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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)

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ABSTRACT

Introduction: Postoperative ileus (POI) is a frequent complication after abdominal surgery (AS). Until today, neither a prophylaxis nor an evidence-based therapy exists. This originates from the absence of objective parameters evaluating the severity and duration of POI resulting in clinical trials of modest quality. The SmartPill®, a capsule which frequently measures pH value, temperature and intraluminal pressure after swallowing, offers an elegant option for analysing gastrointestinal (GI) transit times and smooth muscle activity in vivo. As the use in patients in the first months after AS is not covered by the marketing authorisation, we aim to investigate the safety and feasibility of the SmartPill® immediately after surgery. Additionally, we analyse the influence of prokinetics and laxatives as well as standardised physiotherapy on postoperative bowel contractility, as scientific evidence of its effects is still lacking.

Methods and analysis: The PIDuSA study is a prospective, single-centre, two-arm, open-label trial. The SmartPill® will be applied to 55 patients undergoing AS having a high risk for POI and 10 patients undergoing extra-abdominal surgery rarely developing POI. The primary objective is the safety of the SmartPill® in patients after surgery on the basis of adverse device effects/serious adverse device effects (ADE/SADE). The sample size suggests that events with a probability of 3% could be seen with a certainty of 80% for at least once in the sample. Secondary objective is the analysis of postoperative intestinal activity in the GI tract in both groups. Furthermore, clinical signs of bowel motility disorders will be correlated to the data measured by the SmartPill® to evaluate its significance as an objective parameter for assessing POI severity. Additionally, effects of prokinetics, laxatives and physiotherapy on postoperative peristaltic activity recorded by the SmartPill® will be analysed.

Ethics and dissemination: The protocol was approved by the federal authority (94.1.05-5660-8976) and the local ethics committee (092/14-MPG). Findings will be disseminated through publications and conference presentations.

Trial registration number: NCT02329912; Pre-results.

Strengths and limitations of this study

- This is the first clinical study investigating development, severity and resolution of postoperative paralytic bowel disorders in different parts of the gastrointestinal (GI) tract in vivo using real-time monitoring for bedside analysis and data recording for later analysis.
- Postoperative ileus (POI) is currently estimated with imprecise and inconsistently used clinical parameters. This study could lead to the establishment of the SmartPill® as a tool providing reproducible and objective parameters for the quantification of bowel paralysis in future clinical trials investigating the development of paralytic bowel disorders of different aetiology (POI, septic ileus, etc) as well as their prophylaxis or therapy.
- Despite lack of evidence and well-known side effects of prokinetic drugs and laxatives, both are routinely used for treatment of POI. In case of use of prokinetic medications, recorded parameters in the postoperative time course will be analysed for any medication-associated alteration of the measured parameters. A failure to prove peristaltic enhancing effects would challenge the commonly used therapeutic concept.
- The SmartPill® can record data during its passage through GI tract consecutively, but it is not able to cover the whole GI tract simultaneously.

INTRODUCTION

Surgical interventions, particularly visceral surgery,[1] cardiovascular surgery[2] and spine surgery,[3] often lead to postoperative paralytic

bowel disorder, also referred to as postoperative ileus (POI). POI is characterised by delayed gastric emptying, nausea, vomiting, distension of the bowel resulting in pain and the absence of intestinal gas and stool passage.[1] These complications result in increased gastro-oesophageal reflux with the risk of aspiration pneumonia, stasis of the intestinal content with bacterial overgrowth, disrupted mucosal barrier and the threat of bacterial translocation , potentially leading to sepsis and distant organ failure. After colorectal surgery, POI has an incidence of up to 40% and plays a key role in the reconvalescence after surgical interventions.[4] Prolonged hospitalisation leads to a high economic burden with costs exceeding US$1 billion per year in the USA.[5]

