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1.0	April 3, 2022	Original Version (initial submission to IRB)
2.0	**February 8, 2023**	**modified version**

Presence or Absence of blood in the GI lumen – Correlating a HemoPill acute measurement with a subsequent endoscopic finding

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NYULMC Study Number:	s22-00387
Funding Sponsor:	Ovesco Endoscopy USA, Inc. James B. Potts 120 Quade Drive, Cary, NC 27513 919 651 9449
Regulatory Sponsor	Melissa Latorre, MD Division of Gastroenterology and Hepatology 550 1st Avenue, New York, NY 10016
Study Product:	HemoPill acute HemoPill Receiver
Study Product Provider:	Ovesco Endoscopy USA, Inc.
Regulatory Status	Abbreviated IDE Abbreviated IDE holder: Melissa Latorre, MD
ClinicalTrials.gov Number	*Include the National Clinical Trial (NCT) Number assigned once the trial is registered on the ClinicalTrials.gov.*

Initial version: 03/18/2022
Modified: 02/08/2023

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HI	HemoPill Index
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UGIB	Upper Gastrointestinal Bleeding
US	United States

Protocol Summary

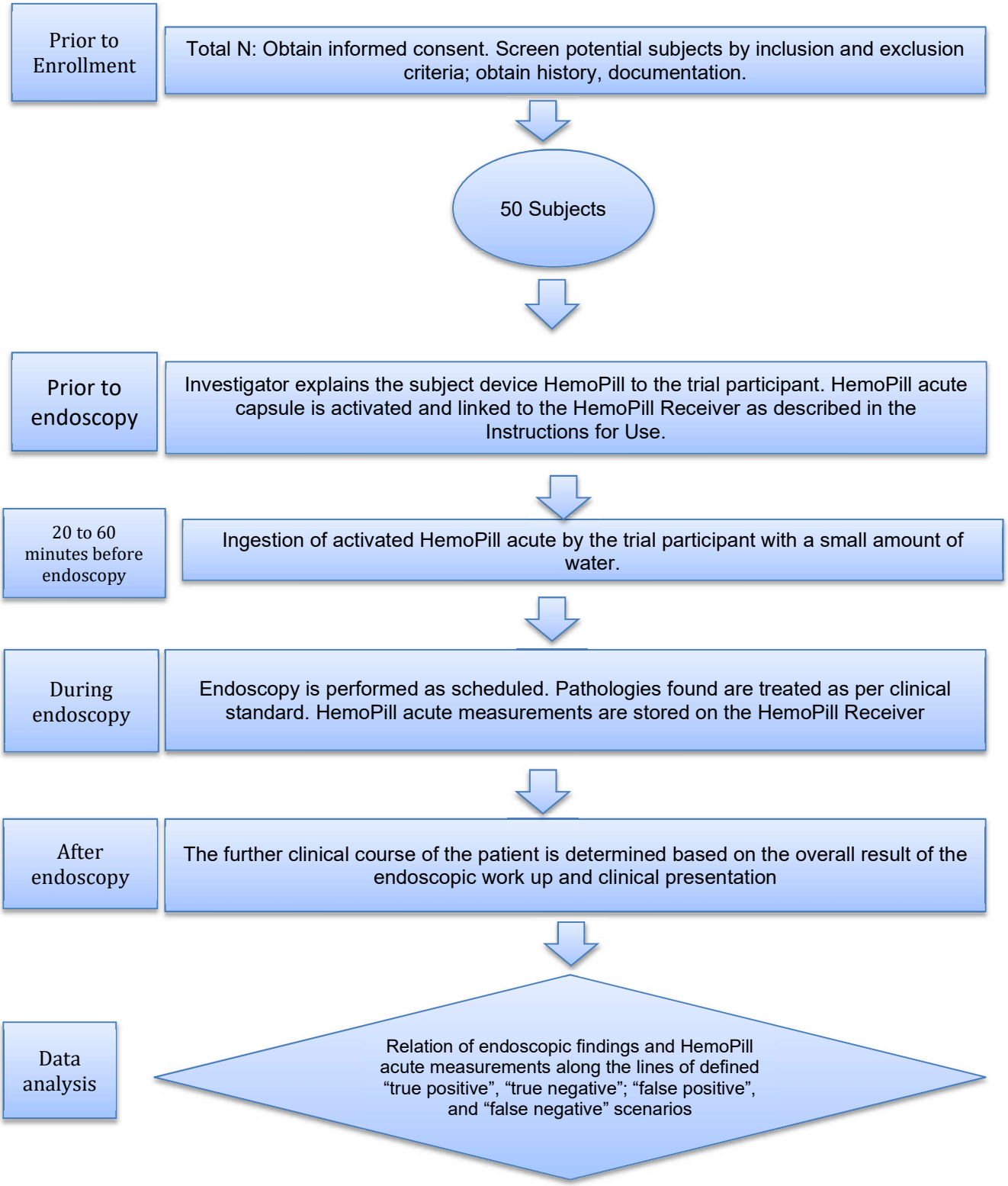
Title	Presence or Absence of blood in the GI lumen – Relation between a HemoPill acute measurement with a subsequent endoscopic finding
Short Title	PROOF (**Pr**esence or Absence of bl**oo**d in the GI lumen – Relation between a HemoPill acute measurement with a subsequent endoscopic **f**inding)
Brief Summary	Patients scheduled for endoscopy on the basis of suspected UGIB are generally eligible for inclusion into the trial. After patient screening, information and obtaining informed consent, a patient is enrolled into the trial. Shortly before the scheduled endoscopy is performed, the patient ingests a HemoPill acute. Endoscopy is performed as scheduled. Blood within the GI lumen is identified if present and pictures are taken. Pathologies, if found, are treated as per clinical standard. The HemoPill acute measurement regarding presence or absence of blood in the GI lumen is compared to observations made during endoscopy. For statistical validity, 43 patients are required. Considering dropouts, a recruitment goal of 50 patients is defined.
Phase	N.A.
Objectives	The objective of the study is to determine the clinical relation between the detection of blood in the GI lumen using the HemoPill acute (trial procedure) with the detection of bleeding / a bleeding source during an endoscopic examination (control procedure).
Methodology	Intraindividual comparison of HemoPill acute measurement to endoscopic work up.

Endpoint	Effectiveness Endpoints: - Technical effectiveness endpoint Technical success, defined as: Successful data transmission of the HemoPill acute to the HemoPill Receiver - Clinical effectiveness endpoint Result accuracy: Clinical relation between HemoPill acute measurement (trial procedure) and endoscopic findings (control procedure) according to defined events for true positive, true negative, false positive, false negative. Safety Endpoints: - Adverse events / complications associated with trial or control procedure, such as: Trial procedure: o Aspiration of the capsule on ingestion o Delayed excretion, or failure to excrete the capsule (capsule retention) o Obstruction of the digestive tract o Injury to tissue structures during the passage of the HemoPill acute through the digestive tract. In particular, this may involve: ▪ Injury to the mucosa ▪ Bleeding, e.g., variceal bleeding ▪ Perforations Control procedure: o Cardiopulmonary adverse events o Infection o Perforation o Bleeding (iatrogenic)
Study Duration	March 18, 2022 to July 31st, 2022
Participant Duration	Single visit, patient participation ends with conclusion of endoscopy
Population	Adult subjects (meeting inclusion criteria) with suspected UGIB due to clinical and / or laboratory findings and therefore scheduled for endoscopy
Study Sites	NYU Langone Health 550 First Avenue New York, NY 10016
Number of participants	Recruitment goal: 50 Patients; Statistical validity reached at 43 Patients w/o dropouts.

Description of Study Agent/Procedure	HemoPill acute: A capsule equipped with a photometric sensor for the detection of blood or hematin in the gastrointestinal tract. The capsule can be ingested and travels through the gastrointestinal tract naturally. For approximately 9 hours, the photometric sensor measures the absorption of light at specific wavelengths through the contents of the gastrointestinal lumen. Blood and hematin have a specific absorption behavior for the defined wavelengths used. The HemoPill acute capsule makes a measurement every 12 seconds and wirelessly transmits data to the HemoPill Receiver that displays the HemoPill acute data. HemoPill Receiver: Handheld device that displays HemoPill acute data. The HemoPill Receiver displays the data in a graphical form as well as the current value and the highest measured value. The threshold value for confirmation of presence of blood or hematin is displayed for reference.	
Reference Therapy	Endoscopy	
Key Procedures	Diagnostic procedures used leading to a suspicion of UGIB are not within the scope of this trial as these procedures are necessary irrespective of trial participation. A suspicion of UGIB, however justified, is a prerequisite for trial participation. Endoscopy and associated procedural steps are omitted as endoscopy is scheduled for trial participants irrespective of trial participation. Provide patient information and obtain informed consent. Screen by inclusion and exclusion criteria, document. Activation of the HemoPill acute by the investigator as per instructions for use. Ingestion of HemoPill acute capsule by the trial participant with a minimal amount of water. Data collection on the HemoPill Receiver from ingestion of the HemoPill acute capsule until conclusion of endoscopy.	
Statistical Analysis	Relation between HemoPill acute measurements and endoscopic findings along the lines of the following definitions for “true positive”, “true negative”, “false positive”, “false negative”:	
	True Positive	HemoPill acute measurement indicates presence of blood; Endoscopy identifies fresh blood or hematin in the GI lumen.

	True Negative	HemoPill acute measurement does not indicate presence of blood; Endoscopy does not identify fresh blood or hematin in the GI lumen in quantities > 20 mL; Minimum latency of 20 minutes achieved.
	False Positive	HemoPill acute measurement indicates presence of blood; Endoscopy does not identify fresh blood or hematin in the GI lumen.
	False Negative	HemoPill acute measurement does not indicate presence of blood in the GI lumen; Endoscopy identifies fresh blood or hematin in the GI lumen in quantities > 20 mL; Minimum latency of 20 minutes achieved.

Schematic of Study Design



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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Gastrointestinal hemorrhage is the 19th most common diagnosis for hospital admissions. A total of 86 % of patients with gastrointestinal hemorrhage are admitted to the hospital. However, when esophagoduodenoscopy is performed in the emergency department (ED), 30 % to 46 % of ED patients with acute UGIBs can be safely discharged. Risk stratification in the ED presents a logistic issue because gastroenterologists are frequently unavailable to conduct ED-based esophagoduodenoscopies. As a result, many patients with benign diseases are admitted to the hospital only to have a negative endoscopy result (Meltzer AC et al., 2013). The HemoPill has the potential to provide information on the presence or absence of blood in the GI-lumen which is a valuable information on the urgency of a situation if viewed in the general clinical context of a given patient. The HemoPill is a CE-marketed device and has been on the European market since 2019. Since market entry, the following literature on the use of the HemoPill has been published:

Telemetric capsule-based upper gastrointestinal tract – blood detection – first multicentric experience

Brunk and colleagues presented results from an observational study on the use of the HemoPill in terms of safety and usability under real-life conditions from experiences in 12 hospitals (Brunk T et al., 2021). The use of the HemoPill in 61 patients was retrospectively analyzed. Indications for HemoPill application were clinical suspicion of UGIB, suspected small bowel bleeding after uneventful esophagoduodenoscopy (EGB) and colonoscopy if symptoms persisted, or exclusion of rebleeding after hemostasis. Primary endpoints were technical success and bleeding detection/exclusion. Secondary endpoints included adverse events and change of clinical course. Complete baseline characteristics were available in 49 of 61 patients (80.3 %). Mean age was 70 (± 10.7) years, 41 % were female. Mean hemoglobin level at admission to the emergency department was 8.1 g/dL (± 1.6). Over signs of bleeding such as melaena and/or hematochezia were present in 27 patients (55 %). Median Glasgow-Blatchford score (GBS) was 10 (range 0 – 19). 46 patients (94 %) had a GBS > 1. 61 patients received the HemoPill; in 45 patients (74 %), the capsule was administered due to the suspicion of UGIB, in 12 patients (20 %), the capsule was used for detection of a suspected small intestinal bleeding and in 4 patients (7 %), HemoPill was used as a "second look" tool after primary hemostasis in the upper GI-tract. One patient was excluded as data transfer was stopped after 10 minutes of recording. Of the remaining 60 patients, 35 (58 %) had a positive capsule signal while 25 (42 %) had a negative HemoPill result. In 20 of 35 patients (57 %) with a positive HemoPill signal, evidence of bleeding was seen in a subsequent endoscopic work up. The bleeding sources were angiodysplasia (n = 10), peptic ulcer (n = 5), Dieulafoy lesion (n = 1), esophageal varices (n = 1), esophagitis (n = 1), erosive gastritis (n = 1), unknown as only blood was seen (n = 1). In 15 of 35 patients with a positive HemoPill signal, no bleeding source was detected, yet only in 11 of these 15 patients an EGD was performed.

In 20 of 25 HemoPill negative patients, endoscopy was performed and did not reveal a bleeding source or blood/hematin. Until discharge, no clinically relevant bleeding was detected in HemoPill negative patients.

The authors state that all endoscopically confirmed bleedings had been detected by the HemoPill and no HemoPill negative patients showed an endoscopically or clinically proven bleeding site. In HemoPill negative patients (25 / 60), the further clinical course was changed in 18 cases (72 %). Change from urgent to elective regarding timing of endoscopy was reported in 40 % of cases (10 / 25). Small bowel enteroscopy was avoided in 5 / 25 patients (20 %) and EGD was avoided in 3 / 25 patients (12 %). In 7 / 25 patients, no change of the clinical course occurred. Brunk T et al. conclude that HemoPill is a promising tool for real-time blood detection to aid stratification of patients with UGIB (Brunk T et al., 2021).

