as a proof of principle - whether the SmartPill is suitable to detect changes in bowel motility and peristaltic activity not only after colorectal surgery but also after surgical procedures for example in the upper gastrointestinal tract or after pancreatic surgery. Therefore, including only patients undergoing colonic resection may rather be detrimental than beneficial for our intention.

4. The time and method of introduction of the smart pill needs to be consistent across both groups and in all patients. It would seem to me that the smart pill should be introduced orally in the immediate postoperative period in all patients to ensure as much uniformity as possible.

The reviewer mentioned a crucial point. We decided not to let the patients swallow the SmartPill because of occasionally occurrence of nausea and vomiting after surgery (PONV), to avoid an increased risk of aspiration and to minimize stress for the subject. Furthermore some patients remain in deep sedation for 24 hours or longer not being able to swallow the capsule on their own.
To standardize capsule application we use two standardized methods: The SmartPill will be directly placed in the stomach at the end of the operation if a gastrotomy is performed during the operation (for example during esophagectomy or pancreas head resection with pancreatogastrostomy). In all other patients the SmartPill will also be inserted at the end of the operation using a delivery device for video capsules or wireless motility capsules. We added a brief explanation of the procedure to the manuscript (page 8).

5. There needs to be more detail as to how a prolonged postoperative Ileus is going to be defined clinically. I would recommend the consensus paper by Ryash Vather (VATHER R, TRIVEDI S, BISSETT I. Defining Postoperative Ileus: Results of a Systematic Review and Global Survey. Journal of Gastrointestinal Surgery. 2013;17(5):962-72.)

In principle, the reviewer´s comment is an important and a good remark. However, as described in point 2, the trial is not exclusively focusing on the analysis of pPOI. Instead we want to demonstrate, whether the SmartPill is able to act as a reliable parameter for the severity of bowel motility disorders

after abdominal surgery. Nevertheless, the clinical symptoms mentioned in the consensus paper of Vather et al are gathered during rounds and collected in our case report forms. During final data analysis we will turn our attention on this important issue. Therefore we added the paper by Vather et al to the citation list in the revised manuscript.

6. There is no indication as to whether there is any involvement of the manufacturer of the Smart pill in the trial either as a sponsor or in any other way.

All SmartPills were purchased according to the regular procedure of the university hospital. We did not receive any monetary or non-cash benefits from the manufacturer, the whole trial is financed by third party funds. Therefore the PIDuSA trial is not influenced by the manufacturer. We added this to the revised manuscript (page 14).

7. The use of different prokinetic and antiemetic medication is at the discretion of the clinician but this needs to be protocolised so that there might possibly be enough patients to demonstrate a difference between medications.

The time point of application of prokinetic medication as well as laxatives or standardized mobilization will be exactly recorded by the study personnel. Furthermore, the event button of the data receiver will be pressed at the beginning and at the end of the application of prokinetics or mobilization by physiotherapists or study personnel highlighting the period of the recorded data (see Figure 2B for example) and allowing an easy and exact analysis of peristaltic patterns before and after an intervention. To our experience, most of the patients with postoperative motility disorders will receive prokinetics or laxatives for several times resulting in enough data to investigate the effect of prokinetics, laxatives or physiotherapy on postoperative bowel motility.
We clarified this in our manuscript (page 8 and 9).

Reviewer: 2
Reviewer Name: David I Soybel

1. The utility of reporting a trial design prior to publication is based on concerns that trials with negative results will not find a home in publication, resulting in reader and policy biases favoring trials that have positive results. An additional concern is other investigators will design and execute such trials, resulting in inappropriate use of resources and exposing experimental subjects to needless risks. This latter concern is addressed by registration of the trial per se: to be effective, there should be requirements by institutional review boards that investigators proposing any trial first check to see if others are underway that will address the same question and, if so, to show how the proposed design improves on trials underway. I mention these components of the rationale for publishing a trial proposal, in order to ask the authors to more explicitly discuss how publication of this proposal will contribute value to the research community and be of interest to the readership-- before any results are known?

