HEDOS

Thyroid HEmorrhage DetectOr Study

A prospective, single-arm, multi-centre, blinded, observational, diagnostic accuracy study with a diagnostic medical product

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ISAR-M GmbH,
Bergfeldstraße 9, 83607 Holzkirchen, Germany

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CHIEF INVESTIGATOR

PD Dr. Markus Albertsmeier
Klinik für Allgemein-, Viszeral-, Gefäß- und Transplantationschirurgie – Campus Großhadern,
Marchioninistraße 15, 81377 München, Germany
Email: markus.albertsmeier@med.uni-muenchen.de
Phone: +49 89 440 00

SPONSOR

ISAR-M GmbH
Bergfeldstraße 9, 83607 Holzkirchen, Germany
Sponsor representative: Olivia Fedunik-Brehm, CEO

Email: olivia.fedunik-brehm@isar-m.com
Phone: +49 173 566 7761

CONTRACT RESEARCH ORGANISATION (CRO)

CRI – The Clinical Research Institute GmbH
Arnulfstr. 19, 80335 Munich, Germany

Email: hedos@cri-muc.eu
Phone: +49 89 990 1649 975 (study hotline)
Fax: +49 89 990 1649 875

This protocol has been written in accordance with applicable EU guidelines and regulations for clinical investigations using medical devices, especially EU Medical device Regulation and ISO 14155. The clinical trial is to be conducted in compliance with this study protocol and with the principles of Good Clinical Practice as defined in ISO 14155.

The terms “trial” and “study” are being used interchangeably throughout this protocol, however, “study” is the umbrella term with “trial” to be used for controlled studies, only.

The terms “bleeding” and “hemorrhage” are being used interchangeably throughout this protocol.

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The study protocol was prepared by CRI and the HEDOS Steering Committee.

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1. Summary

TITLE	**Thyroid HEmorrhage DetectOr Study - HEDOS**
CHIEF INVESTIGATOR	PD Dr. Markus Albertsmeier
SPONSOR	ISAR-M GmbH, Bergfeldstraße 9, 83607 Holzkirchen, Germany
BACKGROUND AND RATIONALE	The investigational product (IP) in focus is a purely diagnostic device without any therapeutic effect per se and without influence on treatment procedures but on timing and precision of treatment decisions, only. Thus, a diagnostic test design is used to first evaluate the diagnostic accuracy based on pre-defined cut-off values in patients with unknown disease status (phase III according [1]), subsequently followed by phase IV which aims to determine patients' benefit of the test-treatment combination. The two study phases will be combined into one phase III/IV seamless design in which a confirmatory phase III **diagnostic accuracy study (stage 1)** and a subsequent phase IV cluster-randomised **test treatment study (stage 2)** are connected to each other and data from the diagnostic accuracy study will also be used for the randomized test treatment study [2]. After thyroid surgery, 0.6 to 4% of patients develop post-operative bleeding [3]. A recent opinion paper from British experts determines the average frequency at 2% [4], a recent meta-analysis found the rate of post-operative hemorrhage to be 1.48 % in 424,563 patients [5]. Only 40% of these complications occur within 8 hours [6] after of surgery while 90% of post-operative bleeding occurs within the first 48 hours [6]. In most cases, these are rapidly progressing complications that require immediate intervention, as the bleeding is caused by arterial bleeding sources [3, 6, 7, 8], recently shown by the correlation of increased cervical pressure and decrease in cerebral perfusion and cerebral oxygenation in an animal experimental series [9].Although for thyroid surgery post-operative bleeding is significantly less common than recurrent nerve palsy or iatrogenic hypoparathyroidism [11], it is always a potentially fatal complication. Up to 0.6% of patients with post-surgical bleeding die, while others suffer from hypoxic brain damage [7]. The cause of death or of hypoxic brain damage in these patients is a lack of oxygen assumed to be caused by a cervical compartment syndrome. Thyroid surgery patients are mostly female (75%) and young. This makes serious complications such as post-surgical bleeding with its risk for additional morbidity and life-threatening consequences particularly tragic. In a clinical study with post-operative pressure measurements [19] it could be demonstrated that post-surgical bleeding leads to a continuous increase in pressure in the neck without interruption as it is observed when coughing and pressing. The authors suggested that pressure alert starting with 10 mmHg would be beneficial in a clinical setting to provide early life-saving interventions. Systematic invasive pressure measurement in the thyroid compartment after surgery might detect a continuous increase in pressure which is often caused by a growing haematoma, indicating serious post-surgery bleeding at a much earlier time compared to state of the art diagnostic workflow. In routine clinical care, detection of serious hemorrhage depends on the patients alerting symptoms even if post-operative intermittent monitoring of vital parameters and wound conditions is performed according to current medical guidelines and local instructions. Device-based, continuous