Until today, with the exception of epidural anaesthesia, neither a prophylaxis nor an evidence-based therapy approach for POI exists.[6] Furthermore, it is largely unknown which components of the current multimodal therapeutic concept have an influence on the peristaltic activity of the bowel. For example, prokinetics such as erythromycin, metoclopramide or Prostigmine are widely used to achieve recovery of peristalsis during POI. However, according to a Cochrane meta-analysis, evidence for the broad use of substances promoting gastrointestinal (GI) motility after surgery is still missing.[7] An essential reason for this lack of evidence is seen in the absence of available objective parameters or biomarkers for estimation of the severity and the duration of POI. Although objective parameters are necessary for clinical trials of high quality providing powerful evidence, patient-dependent and investigator-dependent criteria prevailed in clinical trials investigating POI so far.[7–9] A variety of those soft criteria used in clinical trials result in inconsistent data and significance as shown by several meta-analyses.[7–9] For instance, some trials defined 'first postoperative defecation' or 'first postoperative flatus' as the end point of POI, whereas other studies focused on 'tolerance of solid food', 'lack of abdominal distension' or a combination of all criteria.[4 8 10 11] However, it remains unclear whether those parameters indeed reflect resolution of POI and transition to regular peristalsis or whether first postoperative defecation is rather resulting from disposal of faecal residues or gas in the distal colon, which has been accumulated preoperatively.[8]

For the future progress in POI research, in particular the development and evaluation of prophylactic or therapeutic agents advancing from preclinical into clinical development,[12–15] the definition of reliable and objective patient-dependent and investigator-independent parameters for the quantification of bowel paralysis is a prerequisite.

Technical progress within the past decades led to the development of electronic capsules applicable for visualisation or physical and chemical monitoring of the complete GI tract. By measurement of intraluminal pH value, temperature and pressure, the so-called SmartPill® (figure 1) is able to indicate gastric emptying time (figure 2A, B, sudden pH increase), small bowel transit (figure 2B, C, slow pH increase followed by a decrease at the ileocaecal junction), large bowel transit (figure 2C, D, sudden decrease of temperature after excretion) and whole-gut transit.[16–19] Furthermore, the capsule is able to analyse intensity (minimum pressure, maximum pressure, mean) and frequency of peristaltic activity (contractions per minute, motility index) in every part of the GI tract (figure 2A–D).[19 20] Wireless data acquisition and storage within a transportable receiver (figure 3) allows continuous monitoring. By connecting the receiver to a notebook, data recorded by the SmartPill® can be immediately accessed, allowing a live and in vivo analysis too.

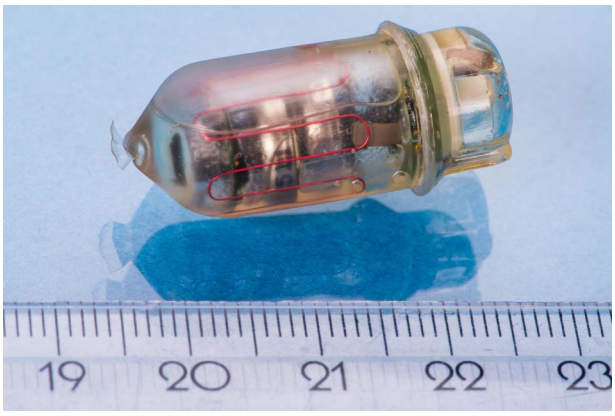

Figure 1 SmartPill®.

The SmartPill® is approved for marketing authorisation and is routinely used for patients with delayed gastric emptying (diabetic gastropathy), slow transit syndromes or undetermined constipation in the USA (FDA, 2006).[18 20] Furthermore, few trials with only a very limited number of patients have been accomplished in the past years, demonstrating significantly altered transit times in adult and paediatric patients with gastroparesis, liver cirrhosis, intestinal bacterial overgrowth, cystic fibrosis or traumatic brain injury (figure 4).[21–25] Together, the SmartPill® appears to be a promising tool for determination of POI in trials investigating therapeutic options for postoperative bowel disorders. However, its use is not intended in surgical patients, particularly in those who underwent visceral surgery in the last 3 months.

