Safety and Suitability of the SmartPill® after Abdominal Surgery: Results of the Prospective, Two-Armed, Open-Label PIDuSA Trial

Cornelius J. van Beekum^a Anke Esmann^a Franziska Heinze^a
Martin W. von Websky^a Burkhard Stoffels^a Sven Wehner^a Martin Coenen^b
Rolf Fimmers^c Thomas M. Randau^d Jörg C. Kalff^a Tim O. Vilz^a

^aDepartment of General, Visceral, Thoracic and Vascular Surgery, University Hospital of Bonn, Bonn, Germany;

^bClinical Study Core Unit, Study Center Bonn (SZB), University of Bonn, Bonn, Germany; ^cInstitute of

Medical Biometrics, Informatics and Epidemiology, Study Center Bonn (SZB), University of Bonn, Bonn, Germany;

^dDepartment of Orthopedics and Trauma Surgery, University Hospital of Bonn, Bonn, Germany

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Abstract

Introduction: Postoperative ileus (POI) is a common complication after abdominal surgery. Until today, an evidence-based treatment of prolonged POI is still lacking, which can be attributed to the poor quality of clinical trials. Various different surrogate markers used to define POI severity are considered to be the cause of low-quality trials making it impossible to derive treatment recommendation. The SmartPill®, which is able to record pH values, temperature and pressure after ingestion, could be an ideal tool to measure transit times and peristalsis and therefore analyze POI severity. Unfortunately, the device has no approval for postoperative use due to safety concerns. The primary objective of the study is to determine safety of the SmartPill® in patients undergoing surgery. Secondary objectives were the quality of the recorded data and the suitability of the SmartPill® for analyzing intestinal motility after different surgical procedures. **Methods:** The PIDuSA Study is a prospective, 2-arm,

open-label trial. At the end of surgery, the SmartPill® was applied to 49 patients undergoing abdominal surgery having a high risk for impaired intestinal motility and 15 patients undergoing extra-abdominal surgery. Patients were visited daily to access safety data of the SmartPill® on the basis of adverse and serious adverse events (AEs/SAEs). Suitability and data quality were investigated by analyzing data completeness and feasibility to determine transit times and peristalsis for all sections of the gastrointestinal tract. **Results:** In total, 179 AEs and 8 SAEs were recorded throughout the study affecting 42 patients in the abdominal (158 AEs) and 9 patients in the extra-abdominal surgery group (21 AEs, $p = 0.061$); none of them were device related. Primary capsule failure was observed in 5 patients, ultimately resulting in an impossibility of data analysis in only 3 patients (4.4%). 9% of the recorded data were incomplete due to the patient's in-compliance in keeping the receiver close to the body. In 3 patients (4.4%), isolated small bowel transit could not be determined due to pH alterations as a result of prolonged POI. **Discussion:** Our study demonstrates that the use of the SmartPill® is safe after surgery but requires a reasonable patient compliance to deliver meaningful data. An objective analysis of transit times and peristalsis was possible irrespec-

tive of type and site of surgery in over 95% indicating that the SmartPill® has the potential to deliver objective parameters for POI severity in future clinical trials. However, in some patients with prolonged POI, analysis of small bowel transit could be challenging.

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Introduction

Postoperative ileus (POI) is a frequent and unfavorable complication after abdominal, but also after nonabdominal operations. The incidence of POI varies between 10 and 40% among surgical specialties [1–4].

Multimodal fast track surgery protocols with minimally invasive surgery reduce the incidence of POI [5]. Still, a recent study found a 15% incidence of POI after surgery under fast track conditions, highlighting its persistent relevance, even in times of fast track surgery and minimally invasive procedures [1].

Once POI has occurred, an evidence-based treatment is lacking [6, 7]. The absence of evidence in therapy can be attributed to the poor quality of meta-analyses and randomized clinical trials, which is a result of various different outcome measures and parameters used to define POI's severity and duration. Additionally, there is an absence of reliable end points to define resolution of postsurgical motility disorders. A variety of doubtful

soft surrogate markers [8] are used instead, including solid food tolerance, time to first defecation, time to first flatus or combinations [7]. Conclusively, it is impossible to perform meta-analyses, hindering evidence-based recommendations for POI therapy [8]. Therefore, objective, investigator- and patient-independent parameters are required, enabling further clinical and translational investigation concerning POI treatment in the future.