Dr. Soybel mentioned a general problem when publishing study protocols. We cannot substantiate the remarks with reliable data, but we think that publishing protocols can give a time and organizational advantage. Furthermore, the expectations of the readership being interested in POI research can be increased and a better propagation of the trial can be achieved. We added a sentence at the end of the introduction why (to our opinion) the dissemination of study protocols has its rationale. In general, we agree with the statements of the reviewer that publication of trial protocols will prevent policy bias favouring trials with positive results and to save resources as well as protect participating subjects

from unnecessary risks. Therefore the dissemination of trial protocols will help to improve quality in clinical research.
However we also believe that the reported approach of using the SmartPill for investigation of motility disorders is of that particular methodological and scientific interest to justify the dissemination of the trial concept to the scientific community in the field of postoperative ileus in advance. As we gladly realize by the reviewer´s comments and their modification suggestions, we see our expectations confirmed that the publication of the protocol is able to initiate a fruitful discussion within the community about the approach leading to an improvement of the trial procedure or further trials in the future.

2. An additional concern is that the study group is quite heterogeneous. It could include people undergoing all kinds of operations, with anastomoses in the colon, small intestine and upper GI tract, or a major abdominal wall reconstruction. Moreover, it may include-- at the discretion of the authors-- patients undergoing laparoscopic procedures. Implicit in the broad inclusion criteria is an assumption that the patterns of resolution and recovery will be similar in all patients. This assumption, which is really an hypothesis, should be tested in a patient cohort that is more homogeneous-- for example patients undergoing standard right or left colectomies, or patients undergoing open ventral hernia repair with >1 hr lysis of adhesions. Otherwise the diversity of procedures and manipulations may well obscure the correlations the authors are hoping to obtain.

Concerning this comment we want to refer to our reply no. 3 to reviewer 1. Additionally we want to emphasize that the primary objective of the trial is the assessment of the safety of the SmartPill in patients following abdominal surgery independently of the performed operation. The correlation of the data recorded by the SmartPill with the clinical signs of postoperative gut activity is a secondary objective. We are well aware that we have to await the study results to see whether a correlation will be possible in this heterogeneous population. Otherwise additional studies in differentiated populations might be necessary.

3. A third consideration is that while gradients in pH may serve, under baseline conditions, to distinguish passage of the smartpill into different segments, it may be imagined that these boundaries in pH may be blurred in the presence of antibiotic therapy and the presence of ileus itself. Both conditions could alter the pH generated in the colon, where acidity depends on bacterial transformation of organic substrates, and may alter pH in the small bowel where there may be susceptibility to bacterial overgrowth until peristalsis is restored. At the very least the authors should be considering a means of independent verification of the location of the pill as it travels down the alimentary tract.

Dr. Soybel adressed an important issue that needs to be considered. Indeed, one (secondary) objective of the PIDuSA trial is to analyse whether the previous experiences with the SmartPill concerning the investigation of transit times and peristaltic activity can be transferred to the setting of postoperative patients and their special conditions.
However, we do not expect any major problems in analysing the gastric emptying time: As any medication influencing the gastric acid production is forbidden as mentioned in the study protocol (page 7 of the manuscript). The transfer of the SmartPill from the small bowel via the ileocecal junction into the colon could be challenging to detect due to bacterial overgrowth and pH value alteration as suspected by Dr. Soybel. However, we considered the experience from a previous clinical trial from Roland BC et al demonstrating that the SmartPill is suitable for analysing small bowel transit times even in patients with small bowel bacterial overgrowth.[4] Furthermore, we added the graph of a patient of our cohort after sigmoid resection showing the sudden increase of pH value after passage of the pylorus and the decrease of pH value after passing the ileocecal valve (figure

2C) maybe demonstrating the probable feasibility of the SmartPill in analysing transit times.

Unfortunately we do not have any feasible possibility of an independent verification of the SmartPill´s position:
- By plain X-ray it is nearly impossible to locate the SmartPill precisely as we just experienced in a participant. We are just able to distinguish between “capsule retention in the stomach”, “capsule is not in the stomach but still in situ” and “capsule has passed the body”.
In contrast we would be able to clearly detect the SmartPill during its passage through the gastrointestinal tract by using a CT scan. Unfortunately, both methods are associated with the use of radiation and it is not feasible to use frequent X-rays to locate the capsule due to ethical considerations.
- We tried to verify the localization of the capsule using ultrasound in the early postoperative course. Unfortunately, due to abdominal distension and gas filled intestinal loops we were not able to detect the SmartPill reliable.
In summary, we have no possibility for a localization of the SmartPill without using radioactive radiation resulting in a reduced participation in the trial if ethically justifiable at all.