The primary aim of the present study is to investigate the safety of the SmartPill® in patients who have undergone abdominal surgery. Secondarily, we will analyse the suitability of the SmartPill® to be used as an objective and reproducible parameter for the analysis of postoperative motility disturbances in these patients. To this end, we will also estimate the effect of routinely used prokinetic substances, laxatives as well as physiotherapeutic intervention on the recorded parameters in the postoperative time course. We hypothesise that capsule recordings will identify reliable and precise parameters to describe the course of postoperative motility disturbances. This would add significant advantage and

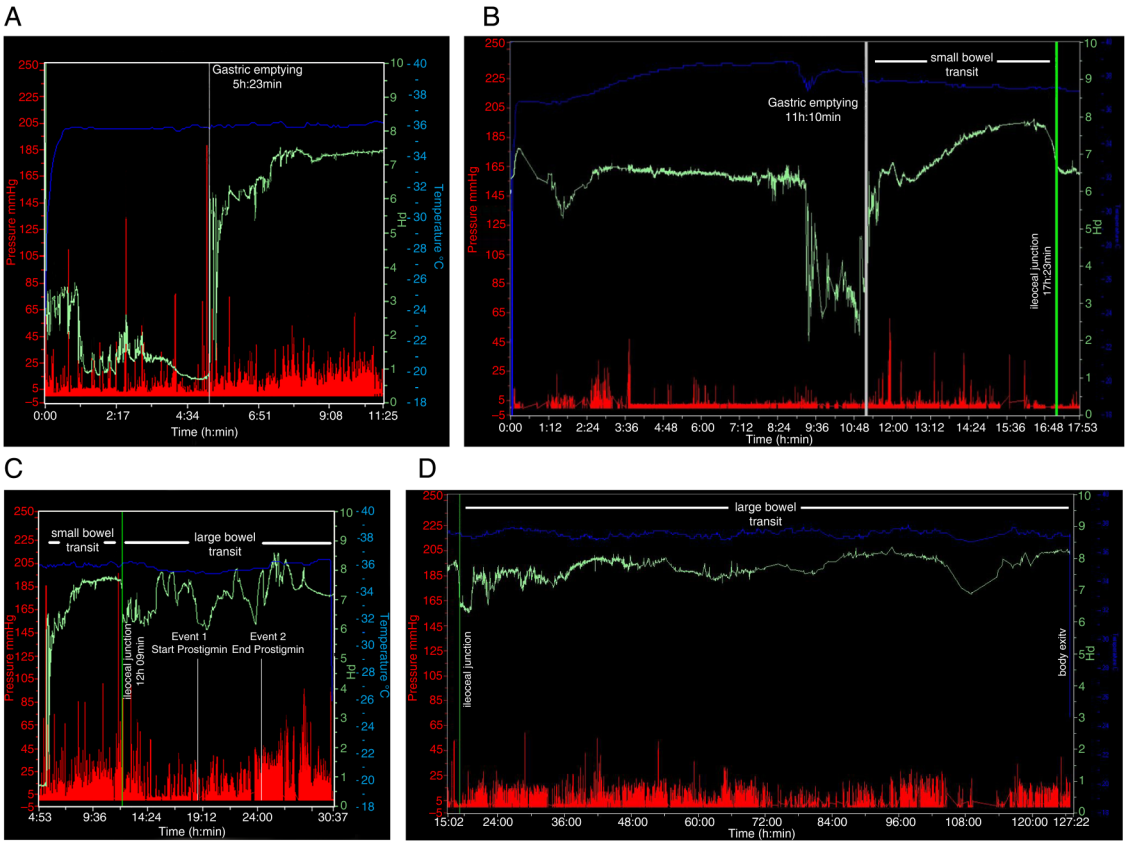

Figure 2 Analysis of gastrointestinal passage and peristaltic activity in a healthy man aged 37 years (A and C) and a woman aged 57 years after laparoscopic sigmoid resection demonstrating decelerated transit times (B and D). Gastric emptying time can be measured by a sudden increase in pH value (figure 2A, B). Small bowel passage is characterised by a slow pH increase followed by a sudden decrease at the ileocecal junction (figure 2B, C). Excretion of the SmartPill® is determined by a sudden temperature drop and a loss of capsule signals (figure 2C, D). Furthermore, peristaltic activity can be analysed using frequency, minimum and maximum pressure of peristalsis as well as the motility index calculated by MotiliGI software. Exemplary, a highlighted period was added in figure 2C after using the 'event button', allowing an easy analysis of bowel contractions during the marked period.

increased quality in future clinical trials, thereby filling a long existing gap of an objective parameter for the determination of POI.

Publication of the current protocol should raise academic surgeons' anticipation to the forthcoming results of this trial, expected to result in the definition of more reliable and objective parameters replacing the so-far unspecific and weak criteria used to determine length and severity of POI in clinical trial.