Potential use of a novel telemetric sensor capsule in patients with suspected gastrointestinal bleeding during the COVID-19 pandemic

Elsayed and colleagues evaluated the HemoPill acute in three patients with confirmed or suspected COVID-19 (Elsayed I et al., 2021). Case 1 was a patient with COVID-19, congestive heart failure, and severe obesity who reported melena and had a drop of hemoglobin from 14.6g/dL to 11.3g/dL. The maximum HI value was 1.0 after 89 minutes. Endoscopy subsequently showed a gastric ulcer with a non-bleeding visible vessel. Patient 2 suffered from dyspnea and anemia (hemoglobin 4.3g/dL) with possible gastrointestinal bleeding. She was routinely tested for SARS-CoV-2 and isolated until receipt of her result. The maximum HI value was 0.2. Her endoscopy, which showed no evidence of gastrointestinal bleeding, was postponed for 48 hours until receipt of negative test results. Patient 3 suffered from COVID-19 and was therefore receiving anti-coagulant therapy. He underwent endoscopic retrograde cholangioscopy with papillotomy because of biliary pancreatitis; here ported a single episode of hematochezia 1 week after the endoscopy

and his hemoglobin had dropped by 4.5 g/dL to 7.9 g/dL. His maximum HI value was 0.8 and no endoscopy was performed. No further episodes of bleeding were reported, and the patient's hemoglobin remained stable.

The authors concluded that the sensor capsule might aid in decision-making during the COVID-19 pandemic. In patients with as yet unavailable COVID-19 test results, it might aid in determining the appropriate time-point for endoscopy. In patients who are positive for COVID-19 with suspected gastrointestinal bleeding, it could help in deciding whether to perform an endoscopy or not and thereby potentially help minimizing risk of disease transmission (Elsayed I et al., 2021).

Detection of mid-gastrointestinal bleeding caused by Meckel's diverticulum using a novel telemetric sensor capsule in a non-fasting patient

Wiedbrauck and colleagues used the HemoPill acute to provide further assessment of an acute bleeding situation (Wiedbrauck D et al., 2021). A 52-year-old male patient presented with anemia (hemoglobin 9.9 g/dL) due to episodes of severe hematochezia. He underwent esophagogastroduodenoscopy, colonoscopy and CT-angiography, however, none of these procedures could identify the source of bleeding. After these procedures, the patient was stable and had eaten. Several hours later, his hemoglobin dramatically dropped (6.4 g/dL) and VCE was not possible. Therefore, the authors administered the HemoPill acute which detected blood after 6 h 58 min (HI = 1.1). The time of blood detection indicated a bleeding source at the level of the ileum/terminal ileum. Subsequent video capsule endoscopy revealed a bleeding Meckel's diverticulum. The patient underwent segmental ileal resection. Wiedbrauck and colleagues concluded that this case shows that the HemoPill may serve as an add-on pre-diagnostic tool for detecting and localizing gastrointestinal bleeding in a non-fasting patient (Wiedbrauck D et al., 2021).

2.1.1 Study importance

As described in the above-mentioned publications, further tools for risk stratification in patients with suspected UGIB are in demand to identify high risk patients and adequately allocate resources. The clinical data on the use of the HemoPill in Europe is generally positive and promising. As Brunk T et al. conclude, thus far no HemoPill negative patient developed a clinically significant GI bleeding until discharge and every endoscopically confirmed bleeding pathology was associated with a previously positive HemoPill measurement. The proposed study further investigates the safety and performance profile of the HemoPill by controlling and limiting latency to endoscopy. HemoPill may prove to be a valuable tool for the US healthcare system by reliably providing information on the presence or absence of blood in the GI tract. HemoPill does not require patient preparation and measurement data is displayed in a way that allows for immediate, real-time interpretation. Thus far, HemoPill has a high technical success rate and is well tolerated by patients. Only patients who are already scheduled for endoscopy for suspected UGIB are eligible for participation in the study and endoscopy is neither delayed nor prolonged by the study protocol. The potential benefits for the US healthcare system are already highlighted in publications describing the use of the subject device in Europe.

2.2 Name and Description of the Investigational Agent

The investigational device is the HemoPill, consisting of an ingestible capsule (HemoPill acute), and a wireless data receiver module (HemoPill Receiver) that displays and stores data.

2.2.1 HemoPill acute capsule

The HemoPill acute is an active medical device. It is a wireless, battery-powered ingestible capsule containing an optical sensor, electronics, radio link and software. The electronic assembly (as a stack of three electronic boards) contains software for measurement data acquisition and signal transmissions. These components are encapsulated into a transparent epoxy resin that is coated with Parylene C.

The signals of the HemoPill acute sensor correlate with the presence of blood in the measuring slot of the capsule and are transmitted wirelessly to the HemoPill Receiver.

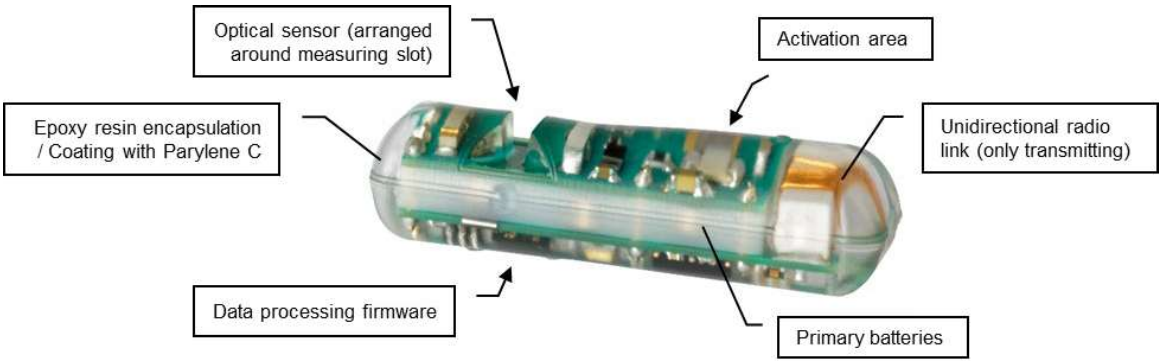

Figure 1: Components of the HemoPill acute

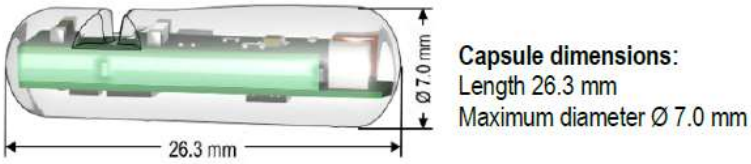

Figure 2: Dimensions of the HemoPill acute

The operating mode of the optical sensor is based on alternating screening of the measuring slot using wavelength of 415 nm (violet) and 700 nm (red). The optical sensor measures the absorption of light by the medium inside the measuring slot for each wavelength separately. The ratio of red to violet light intensity, that has not been absorbed is, calculated. Measurement data is transmitted by radio to the HemoPill Receiver. A more detailed description is provided in chapter 2.1.2.

The HemoPill acute is activated by exposing the activation area to light. The light intensity required for activation is higher than normal environmental light (day light or room light), therefore the exposure to a light-source at close distance is required. The HemoPill Receiver includes a light source for activating the HemoPill acute. The procedure of capsule activation using the activation light source of the HemoPill Receiver is shown in Figure 2-3. In order to ensure sterility, the capsule remains in the blister packaging for activation.

After activation, the capsule conducts one measurement approximately every twelve seconds for at least nine hours. Subsequently, the device changes into a second mode to facilitate monitoring the presence of the device in the patient using the HemoPill Receiver. During this second period, no measurements are conducted, but data packages are transmitted until at least 21 days after activation.

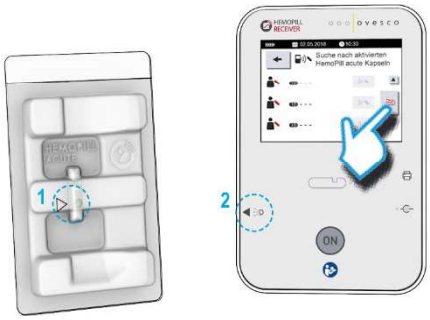

Figure 3: Blister package of HemoPill acute (activation area is marked by triangle, (1) and (2))

Table 1: Specifications of the HemoPill acute

Dimensions and weight			
Product dimensions		26.3 mm x 7.0 mm	
Weight		Approx. 2 g	
Energy source			
Battery type		Silver oxide	
Version			
Software version		02.xx.yy	
Electronics version		01.xx.xx	
CAD version		12	
Wireless specification			
Frequency range		433.05 MHz to 434.79 MHz	
Send frequency		434.42 MHz	
Send bandwidth		100 kHz	
Send rate		0.083Hz	
Transmission period		< 10ms	
Modulation		GFSK	
ERP		-24 dBm	
Range		Short range	
Application related specifications			
General specifications		Single use	
		EO sterilized	
		Latex-free	
Shelf life		21 months	
Technical characteristics			
General characteristics		Unidirectional data transmission	
		MR conditional	
Environmental conditions for operation, transport and storage			
	Operation	Storage	Transport
Temperature	+20 °C to +40 °C	+10 °C to +30 °C	-10 °C to +50 °C
Relative humidity	20% to 90% RH; non-condensing	20% to 85% RH; non-condensing	20% to 90% RH; non-condensing
Air pressure	785 to 1060 hPa	700 to 1060 hPa	700 to 1060 hPa
Max. operating height	≤ 2000 m	-	-

2.1.1.1 HemoPill Receiver

The HemoPill Receiver (Figure 2-4) is an accessory (wireless, handheld device) to the HemoPill acute. The HemoPill acute and the HemoPill Receiver can only be used together. The HemoPill Receiver is designed to receive data from the HemoPill acute via the radio link and display this data to the user.

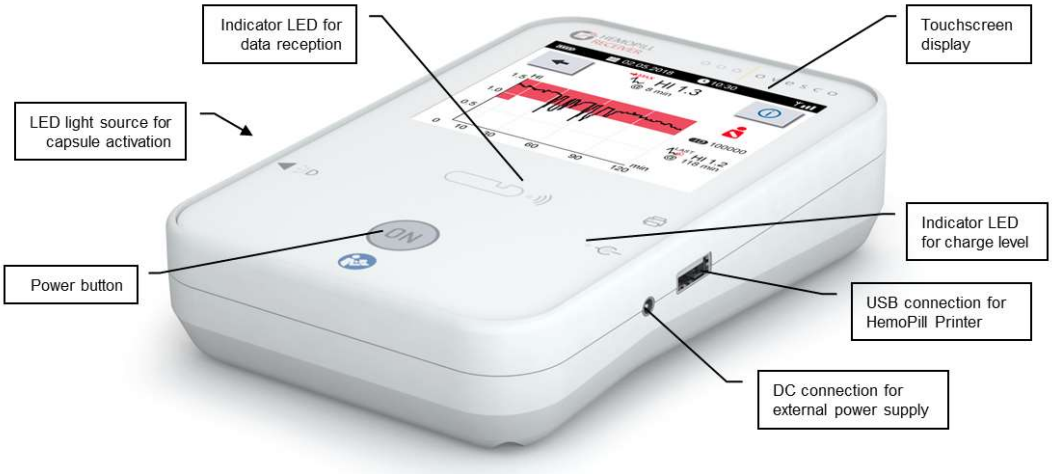

Figure 4: Components of the HemoPill Receiver

The HemoPill Receiver features and is operated by a touch-sensitive color display. After activation of the HemoPill Receiver using the power button, the user controls the device via the touch display. Furthermore, the HemoPill Receiver features an USB-interface to connect to the HemoPill Printer for printing measurement results for documentation, a LED light source for activation of the HemoPill acute, and an indicator LED for data reception and charge level of the internal secondary battery (Figure 2-4). The internal secondary battery can be charged via the DC connection using the supplied external power supply (Figure 2-5). Normal operation of the device is possible also during battery charging. The Receiver power supply is included in the scope of delivery.

The HemoPill Receiver contains a software for displaying the values measured and transmitted by the HemoPill acute. The HemoPill Receiver receives and saves the measured values. The values are displayed numerically and as a curve diagram on the display of the HemoPill Receiver.

The HemoPill receiver can be disinfected using alcohol-based cleaning agents and disinfectants.