Technical progress has enabled examination of the intestinal tract using a wireless capsule, which is specifically designed to assess intestinal motility after ingestion (setup for analysis shown in Fig. 1a, the SmartPill® shown in Fig. 1b). After oral application, the device continuously measures temperature, intraluminal pressure and pH value in the intestinal tract, allowing analysis of gastric emptying time (GET), small bowel transit (SBT), large bowel transit (LBT), whole gut transit (WGT) and peristaltic activity (shown in Fig. 2) [9].

In patients suffering from impaired intestinal motility (e.g., diabetic gastropathy, slow transit syndromes, constipation), the SmartPill® has already been validated as a diagnostic tool [10–13]. Therefore, the device seems to be predestined to assess intestinal dysmotility in patients after surgery. Unfortunately, postoperative use of the SmartPill® is not part of the capsule's market authorization, which prohibits its application in patients after abdominal surgery (AS).

Fig. 1. **a** Setup for capsule activation and data analysis. **b** The SmartPill®. **a** The receiver (A) is wirelessly connected to the SmartPill® after activation (B). The SmartPill® is placed into the patient's stomach either by direct placement via gastrotomy or orally using the AdvanCE® delivery device during general anesthesia. The capsule measures intraluminal pH values, temperature and

pressure levels from ingestion until defecation. Data are immediately sent to the receiver and can be analyzed once the receiver is connected to the computer (C) (see Fig. 2). **b** The SmartPill®. A detailed description of the technical aspects of the device can be found in the online supplementary Material and Methods part (online suppl. Material and Methods).

Fig. 2. Analysis of gastrointestinal (GI) passage and peristaltic activity using the MotiliGITM software. Pressure levels in the GI tract are represented by the red line, in this case over a period of 177 h. Intensity (intraluminal pressure) and frequency of peristaltic activity (contractions per minute) in all sections of the intestinal tract can be detected. pH value is marked by the green, temperature by the blue line. Gastric emptying time is defined as the interval between an increase in temperature (blue line) after placement of the capsule in the stomach until a sudden rise of pH value (green

line at day 1, 2 h 52 min), when passing the pylorus muscle. Small bowel transit determined by sudden pH increase after entering the duodenum, until a further increase in pH value for one point with simultaneous changes in the pressure profile due to altered peristaltic activity (red line at day 2, 3 h 3 min), when passing Bauhin's valve. Large bowel transit and finally whole gut transit are defined from passage of Bauhin's valve until a drop of temperature (blue line at day 7, 8 h 56 min) when the capsule leaves the body and enters toilet water.

Fig. 3. Study patient enrollment. After screening for inclusion criteria, 71 patients were eligible and gave written informed consent. These patients were included in the PIDuSA Study. Five patients dropped out due to unexpected intraoperative complications or high-risk anastomoses according to the operating surgeon. Informed consent was withdrawn in 2 participants preoperatively. Sixty-four patients received the SmartPill®.

The aim of this study was to assess the safety and suitability aspects of the SmartPill® in patients undergoing surgery in order to establish a tool to objectively investigate severity of postoperative motility disorders as a first step to improve the quality of further trials concerning diagnosis and treatment of POI.

Methods and Analysis

The PIDuSA trial is a prospective, 2-armed, open-label study. A detailed description of the study protocol has been published before [14] and is available in the online supplementary material and methods (see www.karger.com/doi/10.1159/000515736 for all online suppl. material) part. Briefly, the SmartPill® was applied into the patient's stomach before closure of the abdomen. During

Table 1. Baseline characteristics of the study population and operative procedures

	Abdominal surgery (n = 49)	Control (n = 15)	Total (n = 64)
Demographics			
Male, n (%)	32 (50)	7 (10.96)	39 (60.9)
Female, n (%)	17 (26.6)	8 (12.5)	25 (39.1)
Age (mean ± SD), years	61.38±13.32	59.94±14.85	61.04±13.58
Height (mean ± SD), cm	173.82±8.99	170.07±9.12	172.94±9.09
Weight (mean ± SD), kg	80.24±12.48	75.87±16.78	79.21±13.59
Procedures, n (%)			
Laparoscopic colorectal surgery with anastomosis	15 (23.4)		
Open colorectal surgery with anastomosis	12 (18.8)		
Open liver resection	7 (10.9)		
Esophagectomy	7 (10.9)		
Pancreatic surgery (distal pancreatectomy or Longmire-Traverso procedure)	5 (7.8)		
Ventral or incisional hernia repair	2 (3.1)		
Multivisceral resection (distal pancreas, transverse colon and spleen)	1 (1.6)		
Thyroid surgery with neck dissection		1 (1.6)	
Thoracotomy		3 (4.7)	
Hip replacement		10 (15.6)	
Knee replacement		1 (1.6)	
Duration of procedures (mean ± SD), min	285.10±120.26	206.13±104.72	266.59±120.80