METHODS AND ANALYSIS

Sample size

The PIDuSA study is an exploratory single-centre, prospective, open-label, two-arm non-randomised trial including patients of the University Hospital in Bonn, Germany. The SmartPill® will be purchased according to the regular procedure of the University Hospital and applied to two different study groups: the experimental group consists of 55 patients undergoing abdominal surgery, thereby having an increased risk for developing POI of up to 40%;[4] and the control group includes 10 patients undergoing extra-abdominal vascular or pulmonary surgery, having nearly no risk for development of POI.

Data collection and management, monitoring, safety management

The Clinical Study Core Unit of the Study Center Bonn (CSSC) will perform the monitoring, safety management, data management and data analysis of the study. The team of the CSSC includes several physicians focusing on clinical trials and their performance, study nurses and biometricians who are independent of the sponsor and have no competing interests.

All data relating to study participants will be stored on a secured and encrypted server only accessed by the investigators. Patients will be assigned by alphanumeric sequential numbers that will be used to identify clinical data. On completion of the study, all participant-identifying information and other study data will be securely archived in accordance with the policy of the University Hospital of Bonn.

Figure 3 Data receiver with 'event button'.

Owing to the German legislation concerning medical devices, the PIDuSA trial will be audited by the district government at least for one time. The government reserves the right for further auditions depending on the occurrence of serious adverse event (SAE) or serious adverse device effects (SADEs).

Primary objective

The primary objective of this study is the evaluation of the safety of the SmartPill® in patients following surgical interventions on the basis of the rate of ADEs and SADEs that are documented during patient rounds twice a day.

Secondary objectives

Secondary objective is the analysis of the postoperative intestinal activity in different parts of the GI tract following abdominal surgery in comparison with vascular or pulmonary operations, respectively. Furthermore, we want to investigate the correlation between gastric emptying time, small bowel transit, colonic transit and whole-gut transit time following surgery in order to correlate the data with clinical signs of POI resolution (time to first flatus, first defecation, abdominal distension and solid food tolerance as suggested by Vather *et al*[11]). Additionally, we will analyse the effects of prokinetics (neostigmine, erythromycin, metoclopramide), laxatives (Epsom salt, bisacodyl, lactulose) and standardised physiotherapy on postoperative peristaltic activity.

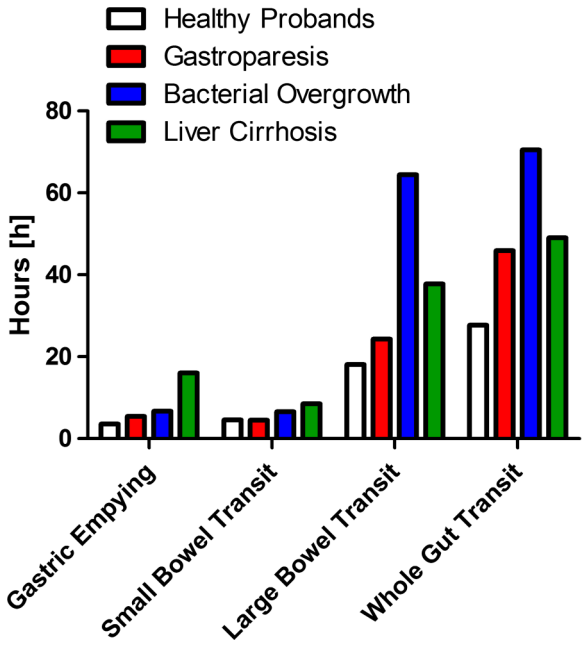

Figure 4 Decelerated gastrointestinal transit times in patients with gastroparesis,[25] intestinal bacterial overgrowth[22] or liver cirrhosis[21] compared with healthy probands.

Inclusion criteria

Two different cohorts will be studied: patients undergoing a visceral surgery (experimental group) and patients undergoing a pulmonary or extra-abdominal vascular operation (control group). Additional inclusion criteria applicable for all individuals in this study: age >18 years, capability and willingness to follow the study instructions and all required study visits (compliance), American Society of Anesthesiologists physical status I–III (ASA I–III), expected duration of the operation ≥90 min and <10 hours, confirmation of a regular course of the operation and the denial of a high-risk anastomosis in the GI tract by the operating surgeon. A negative serum pregnancy test must be obtained in female patients with childbearing potential, except patients after hysterectomy or the onset of menopause. All individuals need to have signed the informed consent form.