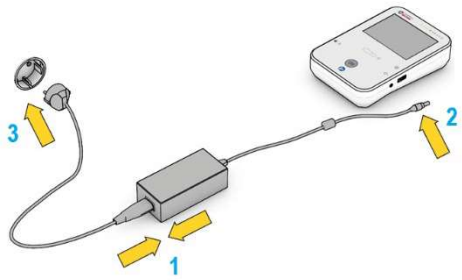

Figure 5: Connecting the HemoPill Receiver to the power supply

Table 2: Specifications of the HemoPill Receiver

Dimensions and weight			
Product dimensions (W x H x D)		96 x 145 x 37 mm	
Net weight		262 g	
Packaging information/dimensions (W x H x D)		Case 465 x 350 x 110 mm	
Gross weight		approx. 4.4 kg (including accessories and packaging)	
Version			
Software version		02.xx.yy	
Device version		1.xx	
Receiver power supply			
Power input		100 V – 240 V AC	
Supply voltage		220 V – 240 V AC	100 V – 120 V AC
Max. power consumption		5 W / 12 VA 5 W / 16 VA	5 W / 8 VA 5 W / 10 VA
Supply frequency		50/60 Hz	50/60 Hz
DC output voltage		5 V	
Max. output current		5 A	
Overcurrent protection (power input)		2 A	
Wireless specification			
Operational Frequency band		433.05 MHz to 434.79 MHz	
Reception frequency		434.42 MHz	
Reception bandwidth		100 kHz	
Modulation		GFSK	
Receiver category		2	
Application related specifications			
General specifications		Reusable	
		Non-sterile	
Environmental conditions for operation, transport and storage			
	Operation	Storage	Transport
Temperature	+10 °C to +40 °C	+10 °C to +40 °C	-10 °C to +50 °C
Relative humidity	20% to 80% RH; non-condensing	20% to 90% RH; non-condensing	20% to 90% RH; non-condensing
Air pressure	785 to 1060 hPa	700 to 1060 hPa	700 to 1060 hPa
Max. operating height	≤ 2000 m	-	-

2.1.1.2 HemoPill Printer

The HemoPill Printer serves to document values measured by the HemoPill Receiver. It is designed solely for use with the HemoPill Receiver. It may only be connected to the HemoPill Receiver using the USB cable supplied. The accessories of the HemoPill Printer furthermore contain the power supply (rated output: 9.0 VDC. 4A) as well as the paper reels for the printer.

HemoPill printer is not a medical device. It must not be used in the patient environment.

Figure 6: HemoPill printer

2.1.2 Operating principle

The HemoPill acute has been specifically developed for detection of blood. The operating principle of the HemoPill acute relies on an optical sensor for alternating screening of the measuring gap in two different wavelengths emitted from LEDs (bicolor) on the other side of the measuring gap, opposite the sensor: red light at 700 nm and violet light at 415 nm (Figure 2-8). The optical sensor measures separately transmitted light intensity that passes the measuring gap, and the ratio of red to violet light transmission is calculated. The intensity of the measured light depends on the absorption characteristics of the medium in the measuring gap (e.g. blood). The measurement data is transmitted to the HemoPill Receiver via a radio link at a frequency of 434.42 MHz.

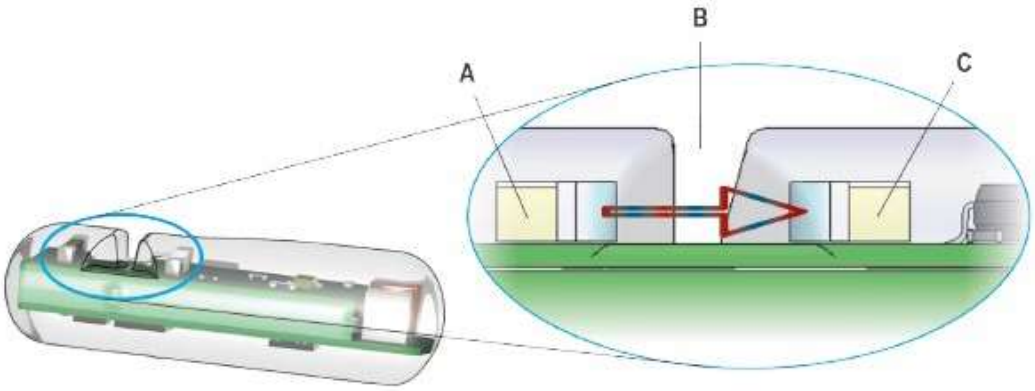

Figure 7: Sensor principle; A: Red and violet light source, B: sensor/measuring gap, C: Light sensor

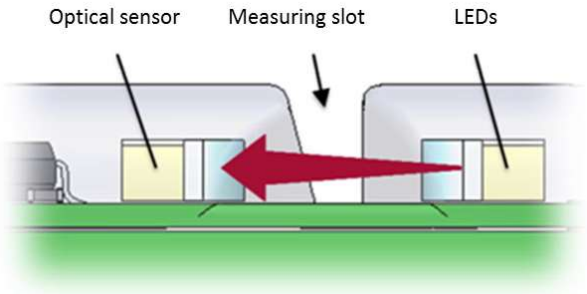

Figure 8: Sensor principle (side view)

2.1.2.1 Sensor principle

The transmission effects depend on the respective digestive tract content in the measuring gap. The two wavelengths being emitted by the bicolor LED have been selected to create a high sensitivity of the sensor

to the presence of blood inside the measuring gap. Blood shows a minimum light transmission rate (maximum light absorption rate) around 415 nm, and a maximum light transmission rate (minimum light absorption rate) around 700 nm (from about 650 nm into the infrared-range). These two wavelengths have been selected for the bicolor LED. Undiluted blood (venous, arterial) or hematin absorbs violet light at 415 nm approx. 1,000-times more strongly than red light at 700 nm. The light sensor has a comparable sensitivity at both of these wavelengths.

The sensor operation follows a fixes sequence:

- First, the red LED (700 nm) is activated, and the resulting voltage signal at the light sensor, indicating the grade of absorption of red light, is digitalized (I_{red}) and stored. The red LED is deactivated subsequently.
- Second, the violet LED (415 nm) is activated, and the resulting voltage signal at the light sensor, indicating the grade of absorption of violet light, is digitalized (I_{vio}) and stored. The violet LED is deactivated subsequently.
- Third, the sensor value Q is calculated on the board of the HemoPill acute capsule and transmitted to the HemoPill Receiver via radio link.

2.1.2.2 Sensor value calculation

The light sensor is translating the light intensity into a voltage, which is digitalized with a resolution of 10 bit. Therefore, the intensities I_{red} and I_{vio} are given as an integer value on a scale from 0 to 1023.

The actual sensor value Q is calculated on the basis of these intensity values and further a correction factor for compensation of gain and offset errors of the intensity measurement. The correction factor is determined during production for each HemoPill acute capsule individually and stored in the non-volatile memory of the capsules. The correction factors are K for the gain error, and $I_{leak,red}$ and $I_{leak,vio}$ fo the offset errors of the two LED wavelengths.

A gain error can be caused by e.g. variances in the characteristics curves of the LEDs, the resistors or the voltage supply of the HemoPill acute capsule as well as variance of the surface structure of the encapsulation in the area of the measuring gap. An offset error can be caused by variances in the gap manufacturing that might allow light to reach the light sensor without passing the measuring gap, e.g. if the depth of the gap does not reach the printed circuit board (PCB) which is covered by a light blocking layer.

The sensor value Q determines the ration between the grade of absorption of violet light and the grade of absorption of red light be the medium or fluid within the measuring gap. For example, if the absorption of violet light is ten times higher than the grade of absorption of the red light, the sensor value Q is 10. A detailed description of the calculation method of is given in the document “002_OVE_HP_Quotient calculation_Rev03_2018-04-06” in Volume 002.

$$Q = I_{corr2,red} / I_{corr2,via}$$

On the display of the HemoPill receiver the HI-value (short for HemoPill Indicator) is presented to the user. The sensor value Q is not appropriate for usability reasons, as the quotient requires a logarithmic scale to be read and interpreted in a way that it is clinically useful. Therefore, the HI-value, which ranges between 0 and 1.5 on a linear scale, is used. It is calculated as follows:

$$HI = 0.5 \times \log_{10}(Q)$$

The resulting decimal values are rounded down to have one decimal number (e.g. 0.88 = 0.8, 1.31 = 1.3). by rounding down, the HI-value has the same clinical significance as the quotient (e.g. a quotient of Q = 99 corresponds to a HI-value of HI = 0.9, therefore both are not crossing 100 and 1.0, respectively).

If the measuring gap is filled with blood, violet light can be almost completely blocked, while red light passes through the sensor gap almost entirely unimpeded. In this case, the HI-value can reach its maximum of 1.5.
Other foodstuffs can return a HI-value of up to 0.7 in individual cases. In empty stomachs the sensor can come into contact with undiluted bile as it passes through the stomach passage. This can lead to a HI-value of approx. 1.0. Several substances have been tested in an animal study, see Volume 005.

2.1.3 Clinical application

For intended examination, the detection of blood in the upper gastrointestinal tract, the patient swallows the HemoPill acute capsule (after activation) ((1) in Figure 2-9). The capsule must be taken with at least 100 ml water, which aids swallowing and promotes the suspension of blood. The HemoPill acute continuously sends measurement data which are received and recorded by the HemoPill Receiver ((2) in Figure 2-9). Measurement data are displayed on the HemoPill Receiver for interpretation by the user ((3) in Figure 2-9). After the data acquisition procedure, the data can be printed using the HemoPill Printer.

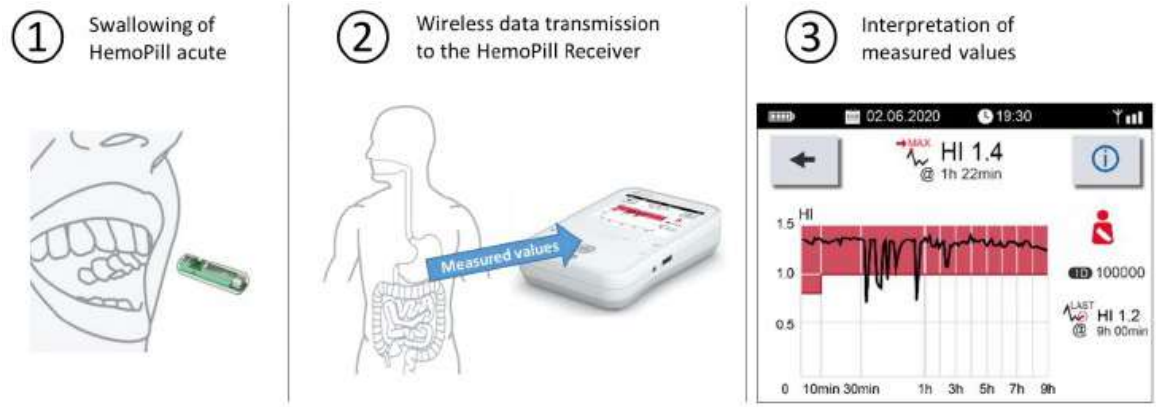

Figure 9: Operation principle of the HemoPill acute system

The HemoPill acute continuously send approx. 5 measured values per minute to the HemoPill Receiver. The duration of the measurement is approx. 9 hours from activation of the HemoPill acute. The values measured by the capsule are displayed numerically and as a curve diagram on the display of the HemoPill Receiver (Figure 2-10). Furthermore, the capsule ID, which is individual for each individual capsule, is shown on the display, ensuring an allocation to the patient. The capsule ID is indicated directly on the blister packaging of the capsule. The separately enclosed patient labels (four stickers) serve the document in the patient file and do also include the capsule ID.

The numerical display shows the maximum HI value (^{MAX}HI) (see (1) in Figure 2-10) and the last measured value (^{LAST}HI) (see (2) in Figure 2-10)). The respective measuring time is located below. ^{LAST}HI is updated with each measured value received (about 5 times per minute). ^{MAX}HI updates every minute during the first hour, after the first hour until the 9th hour about every 8 minutes. The ^{MAX}HI value is also plotted as a curve over time (Figure 2-10). By pressing the information button (see (3) in Figure 2-10) information on interpreting the HI values are shown.

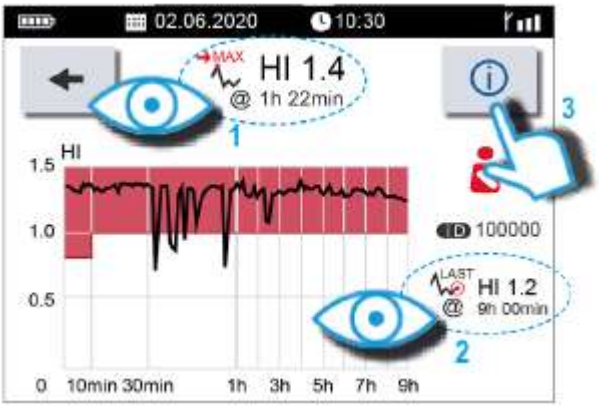

Figure 10: Information on the display of the HemoPill Receiver

For interpretation of the HI values the following procedure is recommended:

1. First, interpret the maximum HI value within 10 minutes from swallowing the HemoPill acute, see Table 3.
2. Then interpret, independently of this, the maximum HI value in the further course of the measurement (≥ 10 minutes after swallowing), see Table 4.

Table 3: Interpretation of the HI value within 10 minutes after swallowing

HI	**Within 10 minutes after swallowing**
< 0.8	**Negative** Liquid blood (or hematin) was not detected. NOTE: Blood may still be present but may be highly diluted or exist in unsuspended, adherent coagula.
≥ 0.8	**Positive** Liquid blood (or hematin) was detected.

Table 4: Interpretation of the HI value ≥ 10 minutes after swallowing

HI	**> 10 minutes after swallowing**
< 1.0	**Negative** Liquid blood (or hematin) was not detected. NOTE: Blood may still be present but may be highly diluted or exist in an unsuspended, adherent coagula.
≥ 1.0	**Positive** Liquid blood (or hematin) was detected.

The HemoPill is excreted through being passed naturally by the patient. To check that this has occurred, the transmission function of the capsule is active for at least 21 days.

2.2.2 Device Category

The subject device is currently part of a DeNovo classification request. Thus, the specific device category is not yet established. If the DeNovo request is granted, a product code is assigned.