Table 2. Outcome and intensity of adverse events

Adverse events (n = 178)	Number (%)
Outcome	
Resolved	161 (90.4)
Resolved with sequelae	1 (0.6)
Ongoing at the end of study	16 (9)
Persons affected	178 (100)
Intensity	
Mild	148 (83.2)
Moderate	24 (13.5)
Severe	6 (3.4)

the daily study visits, patients were screened for adverse events (AEs) and serious adverse events (SAEs). Furthermore, malfunction of the capsule or problems during data analysis were documented. Data were analyzed for suitability to assess intestinal transit times and peristaltic activity.

Results

Patient Demographics and Characteristics

Patient enrollment is described in Figure 3. Finally, 64 patients received the SmartPill®; further patient-related information is summarized in Table 1.

Postoperative AEs and SAEs

178 AEs were recorded during the PIDuSA Study in 51 patients (shown in Table 2). 90.5% (n = 161) of the events resolved in the course of the study. One (0.6%) event resolved with sequelae, 9% (n = 16) were ongoing at the end of the study.

148 (83.2%) events were considered mild, 24 (13.5%) were of moderate intensity. Only 6 events (3.4%) had a severe impact on patients.

Regarding the total number of AEs in the AS group (42 patients affected) and the extra-abdominal surgery (ES) group (9 patients affected), no significant differences (p = 0.061) could be observed (Table 3). To better compare the incidence of AEs between both groups, AEs were further subdivided and analyzed (Table 3). Again, no difference between both groups was observed.

Additionally, we compared the incidence of AEs in patients after colorectal surgery with an anastomosis (n = 27) with the other patients after AS (hernia repair, esophagectomy, hepatopancreatobiliary surgery). Again, no differences concerning AEs could be observed (p = 0.42).

Classification of AEs

To better compare the incidence of AEs between both groups, AEs were further subdivided and analyzed. Brief-

Table 3. Incidence of postoperative adverse events between the groups

Events	Abdominal surgery, n (%)	Control, n (%)	Total, n (%)	p value
Postoperative ileus (according to Vather et al. [15])	17 (34.7)	3 (20)	20 (31.3)	0.354
Gastrointestinal events	11 (22.5)	4 (26.7)	15 (23.4)	0.737
Hemorrhage requiring blood transfusion	7 (14.3)	3 (20)	10 (15.6)	0.687
Coagulopathy	3 (6.1)	0	3 (4.7)	1
Electrolyte imbalance	7 (14.3)	1 (6.7)	8 (12.5)	0.668
Significant changes in bloodwork, without clinical correlate	10 (20.4)	2 (13.3)	12 (18.8)	0.715
Surgical complications	6 (12.2)	1 (6.7)	7 (10.9)	1
Intraoperative events	3 (6.1)	1 (6.7)	4 (6.3)	1
Infectious events	14 (28.6)	1 (6.7)	15 (23.4)	0.096
Anaphylactic events	3 (6.1)	0	3 (4.7)	1
Cardiac events	8 (16.3)	0	8 (12.5)	0.181
Vascular (venous) complications	2 (4.1)	1 (6.7)	3 (4.7)	0.558
Neurological events	6 (12.2)	2 (13.3)	8 (12.5)	1
Respiratory events	11 (22.5)	2 (13.3)	13 (20.3)	0.715
Renal/urinary tract events	3 (6.1)	0	3 (4.7)	1
Total	42 (85.7)	9 (60)	51 (79.7)	0.061

ly, no significant differences could be observed between both groups (Table 3).

When analyzing postoperative intestinal motility using the criteria by Vather et al. [15], 17 (34.7%) patients in the AS group and 3 (20%) patients in the ES group were found to be suffering from POI. Interestingly, no significant difference between patients undergoing AS versus patients undergoing ES were observed.

Severe Adverse Events

Eight SAEs were recorded and reported to the competent authority (Table 4). All patients recovered, whereas 1 patient died due to pulmonary sepsis weeks later, after finishing the trial.