Exclusion criteria

Exclusion criteria have been formulated in agreement with the ethics committee. The *main* exclusion criteria comprise known allergy or hypersensitivity to one of the components of the medical device, pregnancy/lactation, conditions or diseases which do not fit with the study at the investigator's discretion, emergency interventions, condition after radiation therapy at the site of operation in the last 2 months, known dysphagia, non-steroidal anti-inflammatory drug (NSAID) enteropathy in the past, body mass index (BMI) >40, patients with active implantable devices, medication with proton pump inhibitors (PPIs), antacids or H2 blockers, reflux oesophagitis grade III and IV according to Savary and Miller, oesophagojejunostomies, fistulas of the oesophagus and/or stomach, which cannot be repaired during surgery, known or suspected stenoses or fistulas of the gastrointestinal tract, not being repaired by the intervention, active Crohn's disease (Crohn's Disease Activity Index (CDAI) >450), pronounced diverticulosis or diverticulitis not being resected during the operation, patients with several visceral surgical interventions with increased risk of anastomotic leakage (eg, required immunosuppression) and increased risk for capsule retention specified in the protocol in detail or any other conditions which suggest a hazardous anastomosis at the discretion of the investigator or the surgeon.

Intervention

All patients of the Department of Surgery of the University Hospital of Bonn that will need elective abdominal, thoracic or vascular surgery and fulfil inclusion and exclusion criteria will be informed about the trial and further screened for participation (table 1).

During or before the screening visit, each patient has to provide a written informed consent to the study and give their permission to publish the gathered data. The screening consists of reviewing inclusion and exclusion criteria, demographic variables, medical history, concomitant medication, physical examination and laboratory tests, including a pregnancy test obtained by a study nurse and the treating physician.

During general anaesthesia, the SmartPill® will only be applied to the patients in a standardised procedure after confirmation of a regular course of the operation by the surgeon and immediately before closure of the abdominal wall. If the surgical intervention includes a gastrotomy, the SmartPill® will be placed into the lumen directly via this approach. If the stomach is not opened during surgery, the SmartPill® will be applied using the AdvanCE capsule delivery device (purchased from US Endoscopy, Mentor, Ohio, USA) manufactured for capsule application. Subsequently, the capsule measures and transfers pH value, intraluminal pressure and temperature to a mobile receiver, continuously carried by the patient. Patients are allowed to eat and drink and can be mobilised at the treating physician's discretion. The application of prokinetics or laxatives shall be governed by the treating physician.

During the following days, patients will be visited twice a day until excretion of the SmartPill® with the faeces. Patients will undergo a physical examination (focusing on audible bowel sounds, abdominal distension and AEs or SAEs) and will be asked for the occurrence of nausea, vomiting or defecation. Any SAE, which will occur during the trial, will be evaluated by an independent and trained vigilance officer with regard to a possible relationship to the SmartPill®. If the vigilance officer suspects a link to the trial procedure (SADE), the German competent authorities will be informed to further evaluate the safety of the suspects with the opportunity to stop the recruitment immediately or to stop the PIDuSA trial.

Patients, study personnel and physiotherapists will be encouraged and trained, to pay special attention to exact documentation (time and duration) of prokinetics or laxatives administration or standardised physiotherapeutic intervention. In addition, immediately before and at the end of the application of prokinetics or laxatives as well as physiotherapy, the 'event button' on the data receiver will be pressed (figure 3). By pressing the event button, the relevant period of the recorded data will be highlighted in the graphs (figure 2C), allowing an exact analysis of pressure patterns over a time period before and after an intervention. For data analysis, the manufacturer provided the MotiliGI software developed to read out values

Table 1 Schematic timeline of the PIDuSA trial

Timeline of the PIDuSA trial	Screening	Surgery (day 0)	Visit 1 (day 1, a.m.)	Visit 2 (day 1, p.m.)	Visit 3 (day 2 a.m.)	Visit 4 (day 2 p.m.)	Visit et seq. (day a.m.)	Visit et seq. (day p.m.)	Final examination after SmartPill® excretion
Informed consent	X								
Inclusion/exclusion criteria	X	X							
Medical history, demographics, laboratory test	X								
Audible bowel sounds, abdominal distension	X		X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X
Application of SmartPill®		X							
SmartPill® excretion?			X	X	X	X	X	X	
AEs/SAEs		X	X	X	X	X	X	X	X
Nausea/vomiting, flatus and defecation?			X	X	X	X	X	X	
Documentation of physiotherapy and prokinetics/laxatives			<--------	--------	--------	--------	--------	--------	------->
Documentation of defecation and solid food tolerance (patient)			<--------	--------	--------	--------	--------	--------	------->

AEs, adverse events; SAEs, serious adverse events.