2.2.3 Non-significant risk rationale

Under 21 CFR 812.3(m), a significant risk device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject.
  NSR Rationale: The subject device is not an implant.

- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject.
  NSR Rationale: The subject device is not intended for supporting or sustaining human life.

- Is for use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to health, safety, or welfare of a subject
  NSR Rationale: Within the context of this clinical trial, any eligible trial participant is already scheduled for endoscopy based on the individual clinical presentation. The HemoPill acute is ingested prior to endoscopy and does not disrupt the clinical course of the trial participant. HemoPill acute data is retrospectively analyzed and compared to endoscopic findings. The data is however not used for risk stratification and does not influence the further clinical course of a given trial participant. The subject device is therefore not of substantial importance in diagnosing, curing, mitigating, or treating disease. The subject device does not further prevent impairment of human health and does not present a potential for serious risk to health, safety, or welfare of a subject.

- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
  NSR Rationale: The subject device does not present a serious risk to the health, safety, or welfare of a subject. Results from prior studies are provided in chapter 2.1. The described publications report on a total of 65 patients. Within these publications, no HemoPill acute capsule related complications were reported. One patient described discomfort while swallowing the HemoPill acute capsule (Brunk T et al., 2021).

2.2.4 Preclinical Data

Ovesco performed various bench tests on the HemoPill acute which are briefly described in Table 7.

Ovesco further conducted a volunteer trial and animal testing to investigate HemoPill performance. These are described in the following in more detail:

2.2.4.1 Volunteer trial

Prior to market entry in Europe, feasibility testing was performed in a volunteer trial to evaluate the following aspects (Table 5):

Table 5: Aspects and acceptance criteria of the volunteer trial

No.	Aspect	Acceptance criteria
1	Direct, reproducible proof of presence of blood in stomach	The measures sensor value during the course of the test must react specifically and sensitively to the presence of blood
2	Quasi-continuous collection of measurement data	Data transmission from the capsule to the receiver unit must be quasi-continuous at a measurement frequency > 1/min.

No.	Aspect	Acceptance criteria
3	Operating time	The passage duration and therefore the operating time of the capsule must be at least 4 hours.
4	Introduction of capsule by swallowing	Capsule must be able to be swallowed without any problems.

The aspects described in Table 5 were investigated through a series of 8 tests. Before testing started the test subject had an empty stomach (no ingestion of food or drink in at least 4 hours before start of the test). Three different meal scenarios ((1) empty stomach, (2) breakfast, (3) dinner) were planned and the capsule was swallowed a few minutes after the respective meal and blood ingestion (with different concentrations). The dose of blood ingested consisted of autologous blood from the vein of the respective test subject. No additives were added to the blood, which was ingested immediately after it was drawn.

The data was acquired over the time period from the swallowing of the capsule to its expulsion.

Results summary
All capsules were expelled naturally from the test subject's body. Passage duration was in average 79h 01 min (standard deviation: 32h 17min; Max: 129h 58min; Min: 51h 25 min). The minimum measurement duration required (4 hours) was vastly exceeded in all tests.

Several observations were made for the different scenarios. In general, it was shown that the amount of food in the stomach influences the blood detection. In all scenarios with blood ingestion, the presence of blood was shown by the HemoPill acute.

In all 8 tests, swallowing of the capsule was possible without any problems. There were no complications. Bearing in mind that only one test subject was included in the test, it can be stated that neither size nor form of the capsule lead to any limitations with regards to swallowability of complications.

The measurement interval was set to about 1 measurement every 4 seconds. Reception quality was adequate, so that essentially all measured values were recorded. Quasi-continuous collection of measurement data was achieved during all 8 tests.

All acceptance criteria were met.

2.2.4.2 Animal trial

The purpose of the pre-clinical animal study was to assess the sensitivity and specificity of the HemoPill in detection of upper digestive bleeding by means of an elaborate and realistic bleeding model (feasibility study).

Since bleeding cannot be spontaneously induced in the animal by any means, a pre-operated model (pig) was used. Within the animals' stomach, an artificial bleeding site was created: A small laparotomy was performed, a silicone tube was inserted into the gastric cavity and fixated to ensure it remained in place. The end of the tube was tunneled through the subcutaneous tissue of the animal to the area of the pig's neck. This setting allowed the administration of blood from outside into the gastric cavity with variable parameters with regard to blood amount and speed of flow.

The study comprised 10 animals (4 animals for the pilot phase and 6 animals for the main trial) and was performed from October 2011 until August 2014.

The animal trial for the HemoPill has been conducted over a longer period during the development of the HemoPill acute capsule. Therefore, the HemoPill acute capsule and the receiver used for this animal study were prototypes. However, the sensor principle (red vs. violet wavelength, distance between the optical components, position of the measuring gap, as well as the potting material and coating) is unchanged in the final HemoPill capsule compared to the one used in the animal study. Therefore, the differences of the HemoPill acute capsule and Receiver have no negative impact on the quality of this animal study.

In clinical practice the HemoPill acute is swallowed by the patient. However, for this animal study, the HemoPill acute capsule stayed in the stomach for multiple episodes to maximize the data collection. For attaching the HemoPill capsule to the gastric wall for a period of 14 days, the HemoPill acute capsule was fixed to an OTSC clip prior to the intervention and implanted into the stomach endoscopically. Measured data was transferred to the receiver.

Each individual experiment started with endoscopic implantation of the HemoPill, and laboratory animals received the tube for bleeding simulation in the same session. In each animal two HemoPill capsules were implanted at two different locations in the gastric cavity, one in the closer proximity of the gastric bleeding site (entry of the bleeding tube) and one in the gastric antrum. The purpose was to evaluate if sensitivity varies by location. After implantation of the HemoPill the animal was followed and during an observational period of 14 days bleedings were simulated twice a day in order to evaluate the detectability of blood.

The influence of different modalities of food intake (fasting, noodle soup, potato mash and premade mash for infants, occasionally, in the pilot phase of study, high-caloric Fresubin was added to the food) on the detectability of blood by the HemoPill was investigated. The different food types were chosen to simulate liquid food (noodle soup) or more solid food (mashed potatoes, intending to imitate chewed food). For each animal, the feeding and bleeding test followed a specific test set-up. The test set-up und animal preparation are depicted in Figure 11.

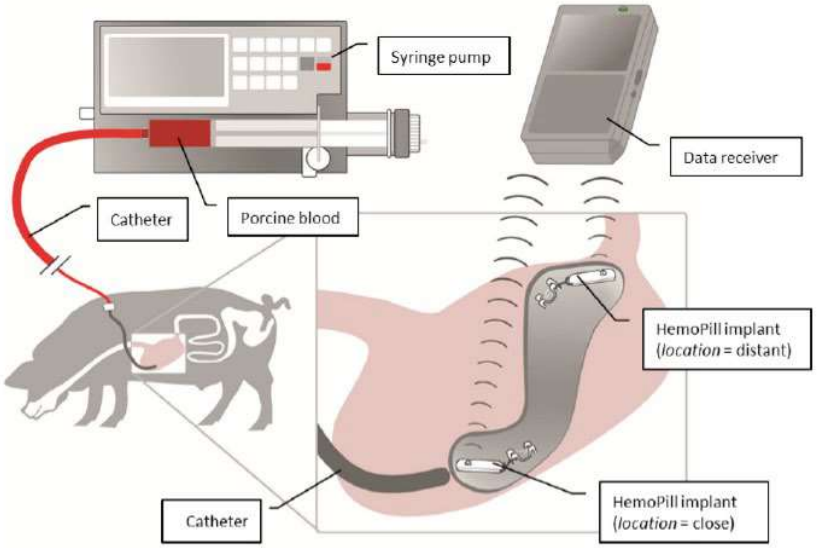

Figure 11: Experimental set up for simulating gastric bleeding in a porcine model

Total amount of bleeding tests is described in the following Table 6:

Table 6: Total number of bleeding tests during the animal trial by type of food and simulated bleeding intensity.

	12 ml/hour	60 ml/hour	300 ml/hour
No food	19	19	--
Noodle soup	19	20	15
Potato mash	17	16	15

The study demonstrates the capability of the HemoPill sensor to detect blood with high sensitivity and specificity values (typically > 80 %). The prototypical HemoPill was robust against food artifacts. Evaluation metrics of true positive, true negative, false positive, and false negative are to be clinically established by the proposed clinical trial at NYU Langone.

2.2.4.3 Bench testing

In the following, performance testing conducted with the HemoPill is briefly described:

Table 7: Performance testing conducted with the HemoPill

Title and objective	Acceptance criteria	Results
Lifetime test Confirmation of a minimum runtime of 21 days in a physiological environment and minimum measurement time of 9 hours.	- The HemoPill capsule sends data packets for at least 21 days. - A runtime of 21 days, after two-year storage time can be derived from the storage time and electrical characteristics (test method: exploration). - The measurement time (active application mode 1) is at least 9 hours.	The average HemoPill acute runtime were 36.77 days (standard deviation: 2.48 days). Thereby, the minimum average runtime after two-year storage could be calculated and resulted in a minimum average runtime of 34.86 days. The test results showed an average measurement time (active application mode 1) of 28.1 hours (standard deviation: 0.55 hours). All acceptance criteria were met
Sensor performance Each HemoPill capsule (n = 22) was submerged into a blood solution (6.25 %). In order to generate a dark environment, the lid of the cup was closed as soon as possible. The capsule (in production made) performed ten measurements and transmitted the data	- A blood solution of 6.25 % leads to a signal (quotient) of at least 41. - In the defined dark environment, the	The results showed a mean maximum quotient of 423 (standard deviation = 174,8) and a mean maximum external light (EL_{max}) of 1 (standard deviation = 0.2). All acceptance criteria were met.

to the measurement computer, where the data was recorded by the sensor performance test software. The quotient was calculated based on the recoded data using the quotient calculation according to the specifications.	extraneous light is < 3.	
Chemical resistance after shelf life test was performed to verify the chemical resistance of the HemoPill acute capsule in a worst-case scenario at the end of the shelf life. The test was performed with the final HemoPill capsule with 11 samples. Initial sensor performance testing was followed by a 45 -day acidic environment test. Then, a second sensor performance test was conducted. Initial performance testing served as reference.	The quotient resulting from the measurement of a 6.25 % blood dilution (in water) reaches 41 or more after the capsule was chemical stressed in total for 45 days (pH 1.1 – 1.3).	All capsules showed a signal (quotient) > 41 when exposed to a blood-water dilution of 6.25 %, before and after chemical stress.
Chemical resistivity Parylene C The chemically inert properties of Parylene C on the actual subject device in a simulated intended use (worst case: pH 1.0 – 1.3 for up to 60 days) were investigated. Three capsules were subjected to simulated gastric fluid for 60 days, three capsules for 30 days and three capsules were not submerged in gastric fluid as reference.	- After the simulated gastric fluid treatment, no visible damages or changes on the capsule surface are visible. - The thickness of the Parylene C layer is within the specified range of 12 µm ± 20 % on the analyzed position.	Within the chosen methodology, no difference between capsules that were exposed to chemical stress according to a worst case scenario and reference capsules from the same batch without exposure have been observed.
Chemical reliability Capsules implanted in pigs for the animal trial described in chapter 2.2.4.2 were explanted after the trial had concluded. Microscopic and macroscopic analysis of the capsule surface was performed.	- No damage of capsule surface, e.g., scratches, notches, holes, splitting. - No capsule staining through the penetration of liquids inside of the capsule.	The test shows that the HemoPill acute is able to operate safely in the harsh chemical environment of the stomach. The capsules showed no discoloration that would alter the sensor performance, nor did any defects on the encapsulation appear. The acceptance criteria were met for all 17 samples, thus the chemical resistance of all 17 capsuled could be verified.
Mechanical strength Capsule structural integrity against chewing. Exposure to 300 N chewing simulation with a genuine tooth, which is twice the normal human chewing	Set Up 1 “Tooth”: No disintegrating damages to the HemoPill after	Relevant damage to the capsule or exposure of electronic components due to biting / chewing is improbable since, even when assuming a high bite force of 300 N for a human molar, no

force. Second set up with metal wedge and force increase until complete disintegration	applying 300 N five times. Set Up 2 "Wedge": No disintegration of the HemoPill below 600 N	damage that would comprise the capsule integrity was observed in this test. Regular voluntary bite force in humans is at about 70 to 150 N. Disintegration in set up 2 occurred at application of 1,800 N.
Intestinal passage Simulated GI-passage: Simulated stomach milieu for 41 hours; simulated intestinal milieu for 653 hours. Visual inspection and functional testing after exposure.	The integrity of the capsule measured by the appearance of any alterations of the encapsulation (defects, discolorations, etc.) is uncompromised. The capsules must also be successfully activated to confirm normal operability of the device after the stress test.	The safety of the device is maintained throughout the entire passage of the GI tract and the exposure to the different environments. Furthermore, all capsules were fully operational, thus, the passage did not lead to any alterations of the encapsulation.
Argon Plasma Coagulation stress test Investigation of HemoPill material behavior in case high frequency hemostasis is performed in close proximity to the HemoPill. Test performed ex vivo in a porcine stomach.	Insulation material does not deteriorate when HF-hemostasis procedure takes place in close proximity to the capsule.	No damages to the insulation of the capsule could be observed. There were no signs of perforation or discoloration. The acceptance criterion was met.