SmartPill®-Related Information, Device Deficiency and Issues during Data Analysis

During the trial, the SmartPill® had an average recording time of 116 h 49 min (± 55 h 12 min) per patient with a maximum of 247 h. In 2 patients, the life span of the battery in the SmartPill® expired before excretion of the capsule as a result of prolonged motility disorders.

Capsule Failure Rate and Data Loss

Capsule Failure Rate. In 2 cases, activation of the SmartPill® failed. These patients were included in the trial with new, functional capsules. The reason for the malfunction remained unclear. Failure of pH measurement immediately after capsule application into the

stomach was observed in 3 patients. This resulted in insufficient data: determination of GET as well as SBT was impossible, whereas data concerning peristaltic activity and WGT were available for further analysis. This complies with a total capsule failure rate after application of 4.4%.

Problems during Data Analysis after Capsule Excretion. To evaluate the quality of the recorded data, it was randomly checked. In 31 patients, almost the complete data could be analyzed. Interestingly, a partial loss of data in nearly half of the patients ($n = 33$) for an average of 11 h 48 min (± 4 h 31 min) during a mean recording time of 128 h 31 min (± 43 h 15 min) was observed. These values represent 9.2% of the recorded data in these 33 patients. Since the capsule connected to the receiver as soon as it was close to the patient again, detailed data analysis was still possible.

Analysis of GET. Analysis of GET was possible in all patients with the exception of the 3 patients with a defective pH analyzer (see above).

Analysis of SBT. In 3 patients (4.4%) with massive and prolonged POI, passage of the ileocecal valve could not be clearly identified due to lack of typical pressure profiles in the whole gastrointestinal (GI) tract and pH alterations. In these patients, a detailed analysis of isolated SBT and LBT failed. Nevertheless, data on GET and WGT were eligible for further analysis.

Analysis of LBT/WGT and Body Excretion. Determination of body exit was possible in 59 patients. Body exit was

Table 4. Characterization of severe adverse events (SAEs)

Surgical procedure before SmartPill® application	Description of SAE	Dindo/Clavien class	Day of occurrence after surgery	Treatment	Outcome	Results of the discussion with the federal authorities (BfArM)
Open Hartmann procedure reversal	Massive pleural effusion resulting in atelectasis of the lungs and consecutive pneumonia	IVa	7	Antibiotic treatment, intubation, noninvasive respiratory therapy	Resolved	No causality to the device or the study procedure
Laparoscopic sigmoidectomy	Bleeding from the anastomosis	IIIb	3	Endoscopic clip application	Resolved	No causality to the device or the study procedure Justification: capsule was in the small bowel during hemorrhage
Open Longmire-Traverso procedure	Insufficiency of a ventral gastric suture	IIIb	20	Relaparotomy and repair of the suture line	Resolved	No causality to the device or the study procedure Justification: the SmartPill® had left the stomach several days before leakage was diagnosed
Laparoscopic esophagectomy	Leakage of the esophagogastrostomy	IIIb	6	Endoscopic SmartPill® removal and intraluminal vacuum therapy	Ongoing at end of study	No causality to the device or the study procedure Justification: the SmartPill® was placed in the stomach via pylorotomy and had never contact to the anastomosis
Open anterior rectal resection with partial mesorectal excision	Leakage of a colorectal anastomosis	IIIb	3	Relaparotomy and manufacturing of a distal colostomy and a Hartmann stump	Resolved with sequelae	No causality to the device or the study procedure Justification: the SmartPill® was in the cecum when leakage occurred
Open sigmoidectomy	Bleeding from the mesentery of the Hartmann stump	IIIb	15	Relaparotomy and evacuation of pelvic hematoma	Resolved	No causality to the device or the study procedure
Open sigmoidectomy	Insufficiency of the Hartmann stump	IIIb	15	Relaparotomy and revision of the suture line	Resolved	No causality to the device or the study procedure Justification: SmartPill® had left the body via stoma 7 days before
Laparoscopic low anterior rectal resection	Cardiac arrest postoperatively upon arrival in the recovery room due to hypoxemia induced by residual opioid effect	IVa	0	Mechanical resuscitation for 1 min with return of spontaneous circulation	Resolved	No causality to the device or the study procedure

missing in 4 patients due to data loss resulting primarily from the subject's failure to keep the receiver close to their body during defecation. In these patients, excretion of the capsule was ensured using X-ray; no retention was observed.