4. The ability to mathematically manage the periodic waveforms of intraluminal pressure and even pH should not be underestimated. The authors have not provided much detail about their methods for managing the data and the statistical methods that may be required when they find a lot of noise and try to understand and quantify the periodicity underneath.

Previous experiences investigating the motility patterns detected by the SmartPill in patients on an intensive care ward after major trauma [3], patients with liver cirrhosis [1] and bacterial overgrowth[4] and other diseases revealed lower pressure values compared to healthy controls. None of the manuscripts report any background noise or problems in analysing the peristaltic activity. We assume that these experiences, especially the trial by Rauch et al using opioids for sedation (with their side effects of constipation) and the manuscript by Roland analysing intestinal bacterial overgrowth can be transferred to the patients undergoing surgery.
As we discussed in the manuscript, there is a lack of evidence for using prokinetics as a treatment of postoperative bowel motility disorders. Despite their severe side effects, the substances are still used to enhance recovery after abdominal surgery. As a secondary end point of the trial we want to investigate the effects of prokinetics on changes in peristaltic activity. Therefore start and end of prokinetic application is precisely recorded, the activation of the “event button” on the data receiver will highlight the period in the recorded data. To analyse the influence of prokinetics on peristalsis we compare absolute values, for example the highest pressure value, lowest pressure value, mean pressure value and the number of pressure patterns over a period of 30 minutes before application of prokinetics. The calculation of the values in the highlighted period is carried out automatically by the MotiliGI software programmed by the manufacturer and provided for SmartPill data analysis. These absolute values will be compared to the highest pressure, lowest pressure, mean pressure and number of peristaltic patterns 30 minutes after application of prokinetics. For statistical analysis of the values, a t-test against the standard deviation and a Wilcoxon signed-rank test will be used.
The aim of our study is to investigate a possible systematic shift of the abovementioned absolute values before and after application of prokinetics (for example increasing mean pressure values, increasing highest pressure values or increasing number of peristaltic patterns before and after application) and not any time-dependent changes after application of prokinetics.
The pH values are not considered when analysing possible changes in peristaltic activity after prokinetics or physiotherapy. A sudden increase in pH value for more than three units or sudden decrease for more than 1.5 units allows determining gastric emptying or passage of the ileocecal junction.
The periodic waveforms / migrating motor complex of the gut will not be analysed in our trial as the

SmartPill is (to our knowledge) not able to measure the curves.
We added a passage in the manuscript describing the analysis of the peristaltic activity in more detail (page 8, 9 and 10).

Literature

1. Chander RB, Garcia-Tsao G, Ciarleglio MM, Deng Y, Sheth A. Decompensated Cirrhotics Have Slower Intestinal Transit Times as Compared With Compensated Cirrhotics and Healthy Controls. JClinGastroenterol. 2013. doi:10.1097/MCG.0b013e31829006bb [doi].
2. Gelfond D, Ma C, Semler J, Borowitz D. Intestinal pH and Gastrointestinal Transit Profiles in Cystic Fibrosis Patients Measured by Wireless Motility Capsule. DigDisSci. 2012. doi:10.1007/s10620-012-2209-1 [doi].
3. Rauch S, Krueger K, Turan A, You J, Roewer N, Sessler DI. Use of wireless motility capsule to determine gastric emptying and small intestinal transit times in critically ill trauma patients. JCrit Care. 2012;27(5):534-.
4. Roland BC, Ciarleglio MM, Clarke JO, Semler JR, Tomakin E, Mullin GE et al. Small Intestinal Transit Time Is Delayed in Small Intestinal Bacterial Overgrowth. J Clin Gastroenterol. 2015;49(7):571-6. doi:10.1097/MCG.0000000000000257.

**VERSION 2 – REVIEW**

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| **REVIEWER** | David Soybel<br>Penn State Hershey College of Medicine |
| **REVIEW RETURNED** | 22-Feb-2016 |

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| **GENERAL COMMENTS** | The authors have responded to each of my concerns. |