	hemorrhage detection within 36 to 48 hours after surgery would allow to objectively measure an increase in cervical pressure before symptoms occur. The IP cannot prevent bleeding complications, but early detection of post-operative hemorrhage is important to avoid additional morbidity and potential mortality. Thus, the risk of serious complications like hypoxic brain damage and death caused by post-operative hemorrhage is minimized. In addition, the intervention team would be able to fine-tune necessary actions during the rescue procedure based on objective pressure values, e.g. the decision to open cutaneous sutures immediately or later in the operation theatre, and therefore reduce additional perioperative morbidity and increase patients' safety.
STUDY OBJECTIVE(S)	The primary study objective of the trial is to evaluate the diagnostic accuracy, i.e. sensitivity and specificity, of the diagnostic IP in detecting clinically relevant hemorrhage within 48 hours following thyroid surgery using 12mmHg of pressure as binary cut-off. In addition, a three-level decision system based on two different pressure cut-offs (10 and 20 mmHg) will be established and validated assessing sensitivity and specificity. A surgical intervention triggered by suspicion of a post-operative hemorrhage detected in routine clinical care which is intraoperatively confirmed as needed is considered as gold standard. Secondarily, the safety of the use of the diagnostic IP is assessed. Primary and secondary objectives are validated in a patient cohort most widely representing the routine clinical care population.
STUDY DESIGN	A prospective, single-arm, multi-centre, blinded, observational, diagnostic accuracy study with a diagnostic medical product.
STUDY POPULATION Medical condition / Main selection criteria	<u>Inclusion criteria:</u> **I1.** Age ≥18 years. **I2.** Indication for thyroid surgery (e.g. total thyroidectomy, subtotal resection, partial resection or lobectomy) in routine clinical care according to applicable medical guidelines using all adequate surgical approaches. **I3.** Signed informed consent. <u>Exclusion criteria:</u> **E1.** Intended use of drains.
Number of patients	N= 1,470 enrolled and measured patients.
Expected number of sites and countries	HEDOS will be conducted in Germany and Austria with about 50 clinical sites participating
INVESTIGATIONAL INTERVENTIONS	Within this purely diagnostic trial by study protocol no medical treatment is defined other than thyroid surgery as inclusion criterion. Indication for thyroid surgery, type of surgery performed (e.g. total thyroidectomy, subtotal resection, partial resection or lobectomy) and procedures before, during and after surgery are at the discretion of the treating physician in routine clinical care according to applicable medical guidelines and local policies, and are not defined in the study protocol. The IP used within this study is ISAR-M THYRO®, a diagnostic device of class IIb according to EU regulation 2017/745 for early detection of