2.2.5 Clinical Data to Date

Publications of clinical data on the use of HemoPill in Europe is described in chapter 2.1. Prior to market entry in the EU, a clinical trial was conducted which is described in the following:

Ovesco conducted a prospective non-randomized, single-center, open-label study to investigate feasibility and safety of the HemoPill acute in patients with symptoms of UGIB. The primary aim of the study was to investigate feasibility and safety of the device in a clinical setting. All patients underwent endoscopy within 12 hours after capsule ingestion. Sensor data from the capsule within 10 minutes after ingestion were compared with endoscopic findings.

From April 2015 to February 2016, 30 consecutive patients with symptoms of acute UGIB were included.

Objective and clinical endpoints of the investigation were:
- Safety of the capsule
- Feasibility of bleeding detection
- Evaluation of threshold values for the sensor capsule data
- Sensitivity and specificity of the sensor capsule data

The clinical investigation population were patients with indications on esophagogastroduodenoscopy (ESG) and with suspected upper GI bleeding. Inclusion criteria were:

- Clinical suspicion based on anamnestic statements of clinical symptoms such as hematemesis, tarry stools/melena
- Alert and conscious patient
- Written informed consent
- Age ≥ 18 years and ≤ 80 years.

The capsule was swallowed by the patient and an external study receiver recorded the capsule sensor data for 4 consecutive hours. Patients underwent endoscopy within 12 hours after capsule ingestion. Afterwards, the endoscopic findings (endoscopy pictures and patient's endoscopy record) were compared to the sensor capsule data results. Capsule excretion was monitored for up to 4 days. If excretion was not recorded during that time, a follow up examination of the patient would have been conducted after 10 days.

30 consecutive patients with symptoms of acute UGIB were included; 28 were eligible for analysis. All together the HemoPill acute was found to be feasible and safe.

Only n=1 serious adverse event occurred during the study which, according to physicians, had no causal relationship to the use of the investigational device. Capsule ingestion was well tolerated in all patients. Passage and excretion of the HemoPill acute was observed without any adverse events or complaints by the patients. Furthermore, no adverse device effects or device deficiencies could be observed during the trial, thus the sensor capsule and the study receiver can be considered as safe devices that performed as expected in all n=30 subjects.

n=1 human failure occurred during the read-out procedure of the sensor capsule data from the study receiver and was due to the wrong order in manual program execution. This failure is not relevant for the final receiver device because the read-out procedure was automated for the final device.
Sensitivity and specificity assessment of the HemoPill acute in detecting the presence of blood in the upper GI tract proved to be favorable in patients with > 20 ml of blood: sensitivity = 100 % (95 % confidence interval (CI), 54 to 100 %) and specificity = 83 % (95 % CI, 60 to 95 %). However, comparatively wide 95 % confidence intervals must be considered due to the low subject number included in the analysis.

2.3 Rationale

Gastrointestinal bleeding is common. Its clinical spectrum ranges from anemia, which can only be detected in laboratory tests, to fulminant bleeding with shock. Gastrointestinal bleeding requires a differentiated approach from the first suspicion to acute care and prevention of renewed bleeding. A number of endoscopic (EGD, colonoscopy, device-assisted enteroscopy, and capsule endoscopy) as well as non-endoscopic procedures (CT angiography, angiography, scintigraphy) are available to localize the source of bleeding.

2.3.1 Epidemiology

Upper gastrointestinal bleeding (UGIB) is defined as intraluminal bleeding derived from a source proximal to the Treitz ligament (Franco MC et al., 2015). Acute UGIB is a common condition worldwide, with an estimated annual incidence of 40 to 150 cases per 100,000 population. Acute UGIB frequently leads to hospital admission (more than 300,000 inpatient admissions in the US annually) and is associated with significant morbidity and mortality, in particular in the elderly (Chuang CH et al., 2020; Cai JX et al., 2018; Gralnek IM et al., 2015). The annual incidence of UGIB indicates that there are great geographical variations, which can be explained due to various factors including the different definitions of UGIB, population characteristics, different prevalence of drug-induced ulcers and Helicobacter pylori infection

(ISG, 2014). However, bleeding from the small intestine is a relatively rare event with 5 – 10 % of all GI bleedings (Gerson LB et al., 2015).

The severity of UGIB is positively correlated with the amount of blood loss. Mixing of blood with gastric contents and feces, in addition to incomplete discharge of accumulated blood, makes it difficult to accurately judge the amount of blood loss according to the volume of hematemesis or melena. Therefore, the volume of blood loss is often determined based on clinical composite indexes such as peripheral circulatory changes caused by hypovolemia (e.g., heart rate, blood pressure) and the shock index rate (heart rate/systolic blood pressure), which are important indicators to determine the volume of blood loss (Bai Y and Li ZS, 2016).

The 2015 German AWMF S2 consensus-based guideline on the quality requirements in gastrointestinal endoscopy (German: S2k Leitlinie Qualitätsanforderungen in der gastrointestinalen Endoskopie, 2015 "Guideline: Quality specifications in gastrointestinal endoscopy") by Denzer and colleagues states that predictive factors for severe UGBI are an underlying tumor disease or liver cirrhosis, hematemesis, hypovolemia and hypotension, as well as shock and an Hb < 8 g/dl. Further, with a strong consensus, the guideline recommends that severe UGIB and increased mortality must be taken into account if certain factors are present, such as additional comorbidities (such as heart, liver, tumor disease), limited clinical and laboratory parameters (Hb < 8 g / dl, INR < 1.5, albumin < 3g / dl, RR sys ≤ 90 mmHg) (Denzer U et al., 2015).

The use of risk scores has been recommended to stratify patients into those at higher or lower risk of poor outcomes. Those at very low risk may be managed as outpatients (Stanley A and Laine L, 2019). A primary goal of initial assessment is to determine whether the patient requires urgent intervention, e.g., endoscopy, surgical intervention or transfusion, or can undergo delayed endoscopy or even be discharged to outpatient management (Hwang JH et al., 2012). Elderly age, multiple comorbidities and hemodynamic instability indicate aggressive treatment (ISG, 2014). In geriatric patients, great care must be taken to obtain a thorough medical history and identify comorbidities. Determination of the etiology and severity of UGIB should be a high priority in light of current diagnostic and therapeutic advances, with consideration given to geriatric-specific causes. Lab tests that should be obtained in patients with acute UGIB include complete blood count (CBC), serum chemistries, liver function tests and lactic acid and coagulation studies. An increased BUN/serum creatinine ratio is often identified in patients with UGIB. In addition, serial electrocardiograms and cardiac enzymes may be indicated in patients who are at risk for a myocardial infarction (Stowlow E et al., 2021).

2.3.2 Scoring systems

A number of scoring tools have been developed for predicting outcomes following acute UGIB, with the Rockall Score and the Glasgow-Blatchford Score being the most widely evaluated and adopted. However, no single tool has been shown to excel at predicting all relevant outcomes in UGIB, including re-bleeding, need for intervention and mortality (Gralnek IM et al., 2015; Al Dhahab H et al., 2013; Ramaekers R et al., 2016).

The Rockall Score was primarily developed for the assessment of mortality after 30 days of UGIB (Franco MC et al., 2015). The Rockall score can be calculated using both pre-endoscopic (clinical Rockall) and post-endoscopic data. The full Rockall Score incorporates both pre- and post-endoscopic parameters. It predicts the risk of re-bleeding and mortality using age, the presence of shock (systolic blood pressure < 100 mmHG and heart rate > 100 beat/min), comorbidities and endoscopic diagnosis along with endoscopic findings, such as blood in stomach, adherent clot, visible vessel, spurting vessel, pigmented spot or no stigmata (Table 23). The Rockall Score ranges from 0 to 11. Patients with risk scores of 0 and 1 have a low

incidence of re-bleeding and no associated mortality, allowing the identification of patients at low risk for complications and for early discharge (Al Dhahab H et al., 2013).

Table 8: The full (post-endoscopy) Rockall Scoring System (for a patient with acute upper gastrointestinal bleeding, add up scores at the top of the columns for each of the variables to derive the total risk score*) (Dworzynski K et al., 2012).

	Score*			
	0	1	2	3
Age†	<60	60-79	≥80	
Shock†	No shock (systolic blood pressure ≥100, pulse <100)	Tachycardia (systolic blood pressure ≥100, pulse ≥100)	Hypotension (systolic blood pressure <100)	
Comorbidity†	No major comorbidity		Cardiac failure, ischaemic heart disease, any major comorbidity	Renal failure, liver failure, disseminated malignancy
Diagnosis‡	Mallory-Weiss tear, no lesion identified, and no stigmata of recent haemorrhage	All other diagnoses	Malignancy of upper gastrointestinal tract	
Major stigmata of recent haemorrhage‡	None or dark spot only		Blood in upper gastrointestinal tract, adherent clot, visible or spurting vessel	

*The total score can range from 0 to 11, with a score of 2 representing the clinical cut-off, above which patients are considered to be at high risk of death or rebleeding.
†Scores are calculated on admission.
‡Scores are added after endoscopy.

The Glasgow Blatchford Score (GBS) was developed to identify a patient's need for treatment in order to assist the clinical management of patients presenting with UGIB. The GBS ranges from 0 to 23 and uses data on blood urea and hemoglobin levels, systolic blood pressure, pulse, presentation with melena, presentation with syncope, history of hepatic disease and history of heart failure (Table 9; Hwang JH et al., 2012). A GBS of 0 predicts a 0.5 % risk for needing subsequent intervention, thus, early discharge and outpatient follow-up (Al Dhahab HA et al., 2013). The European Society of Gastrointestinal Endoscopy (ESGE) recommends the use of the GBS for pre-endoscopic risk stratification (Gralnek IM et al., 2015).
Table 9: Glasgow-Blatchford Score (GBS) (Gralnek IM et al., 2015).

	Points
Systolic blood pressure, mmHg	
100 – 109	1
90 – 99	2
< 90	3
Blood urea nitrogen, mmol/L	
6.5 – 7.9	2
8.0 – 9.9	3
10.0 – 24.9	4
≥ 25.0	6
Hemoglobin for men, g/dL	
12.0 – 12.9	1
10.0 – 11.9	3
< 10.0	6
Hemoglobin for women, g/dL	
10.0 – 11.9	1
< 10.0	6
Other risk variables	
Pulse ≥ 100	1
Melena	1
Syncope	2
Hepatic disease	2
Cardiac failure	2

TOTAL GBS _____
GBS restricted for use only in nonhospitalized, ambulatory patients
Risk variables measured at time of patient presentation
GBS = 0 – 1 denotes "low-risk"

The AIMS-65 scoring system provides a more geriatric-adjusted score and may be a useful addition to the risk-stratification approach in identifying high-risk patients. AIMS-65 assigns one point for each of the following: albumin < 3 g/dl, international normalized ratio (INR) > 1.5, alteration in mental status, systolic blood pressure (SBP) ≤ 90 mmHg, and age ≥ 65 years. These values are readily obtainable from patient monitoring and labs in the emergency department. Recent studies suggest that this system may provide a more accurate prediction of in-hospital mortality, need for ICU admission, and length of hospital stay. As referenced by Stolow and colleagues, Robertson et al. found that a score > 3 was considered high risk with a mortality of 12.1 % compared with 1.6 % in the lower risk group ($p < 0.001$). As referenced by Stolow and colleagues, Kawaguchi et al. showed mortality to be as high as 33 % in patients scoring 4 - 5. Directed therapeutics should be based on the evaluation of etiology, comorbidities, and risk. While the International Consensus Group (ICG) did not recommend the use of the AIMS-65 score for risk assessment, its recommendation was based on low quality of evidence, and therefore, more prospective studies are needed to determine its true utility in the geriatric population (Table 25, Stolow E et al., 2021).

Table 10: The AIMS-65 scoring system. Score 1 point for each of the categories. Add the points recorded to find the total score. The in-hospital mortality rates by score are: 0: 0.3 %, 1: 1.2 %, 2: 5.3 %, 4: 16.5 % 5 24.5 % (source: Stolow E et al., 2021).

Risk factors	Score
Albumin <3.0 g/dl	1
INR>1.5	1
Altered mental status	1
Systolic BP≤90 mmHg	1
Age>65 years	1

2.3.3 Summary

While the above-mentioned scoring systems and general clinical presentation of a patient are considered, approximately one third of all endoscopic interventions for suspected UGIB are inconclusive. This is deemed acceptable as patient risks from endoscopy are known and rare. Conducting an endoscopy on a patient that does not require one is considered safer than potentially missing a patient who would have needed endoscopic work up. HemoPill is designed to provide information on the acute presence or absence of blood/hematin in the gastrointestinal lumen. This piece of information has been shown to be valuable in the further risk stratification in patients with suspected UGIB. As described by Brunk T et al., a negative HemoPill measurement influenced the further clinical course of patients in 72 % of cases, mostly by shifting from emergency/urgent endoscopy to elective endoscopy. All HemoPill negative patients who did receive endoscopic work up did not show bleeding stigmata. The proposed clinical value of the HemoPill is that allocation of endoscopic resources can be more adequately planned which is a considerable financial benefit to the patient as well as the health care system. That being said, HemoPill is not intended to replace endoscopic procedures. Endoscopy does require patient preparation but has ultimately various curative possibilities in case pathologies are found. HemoPill solely provides information on the acute presence of blood/hematin in an otherwise unprepared patient in a real time fashion – no more, no less. The reliability of the measurement could already be shown in real-world use of the subject device in the EU. The value of the information on the presence or absence of blood/hematin in the GI lumen needs to be assessed within the context of the broader clinical presentation of a given patient and thus may differ from case to case.