Discussion

It was speculated that the wireless motility capsule could be the ideal tool to deliver objective and precise parameters for duration, severity and resolution of POI and replace soft surrogate markers used until now. Unfortun-

nately, the SmartPill® is not covered by the marketing authorization for use during the first months after AS. Therefore, this study's primary aim was to assess the safety and suitability of the SmartPill®, as a first step in establishing its use to analyze postoperative intestinal motility and transit times.

During the activation process, a malfunction of the SmartPill® system occurred in 2 cases (2.9%); the reason remained unclear. Fortunately, the capsule had not been applied yet, and the patients were included in the trial with a new device.

In another 3 of 69 patients (4.4%), malfunction of the capsule's pH sensor after placing the capsule in the stom-

ach was observed. Patients could be included to investigate safety issues, but analysis of transit times was impossible (except for WGT). This failure rate after application was higher than described in the literature and specified by the company, which revealed an incidence of equipment failure of 0.8–0.9% [16, 17]. An explanation could be the use of the AdvanCE[®] delivery device for capsule placement during general anesthesia. This device was developed to release endoscopy capsules during gastroscopy, and not for application of the SmartPill[®]. Possibly, the sensor units at the surface of the SmartPill[®] were damaged when fixing the capsule in the delivery device. We chose to apply the capsule during general anesthesia and before closure of the abdominal wall to avoid aspiration due to limited protective reflexes after anesthesia and because we were then able to manually check the correct placement in the patient's stomach. During specific procedures requiring a gastrotomy (Longmire-Traverso procedure and Ivor-Lewis procedure), we were able to directly place the activated capsule in the stomach. This was the easiest way of capsule application. When no gastrotomy was necessary, we used the AdvanCE[®] delivery device for capsule application transorally. A standardized application process at a comparable time point (before closure of the abdominal wall) without further manipulations of the GI tract was mandatory. Due to the application in general anesthesia, we could ensure minimal stress for the patients. This resulted in a high participation of the study with a short recruiting time and no dropouts due to inability of swallowing the capsule after anesthesia or postoperative nausea and vomiting. Nevertheless, in future trials the capsule should be placed directly into the GI tract via gastrotomy or swallowed postoperatively at a defined time point after the patient's wake from anesthesia.

It was found however that patient compliance was a major requirement to obtain viable data with the SmartPill[®]: in 33 of the patients, a temporary loss of data was observed. In all cases this data loss occurred out of patient noncompliance by leaving the receiver in the room, when taken to postoperative examinations or the patient failed to put the receiver on the charging station resulting in a depleted battery and a temporary disconnection to the capsule. Relating the lost data to the average record time in those patients, 9% of all gathered data were not available for analysis. This is manageable, especially with a structured and detailed instruction of the patients before administration of the SmartPill[®]. After implementing these measures, a substantial decline of data loss was observed.

In 3 patients with massive POI, passage of the ileocecal junction could not be identified due to pH alterations in the small and large bowel. This resulted in an inability of pH increase observation after passage of Bauhin's valve. This phenomenon can be explained by bacterial overgrowth of the small bowel with pH alterations due to stasis of luminal content in the colon and intestine [18]. This might pose a limitation of the SmartPill[®] in analyzing the severity of POI in the small bowel. However, it has to be clearly noted that only 4.4% were affected. The most important values (GET and WGT as well as peristaltic activity) could be analyzed in all cases.

When comparing the AEs between both groups, no significant differences could be observed. It was hypothesized that one of the main risks of the SmartPill[®] is capsule retention followed by bowel obstruction [19–21]. An incidence of 3% for endoscopy capsules with a comparable size has been described before [12, 22]. Until now, neither symptoms of mechanical bowel obstruction nor the necessity of surgical removal has been reported for the SmartPill[®] [19–21]. In our study, no case of capsule retention was recorded. Though the case load of 49 patients after AS and 15 patients after ES is high for a pilot study or a first-in-men trial, it is too small for a qualified prediction of a rare event like capsule retention. In any case, a complete adhesiolysis and a thorough inspection of the bowel by the operating surgeon is crucial to rule out potential risk factors (adhesions, tumors, stenosis) for capsule retention.