(maximum pressure, mean pressure, etc) easily and precisely in the highlighted period.

Furthermore, patients are advised to document the time point of first defecation and the tolerance of the first and the second meal after surgery without nausea or vomiting. These time points will be correlated with the data recorded by the SmartPill®. After excretion of the SmartPill®, observed by a sudden drop of recorded temperature to or below room temperature, the patient will be asked and examined for AEs and modifications of the concomitant medication during a final visit.

If a participant needs PPIs or H2 antagonists during the first days after SmartPill® application due to suspected gastritis or peptic ulcers, the gathered data will not be analysed because of possible pH alterations.

Outcomes and statistical analysis

Primary target variables of the study are the rates of AEs and SAEs associated with the administration of the SmartPill® in both study cohorts, and the difference between the two cohorts will be estimated by indication of 95% CIs.

Secondary target variables of the study are:

1. Analysis of bowel function (peristaltic activity) and transit times measured by the SmartPill® in the experimental group and the control group.
2. Correlation of clinical signs of a directed bowel movement after surgery (time until defecation and solid food tolerance) and the GI passage time measured by the SmartPill®. They will be described under specification of non-Spearman correlation coefficients and illustrated by scatter plots. The relationship will be analysed by regression models in detail.
3. The mean as well as highest and lowest pressure and the number of contractions/pressure patterns are continuously measured by the SmartPill® during its passage through the GI tract and can be easily read out by using the MotilityGI software programmed by the manufacturer for SmartPill® data analysis. Values will be analysed descriptively for both study groups and compared between the cohorts and between the period before and after application of prokinetics by using a t-test and a Wilcoxon signed-rank test. Subsequent analyses include examination of motility and pressure pattern (mean, highest and lowest pressure values as well as number of contractions) during and after application of prokinetics, laxatives or physiotherapy.

The PIDuSA trial is the first study investigating safety and tolerability of the SmartPill® in patients immediately after abdominal surgery. Nevertheless, the sample size (55 patients with visceral surgical interventions) suggests 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 of patients after abdominal surgery.

It is well known that opioids after surgery lead to delayed gastric emptying, constipation and reduced peristaltic activity. To exclusively investigate the influence of abdominal surgery (and not opioid consumption) on bowel motility, we investigate a cohort of 10 patients, as suggested by other trials investigating transit times and peristalsis in patients with medical conditions, acting as a control group.[21 23 24]

Participants withdrawing their informed consent after receiving the SmartPill® or malfunction of the medical device after application will be treated as dropouts, the corresponding data sets will not be considered for final analysis. An interim analysis is not planned in the PIDuSA trial.

Ethics and dissemination

The study will be conducted according to the principles of ICH-GCP (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice) and the Declaration of Helsinki in the Department of Surgery of the University Hospital of Bonn. All participants are insured by HDI-Gerling, Germany (insurance number 57 010323 03010); an allowance for trial participation is not paid. Any protocol modifications (changes to eligibility criteria, outcomes, etc) need to be approved by the relevant parties (ethics committee and BfArM) before they are implemented.

All participants will be informed by an investigator (physician) about the PIDuSA trial and have to provide a written informed consent before any study-specific procedure is carried out. Participants can withdraw from the study any time. Clinical care will be provided throughout the study according to standardised clinical routine. Study data will be managed confidentially and anonymously.

All investigators have unlimited access to the gathered data set without any contractual agreements. Findings from the study will be disseminated through publications in peer-reviewed journals as well as national and international conference presentations.