Hypothesis:
Relation between HemoPill measurements to subsequent endoscopic findings show an adequate sensitivity and specificity for the HemoPill measurement regarding presence or absence of blood in the GI lumen.

Justification for route of administration and selection of study population:
Only patients already scheduled for an endoscopy on the basis of suspected UGIB are eligible for trial participation. HemoPill ingestion is embedded into the already fixed schedule for endoscopy. Endoscopy is not delayed by trial participation. HemoPill measurements do not influence the clinical course of a trial participant. Thus, no risks from false (e.g., false negative or false positive) measurements arise.

Rational for endoscopy as a control measure:
While there are differences between the function principle of the HemoPill and endoscopy, endoscopy is the most suitable control measure. UGIBs are volatile events as activity of a bleeding can be spontaneous. HemoPill is able to detect fresh blood and hematin within the GI lumen, thus solely requires presence of blood or hematin which can stem from a currently inactive pathology.

Endoscopy is able to identify blood or hematin as well as associated pathologies. Thus, relation between a HemoPill measurement and endoscopic findings is generally possible. Even more so if latency between HemoPill ingestion and endoscopy is a controlled parameter.

The aim of this clinical trial is to further investigate HemoPill's capacity to determine presence or absence of blood/hematin in a clinical setting by comparing a HemoPill measurement with endoscopic findings. Patients eligible for trial participation are already scheduled for endoscopy for suspicion of UGIB. Thus, the HemoPill measurement is not considered for further risk stratification and only put in relation to endoscopic findings after the fact. To allow for a reasonable comparison of HemoPill measurement and endoscopic findings, latency between the two is controlled. However, as scheduling for endoscopy is already in place as a prerequisite for trial participation, planning of HemoPill ingestion is embedded into endoscopy schedule – thus, no delay to endoscopy is introduced. The patient always receives endoscopy as planned, regardless of trial participation.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

As the subject device is already marketed in the EU, foreseeable risks and complications provided in the instructions for use are:

- Aspiration of the capsule on ingestion
- Delayed excretion, or failure to excrete the capsule (capsule retention)
- Obstruction of the digestive tract
- Injury to tissue structures during the passage of the HemoPill acute through the digestive tract. In particular:
    - Injury to the mucosa
    - Bleeding, e.g., variceal bleeding
    - Perforations

The above-mentioned risks are generally associated with capsule endoscopy. So far, no case of harm to a patient from the use of the HemoPill has been reported.

Risks to participants by virtue or trial participation

- Immediate risks
    - Aspiration of the capsule on ingestion
    - Obstruction of the digestive tract
    - Injury to tissue structures during the passage of the HemoPill acute through the digestive tract. In particular:
        - Injury to the mucosa
        - Bleeding, e.g., variceal bleeding
        - Perforations
- Long-range risks
    - Obstruction of the digestive tract
    - Delayed excretion, or failure to excrete the capsule (capsule retention)

- Necessity of exposing human participants to above-mentioned risks
  The above-mentioned risks are generally associated with capsule endoscopy, e.g., video capsule endoscopy. As of today, no incidence of patient harm from use of HemoPill has been reported. Within the trial context, HemoPill is ingested in a closely supervised setting. Within the trial context, a HemoPill measurement does not influence the clinical course of a given trial participant. Thus, any hypothetical risks from false negative or false positive measurements are avoided.

  On the other hand, investigating HemoPill's capacity for reliably providing information on the presence or absence of blood in the GI lumen has the potential to better understand the clinical applicability of the device and provide information on the proposed clinical benefit. In case HemoPill shows to be a reliable and effective tool, it can be safely introduced into clinical routine and unfold its then identified potential.

- Value of the information to be gained outweighs the risks involved
  So far, HemoPill use has not resulted in any harm to a patient. The known risks are controllable and generally associated with capsule endoscopy. A risk from a potential false negative or false positive measurement does not apply within the context of the trial as the HemoPill measurement is disregarded in patient assessment. The value of a side-by-side comparison to endoscopy however further distinguishes the performance profile of the subject device. Scientifically sound determination of accuracy parameters is achievable with the proposed trial design. With these accuracy parameters adequately determined, the use of the HemoPill (once legally marketed) as well as interpretation of HemoPill measurement is tremendously facilitated. Introducing HemoPill into the clinical routine for risk stratification of suspected UGIB patients facilitates adequate allocation of emergency resources and potentially avoids unnecessary endoscopies altogether, as Brunk T. et al have shown.

- Rationale: Exclusion of alternative procedures
  HemoPill is compared to an endoscopy already scheduled regardless of trial participation. Ultimate goal of the trial is establishing accuracy parameters of the HemoPill measurement to provide data needed for an adequate risk evaluation. The HemoPill measurement is however disregarded for further patient evaluation. Thus, no alternative procedure is required as it would also not influence the further clinical course of a trial participant. The control method endoscopy is already indicated and scheduled as per NYU protocol and neither delayed nor prolonged by trial participation.

2.4.2 Known Potential Benefits

With regard to trial participation, no immediate potential benefits are expected for a trial participant. Long range potential benefits stem from an introduction of HemoPill into the US market. On the basis of then established accuracy parameters, adequate consideration of HemoPill measurements for risk stratification will potentially lead to avoidance of endoscopic procedures if overall clinical presentation permits, which is a considerable benefit to a patient. Improving risk stratification precision by taking HemoPill measurements into consideration introduces benefits the health care system in general as decision for urgent or elective endoscopies are made on the basis of additional relevant and previously unavailable information on the presence or absence of blood/hematin in the GI lumen.

HemoPill is designed to provide information on the presence or absence of blood or hematin in the gastrointestinal lumen. The measurement data is depicted graphically and numerically in real time and allows for immediate data evaluation based on the introduced measurement value threshold. Ingestion of the HemoPill acute capsule does not require patient preparation and usability testing as well as clinical use in Europe indicates easy use and data assessment. The information on the presence or absence of blood in suspected UGIB patients is usually only available from nasogastric tube aspiration. However, this procedure has major deficiencies and is associated with a mediocre sensitivity and specificity as well as discomfort to the patient. HemoPill acute ingestion on the other hand has not caused any such discomfort. The value of the information on presence or absence of blood or hematin in a patient with suspected UGIB has to be assessed within the context of the overall clinical presentation of said patient, e.g., scoring systems, blood samples, Hb value, blood pressure etc.

The real-world clinical benefit from HemoPill use is best described by Brunk T et al (see chapter 2.1). Here, a negative HemoPill measurement influenced the further clinical course of patients in 72 %: 40 % of patients were rescheduled from urgent to elective endoscopy, in 20 %, small bowel enteroscopy could be avoided and in 12 %, EGD could be avoided. No HemoPill negative patient has a clinically significant bleeding until discharge. In HemoPill positive patients, median time to EGD was 3 h 18 minutes (range: 12 min – 64 h 52 min), whereas median time to EGD (if performed) was 19 h 52 min (range: 1 h 45 min – 146 h 10 min), which beautifully presents the influence of a HemoPill measurement within the broader context of risk stratification in patients with suspected UGIB.

Further benefits from availability of the HemoPill were reported within the context of risk stratification under COVID-19 pandemic conditions. Elsayed I et al. report on three cases as described in chapter 2.1. The authors conclude that the sensor capsule might aid in decision-making during the COVID-19 pandemic. In patients with as yet unavailable COVID-19 test results, HemoPill might aid in determining the appropriate time for endoscopy. In patients who are positive for COVID-19 with suspected UGIB, HemoPill could help on deciding whether to perform an endoscopy or nor and thereby help minimizing risk of disease transmission.

3 Objectives and Purpose

3.1 Primary Objective

The objective of the study is to determine the clinical relation between the detection of blood in the GI lumen using the HemoPill acute (trial procedure) with the detection of bleeding / a bleeding source during an endoscopic examination (control procedure). The study is an intra-case control procedure.

4 Study Design and Endpoints

4.1 Description of Study Design

Patients are included according to the defined inclusion criteria and prepared for endoscopy. At the latest possible time before endoscopy, a HemoPill acute capsule is administered with a minimal amount of water. The HemoPill receiver is stored in a carrying bag. The transparent part of the bag over the display of the receiver is covered with tape. The LED light is left uncovered, so a successful signal transmission can be checked at any times. The investigator is unaware of the HemoPill acute measurement result until endoscopy has concluded. After a latency of minimum 20 minutes, maximum 60 minutes, endoscopy is performed as scheduled, identifying blood within the GI lumen, if present. A minimum latency is introduced to ensure HemoPill acute is able to make a measurement without interference from endoscopy, e.g., insufflation or endoscopic light.

The amount of blood identified in endoscopy is visually analyzed and pictures are taken. For the estimation of the amount of blood present in a patient, comparative images are provided. Assessment categories are: $x < 20$ mL and $x > 20$ mL. The detection threshold is introduced to provide a point of reference for the HemoPill acute detection rate.

Pathologies, if found, are treated as per clinical standard. HemoPill acute measurements regarding presence or absence of blood are put in relation to endoscopic findings.

Endoscopic images are further analyzed to determine the digestive state of the blood found as HemoPill acute is capable of detecting fresh blood or hematin. Blood digested to a point beyond hematin is no indicator for an acute bleeding pathology. The following foreseeable combination of events are described and allocated to “True Positive”, “False Positive”, “True Negative”, and “False Negative”.

- True positive:
  HemoPill acute measurement indicates presence of blood; Endoscopy identifies fresh blood or hematin in the GI lumen
- False positive:
  HemoPill acute measurement indicates presence of blood; Endoscopy does not identify fresh blood or hematin in the GI lumen.
- True negative:
  HemoPill acute measurement does not indicate presence of blood; Endoscopy does not identify fresh blood or hematin in the GI lumen in quantities > 20 mL; Minimum latency of 20 minutes achieved.
- False negative:
  HemoPill acute measurement does not indicate presence of blood in the GI lumen; Endoscopy identifies fresh blood or hematin in the GI lumen in quantities > 20 mL; minimum latency of 20 minutes achieved.

Patient recruitment goal is set at 50 patients as derived from statistical planning, including potential dropouts. The proposed clinical trial is a single-arm, single-center clinical trial. The control procedure endoscopy is applied in all trial participants as an intra-case relation of HemoPill measurement and endoscopic evaluation is performed.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

Clinical effectiveness endpoint

- Result Accuracy: Clinical relation between HemoPill acute measurement (trial procedure) and endoscopic findings (control procedure) according to the defined scenarios for “true positive”, “false positive”, “true negative”, “false negative” (see above, chapter 4.1).

4.2.2 Secondary Study Endpoints

Technical effectiveness endpoint
Technical success, defined as:

- Successful data transmission of the HemoPill acute to the HemoPill Receiver.

Safety endpoints:
Adverse events / complications associated with trial or control procedure, such as:

Trial procedure:

- Aspiration of the capsule on ingestion
- Delayed excretion, or failure to excrete the capsule (capsule retention)
- Obstruction of the digestive tract
- Injury to tissue structures during the passage of the HemoPill acute through the digestive tract.

Control procedure:

- Cardiopulmonary adverse events
- Infection
- Perforation
- Bleeding (iatrogenic)

These secondary endpoints were chosen as they potentially provide meaningful information on the safety (number and type of adverse events / complications) and performance (successful data transmission) of the subject device.

4.2.3 Exploratory Endpoints

Not applicable.

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Patient is scheduled for endoscopy due to suspicion of UGIB based on clinical and / or laboratory findings
2. Signed informed consent
3. Age ≥ 18 years
4. Willingness and ability to participate in the study procedure

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. The inclusion criteria cannot be met

2. Contraindications to the use of the HemoPill acute, such as:
   a. Known gastrointestinal obstruction, stricture, fistula, or diverticula
   b. Dysphagia or other swallowing disorders
   c. Pregnancy
   d. Incapacity to provide informed consent
   e. In patients with cardiac pacemakers and other implanted medical devices

5.3 Vulnerable Subjects

No vulnerable subjects are to be included in the clinical trial.

5.4 Strategies for Recruitment and Retention

The patient may be recruited from both inpatient and outpatient setting. Patient will be identified by our gastroenterology inpatient consult team when a consult for upper gastrointestinal bleeding has been suspected on admission or by an outpatient provider that is part of the study when they see the patient in their perspective clinics. Patients for suspected upper GI bleed will be asked by a study member of his/her willingness to participate in the study. The target number for subject recruitment is 50. The study team will not be using Epic as part of the recruitment process.

All subjects will be recruited from the PI and sub-investigators' practices or under their care in the inpatient setting. Potential subjects will be approached at one of their clinic visits by the PI, sub-investigator or research coordinator. Potential subjects will be approached after suspicion of a GI bleed led to the scheduling of endoscopy. Patient will be consented prior to scheduled endoscopy and sedation. Time between approaching potential subjects and onset of study procedures may vary as this depends on the scheduling of endoscopy. Scheduling for endoscopy is influenced by, e.g., urgency of the patient's situation and availability. It is not influenced by willingness or unwillingness to participate in the study. No recruitment materials are needed for this process.

5.5 Duration of Study Participation

From screening a likely trial participant to enrollment and to conclusion of the endoscopic procedure, usually 1 hours to 3 days elapse. Screening of a potential trial participant occurs after a NYU patient is scheduled for endoscopy for a suspected UGIB. Scheduling of endoscopy is at the attending physician's discretion and not within the scope of the trial. If patient screening is successful and informed consent is obtained, the study intervention phase starts approximately 20 minutes to 1 hour prior to endoscopy. The study intervention phase finishes with conclusion of endoscopy. No trial related follow-up is required. Scheduling further appointments to follow-up on endoscopic findings are not within the scope of the clinical trial.