Another feared complication is the occurrence of anastomotic leakage. During the study, 3 patients experienced leakage from an intestinal anastomosis. In the first case (leakage from an esophagogastrostomy), the capsule never crossed the anastomosis, as it had been placed into the stomach via pylorotomy. In the second case (rectal resection), the capsule was located near the cecum and had not yet passed the anastomosis when the leakage was diagnosed. In the third case (leakage of the gastrotomy), the capsule had already passed the stomach several days before. Certainly, it might be argued that the diagnosis of insufficiency was delayed, and the suture had been weakened before due to use of the capsule and clinical signs were misinterpreted. But evaluation of the clinical and surgical course of the patient as well as investigation of gastric emptying time in the acquired data makes it rather likely that the gastrotomy was intact until days after the capsule had left the stomach. Nevertheless, we could not rule out with absolute certainty that there might be a relation between the SmartPill[®] and the leakage. We reported the SAE as possibly device related and discussed the case

intensively with the vigilance officer of the trial and the Federal Institute for Drugs and Medical Devices (BfArM). Finally, after thorough investigation and an audit led by the BfArM, no causality to the capsule or its application was found.

Our study had some limitations. The main issue is the small number of participants, potentially resulting in a lack of statistical power. Due to the “first-in-men” character of the trial, we were not able to choose a number of participants, which would have allowed investigation of very rarely described adverse device-related events like capsule retention or induction of anastomotic leakage. In a clinical trial designed to elucidate the rate of capsule retention or anastomotic leakage hundreds of patients would have to be included with a significant increase in costs, bearing in mind that there is no marketing authorization for postoperative use of the wireless motility capsule. Therefore, the primary aim of this study was to show the safety and usability of the SmartPill[®], even after abdominal procedures and in the presence of intestinal anastomoses. Moreover, we included very different types of AS or thoracoabdominal surgery (i.e., Ivor-Lewis’ procedure). This of course possibly results in a heterogeneity of acquired data with a supposed lack of comparability. We specifically chose to include various types of abdominal procedures to investigate whether the SmartPill[®] is able to gather meaningful data in postoperative patients with severely altered physiology, for example, with dysregulation of intestinal pH homeostasis (i.e., major hepatectomy with biliodigestive anastomosis or Longmire-Traverso procedure) or altered anatomy (i.e., hemicolectomy, rectal resection with deviating ostomy).

Again, our case load of 40 patients with an intestinal anastomosis is not high enough to definitely rule out a possible relationship between the SmartPill[®] and anastomotic leakage, especially as patients with high-risk anastomoses were excluded from the trial. Nevertheless, it is a first but clear evidence of the possible application of the SmartPill[®] immediately after AS, even in the presence of an intestinal anastomosis, particularly with regard to the lack of data in the literature, where no documentation concerning application of wireless motility capsules or endoscopy capsules immediately after AS and their influence on anastomotic healing was found.

However, the SmartPill[®] is the only existing device with the ability to measure transit times and peristaltic activity live and in vivo allowing objective analyses of the severity of motility disorders in every part of the GI tract. In the PIDuSA Trial, safety and suitability of the device, irrespective of type and site of surgery was demonstrated.

Therefore, the SmartPill[®] could be an ideal tool to analyze the severity of POI in further clinical trials, without relying on soft and imprecise surrogate parameters like bowel movement, flatus or food tolerance. Nevertheless, the patient’s education and compliance are mandatory to ensure reliable data.

Statement of Ethics

The PIDuSA Study was registered at www.clinicaltrials.gov (NCT02329912) before including the first patient.

The PIDuSA Study was conducted according to the principles of ISO 14155 (Clinical investigation of medical devices for human subjects – Good clinical practice) and the Declaration of Helsinki. All patients signed an informed consent. An allowance for trial participation was not paid. Approval of the German competent authority (Federal Institute for Drugs and Medical Devices, BfArM, reference No. 94.1.05-5660-8976) and the Ethics Committee of the University of Bonn (reference No. 092/14-MPG) was obtained.

Conflict of Interest Statement

The authors have no conflicts of interest to declare. The device was purchased from Promedia (Siegen, Germany); the company did not have any access to the data or the manuscript before the publication of the results. All capsules were purchased regularly and paid for with money from the grants. The data receiver and the docking station, as well as the computer, were lent by the company for a rental fee, as is the usual process.

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Author Contributions

C.J.B. and T.O.V. wrote the manuscript. C.J.B., A.E., F.H., T.M.R. and T.O.V. conducted the study procedure and performed the study visits. T.O.V., M.C., R.F., T.M.R. and A.E. designed the study. B.S. served as the study’s vigilance officer. R.F. performed the biometrical analysis. M.W.W., B.S., S.W. and J.C.K. critically revised the paper.

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