DISCUSSION

POI is a frequent complication after surgery, characterised by abdominal distension, nausea and vomiting, leading to the risk of aspiration and infectious complications.[1 26] Until today, neither a prophylaxis nor an evidence-based therapy approach exists. Owing to the absence of objective parameters, duration and importantly resolution of POI are currently estimated with imprecise and inconsistently used clinical parameters. This rather subjective evaluation of POI is further detrimentally affecting the quality and significance of clinical trials, resulting in inconsistent study results as shown by a recent meta-analysis.[7]

Intraluminal video monitoring, in addition to commonly used endoscopy, is used by gastroenterologist for >15 years with great success.[27] Ongoing technical progresses have led to the development of the SmartPill®, a capsule able to record intraluminal pressure, pH value

and temperature. By estimation of this set of parameters, clinicians are able to estimate GI transit disturbances live and in vivo.[18 19] We speculated that the SmartPill® could be a helpful and objective tool for estimation of duration, severity and resolution of POI in surgical patients. However, the use in recently operated patients is not covered by the marketing authorisation. In the present study, we would like to examine whether the SmartPill® can be used as an objective measure for the precise examination of GI transit and peristaltic activity of the postoperative GI tract.[19]

To investigate the primary and secondary aims of the PIDuSA trial, we chose a two-arm design. In our first arm, we include 55 patients after abdominal surgery to investigate the safety of the SmartPill® as the use is not covered by the marketing authorisation. Furthermore, we investigate its feasibility to detect various levels of decelerated transit times or reduced peristaltic activity after visceral surgery as already demonstrated for other diseases.[21 22 24] In our second arm, we include participants after thoracic or vascular surgery. As the use of the SmartPill® in patients after extra-abdominal surgery is approved by the marketing authorisation, there was no need for safety issues allowing a reduced sample size. However, as it is well known that opioids and narcotics lead to delayed gastric emptying, constipation and reduced peristaltic activity, we investigate a small cohort of patients after non-abdominal operations in order to compare data with the patients after visceral surgery to exclusively analyse the influence of abdominal surgery on bowel motility.

The main risk when using the SmartPill® is an intestinal retention of the capsule. Risk estimation in >10 000 patients noticed capsule retention in 0.33% of cases. Within all cases, a medical treatment using laxatives or endoscopy successfully resulted in capsule recovery. Until now, neither symptoms of ileus nor the necessity of surgical removal has been reported for the SmartPill®.[28–30]

Further data supporting the risk assessment can be taken from studies using wireless capsule endoscopy (WCE). Capsules used for WCE are comparable in size to the SmartPill® and are in clinical use since >15 years, having been administered >2 million times.[27 31] Comparable to the SmartPill® usage, the most common complication reported for WCE is capsule retention with a rate of up to 3% in large meta-analyses.[32] This higher rate of capsule retention in WCE, compared to the SmartPill®, can be explained rather by the chosen indication than by the higher numbers of capsule endoscopies, outnumbering the usage of the SmartPill® >200 times. Predominant indications for WCE are obscure GI bleeding due to neoplasia or diagnosis of suspected Crohn's disease and its response to modern medical treatment. Those indications have a higher risk for stenosis because of the underlying disease.[29] Therefore, in the present study, particular attention is paid during the operation to pre-existing intestinal stenosis or other obstructing processes in the GI tract. Consequently, the SmartPill® will not be applied if pre-existing adhesions or other pathological changes of the bowel, potentially increasing the risk of capsule retention, are discovered and are not expected to be addressed during surgery.

Another rare but hazardous postoperative complication could be an increased risk for bowel perforation or induction of anastomotic leakage by the SmartPill®. For WCE, only a few individual cases of bowel perforations are described in the literature, exclusively originating from a pre-existing stenosis of the intestine (Crohn's disease, adhesion, cancer).[28 33–35] Nevertheless, special attention has to be paid to surgery resulting in creation of intestinal anastomosis, exhibiting a bottleneck, potentially followed by SmartPill® retention, mechanical obstruction and rupture of the anastomosis. Of note, within >10 000 applications of the SmartPill®, no capsule retention with subsequent bowel perforation has been described so far.