5.6 Total Number of Participants and Sites

Recruitment will end when approximately 50 participants are enrolled. It is expected that approximately 50 participants will be enrolled in order to produce 43 evaluable participants. Enrollment will take place solely at NYU Langone Health- Tisch Hospital.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Decision for conducting endoscopy is reversed for any reason

5.7.2 Handling of Participant Withdrawals or Termination

Participant withdrawal or termination does not affect subject safety. If a patient withdraws from participating in the clinical trial, scheduling of endoscopy is not affected. He or she will continue to be scheduled for endoscopy regardless of trial participation and therefore receive appropriate clinical care. Participation may be terminated by an investigator. As the trial procedure does not provide any immediate clinical benefits for a participant (see chapter 2.4.2), he or she is not negatively affected by termination. As the trial uses an intra-case relation of HemoPill measurement and endoscopy, any trial participant is evaluated on the basis of his or hers HemoPill measurement and endoscopic findings. Withdrawal or termination does therefore not require replacement of any individual participant for intra-individual comparison. The total number of participants is determined based on statistical considerations.

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1.1 Acquisition

<u>Subject device</u>
The HemoPill acute and HemoPill Receiver are Ovesco Endoscopy AG products, CE-labeled and marketed in the European Union. The HemoPill acute is provided sterile with a shelf life of 2 years. The HemoPill Receiver is provided non-sterile and is neither required nor intended to be sterilized. Packaging, sterilization and shipping of the HemoPill acute and HemoPill Receiver follow established and verified processes as required for medical devices in the EU. These processes are not altered for the devices provided for clinical trial purposes. The final, finished devices are supplied to NYU by Ovesco USA Inc.

Control product
The control procedure is endoscopy. Endoscopes and associated devices and accessories are chosen as per site protocol, physician's discretion and provided by NYU.

6.1.2 Formulation, Appearance, Packaging, and Labeling

Subject device
HemoPill acute capsules are provided sterile in a transport carton containing single blister packaging and instructions for use. The HemoPill Receiver is provided non-sterile in a transport carton containing blister packaging and instructions for use. The subject device is provided by Ovesco USA Inc. Ovesco Endoscopy AG is the legal manufacturer of the subject device for the European market. For trial purposes, the subject device is to be considered as an investigational device. The subject device is available for human use in the EU and does not require alterations to meet the trial plan.

Control product
The control procedure is endoscopy. Endoscopes and associated devices and accessories are chosen as per site protocol, physician's discretion and provided by NYU.

6.1.3 Product Storage and Stability

Subject device
The HemoPill acute capsules are provided sterile in single blister packaging. As marketed devices, sterilization validation, transport simulation, aging etc. has been conducted. The sterile HemoPill acute capsule has a shelf life of two years. Information on storage conditions is provided on device labeling and used visuals are described in the instructions for use. The HemoPill acute capsules should be stored between 10°C and 30°C and protected from direct solar radiation. Relative humidity during storage should be between 20 % and 85 %, non-condensing.
The HemoPill Receiver is provided non-sterile. It has a service life of 10 years. Storage conditions should be:

- Temperature: between – 10°C and + 50°C
- Relative humidity: 20 % to 90 %, non-condensing
- Air pressure: 700 to 1,060 hPa

While storage temperatures may be as low as – 10°C, the HemoPill Receiver needs to acclimatize to room temperature is stored below + 10°C. Further information is provided in the instructions for use.

Control product
The control procedure is endoscopy. Endoscopes and associated devices and accessories are chosen as per site protocol, physician's discretion and provided by NYU. Respective storage conditions apply as indicated on the device labeling.

6.1.4 Preparation

Subject device
In the following the stepwise clinical use of the HemoPill acute is described

- Switching on the HemoPill Receiver
- Activation of the HemoPill acute using the HemoPill Receiver
- Establishment of a data connection between HemoPill acute and HemoPill Receiver
- Handing the activated HemoPill acute to the patient in the blister
- Swallowing of the HemoPill acute with a small amount of water

- Receiving and reading of measurement data (HI values) using the HemoPill Receiver
- Interpretation of the measured values by the user based on the information provided in the IFUs of the HemoPill acute and HemoPill Receiver (document A01)
- At the end of measurement, deactivation of the data connection with the HemoPill Receiver
- Natural excretion of the HemoPill acute by the patient

A detailed description on the handling of the HemoPill Receiver can be found in the respective instructions for use, provided as a separate document.

Control product
The control procedure is endoscopy. Endoscopes and associated devices and accessories are chosen as per site protocol, physician's discretion and provided by NYU. Use of endoscopy is clinically established, as are requirements for preparation.

6.1.5 Dosing and Administration

Subject device
The HemoPill acute capsule is switched on using the HemoPill Receiver as described in the instructions for use. A data connection between the HemoPill acute capsule and the HemoPill Receiver is established. Every trial participant receives a single, sterile, switched on HemoPill acute capsule for ingestion with a minimal amount of water. The HemoPill acute capsule is not to be chewed. Ingestions is timed under consideration of endoscopy scheduling. Minimum latency to endoscopy should be 20 minutes, maximum latency to endoscopy should be one hour. The HemoPill Receiver is operated by the investigators.

Control product
Application of endoscopy as per clinical standard. Scheduling of endoscopy follows NYU protocol and suspected urgency of a given patient's situation.

6.1.6 Route of Administration

Subject device
Administered orally by ingestion.

Control device
Oral introduction of endoscope.

6.1.7 Starting Dose and Dose Escalation Schedule

Not applicable.

6.1.8 Dose Adjustments/Modifications/Delays

Not applicable.

6.1.9 Duration of Therapy

From HemoPill acute capsule ingestion to start of endoscopy, a maximum of 60 minutes elapse. Duration of endoscopy depends on presence or absence of pathologies and time needed for treating pathologies if found.

6.1.10 Tracking of Dose

Not applicable.

6.1.11 Device Specific Considerations

Subject device

- Device size:
  - Length: 26.3 mm
  - Maximum diameter: 7 mm
  - Weight: 2 g
- Device model
  - HemoPill acute capsule: Software version 02.xx.yy
  - HemoPill Receiver: Software version 02.xx.yy
- Device settings and programming
  - HemoPill acute capsule: No settings or adjustments can be made during the trial. Software version 02.02.xx is implemented.
  - HemoPill Receiver: The HemoPill Receiver is used for activating a HemoPill acute capsule, for establishing a data connection between a HemoPill acute capsule and for displaying HemoPill acute measurements. Up to 50 data sets can be stored on the HemoPill Receiver. The HemoPill Receiver can be used to display, store, and delete data sets. The HemoPill Receiver cannot be used to alter or manipulate data sets.
- Frequency of exposure
  - HemoPill acute capsule: Once, duration of exposure from ingestion to excretion
  - HemoPill Receiver: Once, from establishing a data connection to a HemoPill acute capsule to conclusion of the measurement.

6.2 Study Agent Accountability Procedures

The subject devices are provided to NYU by Ovesco. Distribution of HemoPill acute capsule is within the responsibility of the investigators. For trial purposes, at least 50 HemoPill acute capsules and minimum 2 HemoPill Receivers will be provided to NYU. Requirements for adequate and safe handling are provided by described storage conditions. Unused products are returned to Ovesco Endoscopy AG.

6.3 Study Procedural Intervention(s) Description

Within the scope of the proposed trial, HemoPill acute capacity for providing information on the presence or absence of blood in the GI lumen is controlled by relation to an endoscopic intervention. Latency to endoscopy is controlled. The trial procedure HemoPill acute introduces ingestion of the HemoPill acute capsule by the patient as a procedural intervention. Endoscopy however is not a procedural intervention in the sense that a patient is subjected to endoscopy for trial purposes. Endoscopy is already scheduled for the trial participant to further investigate the suspicion of UGIB and for treatment of lesions if identified.

6.3.1 Administration of Procedural Intervention

The investigator activates the HemoPill acute capsule by using the HemoPill Receiver. A data connection to the HemoPill Receiver is established. The activated HemoPill acute, still within the blister, is handed to the trial participant for ingestion with a minimal amount of water. Ingestion is timed under consideration of the previously established scheduling for endoscopy. Between HemoPill acute ingestion and start of

endoscopy, a minimum of 20 minutes should have elapsed. No more than 60 minutes between HemoPill acute ingestion and start of endoscopy should elapse. A trial participant is subjected to one intervention.

6.3.2 Procedures for Training of Clinicians on Procedural Intervention

Investigators are trained in the use of the HemoPill acute capsule and HemoPill Receiver. Adequate training material is available. As the subject device is already marketed in the EU, usability data and user feedback are available, indicating a safe and easy use. For endoscopy, no additional training is provided. Investigators are however instructed to document finding of blood and/or hematin in the GI lumen if identified. A single investigator trained for estimating amounts of blood and/or hematin on the basis of endoscopic images will assess the amount of blood/hematin found. He or she will be provided reference images. He or she will be unaware of respective HemoPill acute measurements.

6.3.3 Assessment of Clinician and/or Participant Compliance with Study Procedural Intervention

Not applicable.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

Trial specific procedures are only related to the use of the HemoPill acute. With relevance to the patient is HemoPill acute capsule ingestion. While endoscopy is performed as per clinical standard, additionally, images of blood or hematin are taken.

Only patients scheduled for endoscopy for suspicion of UGIB are eligible for trial participation. Suspicion of UGIB is established as per site protocol and/or physician's preference. After suspicion of UGIB is established and endoscopy scheduled, eligible patients are approached. Adequate patient information is provided. Only if informed consent is acquired, inclusion criteria are met and no exclusion criteria apply, may a patient enter into the trial as a trial participant.

7.1.2 Standard of Care Study Procedures

Standard of care procedures are:

- Clinical and laboratory evaluations as per standard of care, including but not limited to, complete blood count, and initial consultation
- Endoscopy: As a diagnostic as well as curative tool for UGIBs, endoscopy is applied in all patients to investigate a suspicion of UGIB. If a pathology is found, it is treated as per clinical standard. If blood or hematin are found, images are taken for later volume evaluation.

7.2 Study Schedule

7.2.1 Screening

In the following, procedures and evaluations necessary for assessing whether a participant meets eligibility criteria are described:

- In case a physician's patients is suspected of having a UGIB and endoscopy is scheduled, an investigator is contacted and introduced to the patient. A physician might also be an investigator.
- Patient information is provided. Any questions a patient may have, are answered. Informed patient consent is obtained. The patient is made aware that he or she may withdraw from trial participation at any time.

- Inclusion and exclusion criteria are applied to further investigate a patient's eligibility for trial participation.
- Screening is concluded and the patient is enrolled.

7.2.2 Enrollment

If a patient is successfully screened and informed consent obtained, he or she is enrolled into the trial.
As endoscopy is already scheduled, a trial participant likely stays at the hospital. Approximately 20 to 60 minutes prior to endoscopy, the HemoPill acute capsule is activated by the investigator and a data connection to the HemoPill Receiver is established. Then, the HemoPill acute capsule is ingested by the trial participant with a minimal amount of water.

8 Assessment of Safety

8.1 Specification of Safety Parameters

Safety parameters are identical to the safety endpoints defined in chapter 4.2.2:
Adverse events / complications associated with trial or control procedure, such as:

Trial procedure:

- Aspiration of the capsule on ingestion
- Delayed excretion, or failure to excrete the capsule (capsule retention)
- Obstruction of the digestive tract
- Injury to tissue structures during the passage of the HemoPill acute through the digestive tract.

Control procedure:

- Cardiopulmonary adverse events
- Infection
- Perforation
- Bleeding

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to subject device is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to subject device assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- ***Related*** *– The AE is known to occur with the subject device, there is a reasonable possibility that the subject device caused the AE, or there is a temporal relationship between the subject device and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the subject device and the AE.*
- ***Not Related*** *– There is not a reasonable possibility that the use of the subject device caused the event, there is no temporal relationship between the subject device and event onset, or an alternate etiology has been established.*

8.2.3 Expectedness

Expected adverse reactions known to occur for capsule endoscope devices and complications associated with the control procedure endoscopy are:

Trial procedure:

- Aspiration of the capsule on ingestion
- Delayed excretion, or failure to excrete the capsule (capsule retention)
- Obstruction of the digestive tract
- Injury to tissue structures during the passage of the HemoPill acute through the digestive tract. In particular, this may involve:
    - Injury to the mucosa
    - Bleeding, e.g., variceal bleeding
    - Perforations

Control procedure:

- Cardiopulmonary adverse events
- Infection
- Perforation
- Bleeding

Dr. Melissa Latorre will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the subject device.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

AEs and SAEs from trial procedure:

- Aspiration of the capsule on ingestion
  Immediate identification through extensive coughing. Localization and retrieval with bronchoscope.
- Delayed excretion, or failure to excrete the capsule (capsule retention)
  Identification
- Obstruction of the digestive tract
- Injury to tissue structures during the passage of the HemoPill acute through the digestive tract. In particular, this may involve:
    - Injury to the mucosa
    - Bleeding, e.g., variceal bleeding
    - Perforations

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

SAEs as defined above, and any adverse events related to the study device (AI) should be reported within 24 hours of the Investigator's knowledge of the event to Sponsor as well as IRB department. Reporting to the IRB will be performed by the Investigator

8.4.2 Serious Adverse Event Reporting

All SAEs, unless otherwise specified in the protocol and approved by the IRB, require expedited reporting by the Principal Investigator to the study's safety monitoring bodies. An expedited report of an SAE can be submitted by telephone, fax, or email and must be reported to the independent safety monitoring body within 24 hours of the event being reported to the Investigator. The expedited report should be followed by a detailed, written SAE report as soon as possible. Follow up information may be required and asked for by the independent safety monitoring body directly. If a second serious event occurs, the study will be halted.

8.4.3 Unanticipated Problem Reporting

Unexpected risks will be evaluated throughout the research study and any modifications, based on serious and unexpected adverse events occurring and reported in these submitted reports and not previously identified in this research study, would be implemented by the study team on an ongoing basis. Any serious or unexpected adverse event related to HemoPill will necessitate review with modification of the protocol to address the specific adverse event.

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and Dr. Jennifer Kats. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

8.4.4 Reporting of Pregnancy

Pregnant women are excluded from trial participation. As from enrollment to trial intervention merely hours elapse, change in pregnancy status of an enrolled patient is highly unlikely. However, if pregnancy is discovered after trial enrollment, trial participation is terminated.

8.5 Reporting Procedures – Notifying the Study Sponsor

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the IRB office and Dr. Jennifer Katz within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the Dr. Katz within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the Dr. Katz and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor contact information is provided in Section 1, Key Roles.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

The PI is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation the reviewing IRB and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as IRB requests.

8.6 Study Halting Rules

Use of subject device will be halted when three grade 3 AEs determined to be “probably related” are reported to the, Dr. Jennifer Katz. Dr. Katz will notify the study sponsor and investigators immediately when the third grade 3 event is reported and enrollment screens will stop accepting new study participants. The study sponsor will inform the DSMB members within 24 hours of this occurrence and will provide the DSMB with AE listing reports. The DSMB will convene an ad hoc meeting by teleconference or in writing as soon as possible. The DSMB will provide recommendations for proceeding with the study to the study sponsor.

8.7 Safety Oversight

Data Safety Monitoring will be conducted by Dr. Jennifer Katz, who is a board-certified gastroenterologist trained in endoscopic procedures including upper endoscopy. Data safety monitoring will be done after each cohort of 10 patients is enrolled.

SAE and AE are defined as:

- Aspiration of the capsule on ingestion
  Immediate identification through extensive coughing. Localization and retrieval with bronchoscope.
- Delayed excretion, or failure to excrete the capsule (capsule retention)
  Identification
- Obstruction of the digestive tract

- Injury to tissue structures during the passage of the HemoPill acute through the digestive tract. In particular, this may involve:
    - Injury to the mucosa
    - Bleeding, e.g., variceal bleeding
    - Perforations

Furthermore, unexpected events are classified as SAE or AE under consideration of the respective definitions provided in chapter 8.1.1 and chapter 8.1.2

9 Clinical Trial Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

The PI will monitor the study. In addition to completed medical records, the procedure report, and any additional supporting documents will be made available for review and verification during each monitoring visit.

Study monitoring will be conducted routinely throughout the study. The monitors will confirm that the study is being conducted according to the protocol.

10 Statistical Considerations

10.1 Statistical and Analytical Plans (SAP)

No additional formal SAP is provided.

10.2 Statistical Hypotheses

Formal hypotheses are only specified for the primary clinical effectiveness endpoint, the detection of blood in the gastrointestinal lumen with both measurements[1].

The assumed null hypothesis is that the accuracy of the HemoPill acute measurement in comparison with endoscopic finding is 50%, equaling a random distribution and no relation between these measurements. As the alternative hypothesis, it is assumed that the accuracy is equal or higher to 75%. This concrete accuracy value is derived from previous results of Brunk et al. (2021), see section 2.1.

10.3 Analysis Datasets

All patients with full study protocol participation are included in the analysis dataset, i.e. with results on both measurements, the subjective device (HemoPill acute capsule) and the control product (endoscopy). Therefore, only patient withdrawal or termination by the investigator can lead to exclusion from the analysis dataset (described in detail in section 5.7).
No further (sub-)analysis datasets are planned.

10.4 Description of Statistical Methods

10.4.1 General Approach

This study has a double blinded, prospective diagnostic case-control design. This prototypic design of diagnostic accuracy study is a consecutive series of individuals in whom the target condition is suspected, here GI lumen bleeding. The index test, here HemoPill acute, is performed first in all participants. Subsequently, the presence of the target condition is also measured in all participants with the reference standard, in this case endoscopy (Rutjes et al. 2005).
In more detail, this study is performed:

- on one sample: the study is conducted on a single sample (single-arm) at a single center
- double blinded: neither the patients nor the investigators are aware of the result of the subjective device, the HemoPill acute capsule, during the examination of the control product, the endoscopy.
- with repeated measurement: all patients are measured with the subjective device and additionally with the control product
- case-control design: the status of a patient with positive endoscopy result equals as classification in the case group, the status of a patient with negative endoscopy result equals as classification in the control group. This classification is determined after the study process, during the statistical analysis to ensure double blindness.

The categorical variables (such as positive or negative test results) will be summarized with subject counts, respectively frequency, and percentages.
As inferential test a χ^2 test, goodness-of-fit test of a 2 x 2 contingency table with two tailed p-value of $\alpha \leq .05$ will be used.
The assumption of the χ^2 test, goodness-of-fit test, a required minimal expected cell size of 5, will be controlled (and is a priori controlled in the power analysis, see section 10.5). The dichotomous data level of the two factors, results of subjective device and results of control product, are transformed into a cell count, observed cases, in the 2 x 2 contingency table.

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

The original continues data level of the subject device, HemoPill acute, the so-called HI-value, is transformed during the study process by the investigator in dichotomous values, negative or positive for GI lumen bleeding, i.e. negative or positive output results (described in detail in section 2.1.2.2).
The qualitative visual data of the control product, the endoscopy, is also transformed during the study process by the investigator in dichotomous values, negative or positive for GI lumen bleeding, i.e. negative or positive output results (described in section 4.1).

After the study process the values of these two factors (HemoPill acute: negative or positive, endoscopy: negative or positive) are combined in a 2 x 2 contingency table with four possible results:

- True positive: HemoPill acute measurement positive; Endoscopy measurement positive
- False positive: HemoPill acute measurement positive; Endoscopy measurement negative
- True negative: HemoPill acute measurement negative; Endoscopy measurement negative
- False negative: HemoPill acute measurement negative; Endoscopy measurement positive

(for detailed description see section 4.1)

From this 2 x 2 contingency table the summary three test indices are calculated accuracy (ACC, = (TP + TN) / pop), sensitivity (true positive rate) and specificity (true negative rate).
The significance of these results will be analyzed using the χ^2 test, goodness-of-fit test of a 2 x 2 contingency table with two tailed p-value of $\alpha \leq .05$.

The data assumption of the χ^2 test, goodness-of-fit test, a required minimal expected cell size of 5, will be controlled. After the inference analysis the 95% confidence intervals of the test indices can be calculated. If either of both measurement results is missing for a patient, the whole subject is omitted from the data analysis.

10.4.3 Analysis of the Secondary Endpoint(s)

Secondary study endpoints as described in chapter 4.2.2 are technical and safety endpoints. These are solely documented, and their respective prevalence is calculated and described in relation to the total number of participants. Presentation in study reporting will either be as a percentage value (e.g., "in 2 % of patients, …"), as a number of occurrences as a fraction of total number of patients or a subgroup thereof (e.g., "in 4 of 50 patients, …"; "in 3 of the 22 patients with an endoscopically identified bleeding pathology).

10.4.4 Safety Analyses

Among the secondary endpoints, safety endpoints are defined (see chapter 4.2.2). Occurrences are documented, and their respective prevalence is calculated and described in relation to the total number of participants. Safety oversight measures are described in chapter 8.7. The Study will be halted after two SAEs (see chapter 8.4.2).

10.4.5 Adherence and Retention Analyses

The successful consumption of the subjective device, the HemoPill acute capsule, is controlled by the administering investigator (see section 6.3.1). No further adherence analyses are planned. Retention analyses are not applicable in this study design.

10.4.6 Baseline Descriptive Statistics

Baseline demographic, clinical and procedural data will be summarized using descriptive statistics.
For continuous variables (such as age), results will be summarized with the numbers of observations, minimums, maximums, means, and standard deviations and where specified in table or figure conventions with quartiles.
For categorical variables (such as gender) results will be summarized with subject counts and percentages.
Inferential statistics are not planned for the baseline statistics, because no subgroups are compared within the sample, nor comparisons with epidemiolocal or demographic data are planned.

10.4.7 Planned Interim Analysis

Not applicable.

10.4.8 Additional Sub-Group Analyses

No analyses of based on age, sex, race/ethnicity or other demographic characteristics are planned.

10.4.9 Multiple Comparison/Multiplicity

Not applicable.

10.4.9.1 Tabulation of Individual Response Data

The individual participant data will be listed by subject with measurement result and time point for each subject.

10.4.9.2 Exploratory Analyses

No exploratory analyses are planned.

10.5 Sample Size

The study will enroll in total n = 50 participants:

- at least 43 eligible for statistical analyses
- plus 7 as highest expectable dropout count.

The required sample size of n = 43 was calculated for the planned χ^2 test for the test indices (accuracy, sensitivity and specificity). The calculation was based on the previous clinical study of Burk et al. (2021) which provide an accuracy of 75% (sensitivity of 100% and specificity of 63%) equaling an assumed effect size w = 0.62. The calculation was done with an a priori set α error of .05 and a targeted power (1-β) equal or higher than .90.

Based on the previous studies dropout ratios between 2% (Burk et al., 2021) and 7% (Caca & Zimmermann, 2017) could be expected. By reason of clinical judgement, a maximal dropout ratio of 14% was assumed (which equals two times the maximal previous dropout ratio). An assumed maximal dropout of 14% equals 7 additional participants (when targeting at least 43 participants eligible for statistical analyses).
The targeted n = 43 also assures the required minimal expected cell size of 5 for a χ^2 test being applicable.
The method of power analysis was an a priori required sample size computation with given α, power and effect size. The power analysis was conducted with the computer program G*Power 3.1 (Faul et al., 2009).

10.6 Measures to Minimize Bias

10.6.1 Enrollment/Randomization/Masking Procedures

While the study is an intra-individual relation between a HemoPill acute measurement and an endoscopic examination and thus not randomized, masking is achieved by application of the following considerations:

- Patient: Sedated during endoscopy. Does not know how to interpret information displayed by the HemoPill Receiver. He or she does not provide an interpretation of measurements.
- Endoscopist: While aware of the endoscopic presentation of the patient as it unfolds, the investigator is unaware of the HemoPill acute measurement. The relation between the HemoPill acute measurement and endoscopic findings is investigated after endoscopy has concluded.
- Blood quantification: A third person quantifies the amount of blood depicted on endoscopic images. This person is unaware of the respective HemoPill acute measurement. A relation to the HemoPill acute measurement is made only after the quantification of blood depicted has been made.

10.6.2 Evaluation of Success of Blinding

Success of blinding cannot retrospectively be evaluated in this study.

10.6.3 Breaking the Study Blind/Participant Code

In this study, the HemoPill acute measurement is blinded to the investigator who is conducting the endoscopy as not to influence the evaluation of endoscopic findings. After endoscopy has concluded, blinding is no longer required here. As for the quantification of blood from endoscopic images, the evaluator is unaware of the respective HemoPill acute measurement. As soon as the quantification process has concluded, blinding is no longer required.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing

records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be

obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

The consent form will be submitted for approval by the IRB and contain all elements required by federal, state, local, and institutional regulations or requirements. The study procedures, risks and benefits, and voluntary nature of involvement must be completely explained to every study subject. Each subject found to be eligible for the study must voluntarily provide written informed consent on the form approved by the IRB and also provide written authorization for use, collection, and disclosure of PHI information. Each subject must be allowed adequate time to consider the potential risks and benefits associated with his or her participation in the study. Informed consent must be in language understandable to the subjects.

It will be the responsibility of the investigator to provide each subject with full and adequate verbal and written information using the IRB approved informed consent document, including the objective and procedures of the study and the possible risks involved before inclusion in the study. Informed consent must be obtained prior to performing any study-related procedures. A copy of the signed informed consent must be given to the study subject.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

13.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into TrialMaster, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.4 Publication and Data Sharing Policy

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

The proposed clinical trial will be registered at ClinicalTrials.gov.

15 Study Finances

15.1 Funding Source

The study is funded by OVESCO USA and NYU Langone Health Division of Gastroenterology. OVESCO USA provides HemoPill acute capsules as well as HemoPill Receivers. OVESCO supports this IIT investigating the performance of the HemoPill acute. The data aids users in interpreting a HemoPill acute measurement. Data shared with OVESCO will be HemoPill acute measurements, endoscopic findings and images, available baseline data. Data will be provided pseudonymized. No identifiable information will be shared. Data will be shared to OVESCO via TrialMaster.

15.2 Participant Reimbursements or Payments

Participants receive a $100 gift card.

16 Conflict of Interest Policy

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

17 References

No.	Citation
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2	Bai Y, Li ZS. Guidelines for the diagnosis and treatment of acute non-variceal upper gastrointestinal bleeding (2015, Nanchang, China). J Dig Dis. 2016 Feb;17(2):79-87.
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