According to a Cochrane analysis and other high-ranked reviews about POI pathophysiology and treatment, the poor quality of trials originates from the commonly used imprecise measures for POI duration, exclusively based on clinical examination.[7 8] Furthermore, those clinical parameters were randomly chosen to define POI resolution. For example, in the recent five trials published in renowned international journals, five different primary end points were chosen to define end of POI:[4 10 36–38] Müller *et al*[10] defined 'first postoperative defecation' as the primary end point and a hallmark for POI resolution. The end of gastroparesis as a sign of normalised peristalsis in the upper GI tract is not considered. In another trial examining the effect of Ipamorelin, a ghrelin agonist with promotility effects in the upper and lower GI tract, the investigators defined the end of POI as 'tolerance of a standardised solid meal', not taking recovery of the lower GI tract into account.[37] In contrast, van den Heijkant *et al*[4] defined POI as a lack of passage of flatus or stool and intolerance of solid food within the first 24 hours after surgery considering upper and lower GI tract. Interestingly, the same researchers used different criteria (lack of flatus or stool and intolerance of solid food within the first 4 days after surgery) in a trial actually recruiting (**S**timulation of the **A**utonomic **N**ervous System **i**n **C**olorectal **S**urgery by Perioperative Nutrition, SANICS II trial)).[36] The inconsequent use of clinical parameters is indeed based on the absence of any consensus and indicates that establishment of reproducible and objective parameters for POI duration is imperative. Hence, a major secondary objective of the PIDuSA trial is the comparison of the SmartPill®-based GI transit and motility estimations and the commonly used imprecise clinical signs of POI resolution including time until solid food tolerance, first flatus and first defecation. By demonstrating the suitability of the SmartPill® for exact resolution of POI, that is, as by detection of recurrence of peristalsis or an enhanced transit time, a patient-independent and investigator-independent parameter for the analysis of

postoperative bowel disorders would be available. This will allow an objective comparison of future clinical trials for prophylaxis and therapy of POI. By using a reliable parameter, the quality of all future studies concerning POI, septic ileus or GI failure during treatment on an intensive care unit will be increased significantly.

During its passage through the GI tract, the SmartPill® continuously measures intraluminal pressure allowing accurate analysis of peristaltic activity. Another secondary objective includes estimation of prokinetics (ie, metoclopramid, Prostigmine, erythromycine) administered after exhibition of clinical signs of POI. Importantly, a Cochrane analysis demonstrated lack of evidence for prokinetics as a therapeutic concept for POI, despite their broad use based on 'expert' opinion.[7] The present trial will analyse the intraluminal pressure changes before, during and after intravenous application of these drugs. We hope to provide first information whether those prokinetics are able to enhance peristalsis compared to the time course before application and to treat manifest POI or whether they are useless. A failure to prove a prokinetic effect would challenge the common concept of prokinetic substances, partially causing considerable side effects as abdominal cramps, bronchospasm, arrhythmia and bradycardia.[7]

Similar considerations apply to postoperative physiotherapy: it is well known that postoperative physiotherapy reduces the risk of thrombosis and pneumonia.[39] However, analysis of peristaltic activity early after abdominal surgery in a small patient cohorte some decades ago using a seromuscular recording electrode on the stomach, jejunum and colon did not show any changes in myoelectrical activity before and after mobilisation.[40] Furthermore, a prospective randomised trial indicated that early rehabilitation after colorectal surgery leads to more complications (especially collapses) without shortening recovery time or length of hospital stay.[41] As the SmartPill® will pass the entire length of the GI tract, we circumvent the limitation of the locally limited estimation of peristaltic activity and contractility as previously measured in the course of physiotherapy.

In conclusion, the present study is the first approach to determine a diagnostic tool for pan-enteric, reliable and precise estimation of POI duration and severity. Simultaneously, effects of therapeutic measures applied for treatment of intestinal dysmotility as well as the safety of the SmartPill® for use in patients undergoing abdominal surgery will be estimated.

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Contributors TOV, MC and SW wrote the study protocol. TOV, MC, PL, DP, TR and AE designed the study. RF planned and designed the biometrical analysis. SW and JCK critically revised the protocol.

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Disclaimer The trial design and the design of study protocol were developed without any influence of the sponsor or the funders.[7]

Competing interests None declared.

Patient consent Obtained.

Ethics approval The study protocol was approved by the responsible Ethics Committee of the Medical Faculty of the University of Bonn (reference number 092/14-MPG) and the German competent authorities (Federal Institute for Drugs and Medical Devices, BfArM, reference number 94.1.05-5660-8976).

Author note Trademark details for SmartPill® can be viewed at https://trademarks.justia.com/785/92/smartpill-78592007.html

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