	hemorrhage following thyroid surgery. The device uses a sterile disposable compartment pressure probe to be placed in the operating field at the end of thyroid surgery before wound closure. It will be connected to a wearable, external device fixed as a small box at the upper arm of the patient by a soft silicone bracelet. In case of surgery on both neck sides two pressure sensors have to be used but both connected to just one external device box.
PRIMARY OUTCOME PARAMETERS	There is a first co-primary endpoint pair and a hierarchically subordinated third endpoint. The third endpoint is only evaluated in a confirmative way if the first pair of endpoints leads to a significant result. The primary endpoints are defined as follows: EP1. Sensitivity and specificity (co-primary) of the IP for detection of clinically relevant hemorrhage within 48 hours following thyroid surgery using 12 mmHg of pressure as cut-off compared to detection in routine clinical care. EP2. Area under the Receiver Operating Characteristic (ROC) curve for detection of clinically relevant hemorrhage within 48 hours following thyroid surgery by the IP in a three-level decision system using 10 and 20 mmHg of pressure as cut-offs compared to detection in routine clinical care
SECONDARY OUTCOME PARAMETERS	EP3. Safety of the use of the diagnostic IP by means of adverse events within 1 month following thyroid surgery. EP4. Sensitivity and specificity of the IP for detection of clinically relevant hemorrhage within 48 hours following thyroid surgery in a three-level decision system using 10 and 20 mmHg of pressure as cut-offs compared to detection in routine clinical care. EP5. Positive and negative predictive values of the IP for detection of clinically relevant hemorrhage within 48 hours following thyroid surgery using the two-level and the three-level decision system compared to detection in routine clinical care.
ASSESSMENT SCHEDULE	<u>Baseline visit</u> ▪ Informed consent ▪ Check of eligibility ▪ Baseline data ▪ Quality of life questionnaires (EQ-5D-5L and GAD-7) ▪ Index thyroid surgery <u>Follow-up</u> One month after day of index thyroid surgery safety outcome assessment by means of AEs (with subsequent ERC evaluation), and quality of life questionnaires (EQ-5D-5L and GAD-7).
STATISTICAL CONSIDERATIONS	Analyses of the co-primary endpoints in the stage 1 diagnostic study are based on the population of all enrolled patients with subsequent index thyroid surgery. This corresponds to the intention to diagnose (ITD) principle, whereas missing or inconclusive values are imputed by false positive or false negative results, respectively [25].

	In the first pair of primary hypotheses, sensitivity and specificity are considered as co-primary endpoints. They are combined via the Intersection-Union Test. The global null hypothesis can only be rejected if both individual null hypotheses of sensitivity and specificity are rejected. The corresponding first global alternative hypothesis states that the IP exceeds a pre-defined minimum sensitivity of 80% and specificity of 65%. The second primary global hypothesis considers the three-level decision system. Due to the hierarchical order of primary hypotheses, the second primary global hypothesis can only be evaluated in a confirmative way if the first global primary hypothesis leads to a significant result. The analysis of the first global primary hypothesis contains the estimation of the resulting sensitivity and specificity of the IP according to the defined cut-off value of 12 mmHg. For the estimation, a mixed binary logistic regression model is used [26]: The binary test result represents the dependent variable, the true disease status is included as fixed effect. Additionally, a random-intercept is estimated for each centre. Sensitivity is estimated via the calculation of the marginal mean for a diseased individual (=surgical intervention performed which confirmed post-operative hemorrhage needing intervention). False-positive rate, which is the counter probability of the specificity, is estimated via the calculation of the marginal mean for a non-diseased individual. Two-sided 95%-logit confidence intervals with p-values are reported. The positive and negative predictive values are reported descriptively with 95%-logit confidence intervals. Their calculation follows from the analysis method chosen for the primary endpoints. To estimate predictive values with the mixed binary logistic regression model, the true disease status represents the dependent variable. The test results are included as fixed effects and again a random-intercept is estimated for each centre. Positive predictive value is estimated via the calculation of the marginal mean for a test positive result. False-negative rate, which is the counter probability of the negative predictive value, is estimated via the calculation of the marginal mean for a non-diseased individual. Two-sided 95%-logit confidence intervals with p-values are reported. Other secondary endpoints, including safety endpoints, will be analysed descriptively. The sensitivity of the IP is assumed to be 99%, the specificity is assumed to be 95%. The pre-defined minimum sensitivity equals 80%, the minimum specificity is 65%. A higher minimum sensitivity than minimum specificity is chosen as false negative results are much more relevant for the patient than false positive results. The assumed prevalence of clinically relevant hemorrhage within 48 hours following thyroid surgery is 1.5%. The two-sided significance level is set to 5% for the endpoint considering sensitivity and the endpoint considering specificity, respectively. An overall power of 80% is aimed. This leads to a total sample size of 1,470 patients enrolled and measured which is based on the assumed prevalence of 1.5%. Due to the optimal sample size calculation, the endpoint considering the sensitivity reaches a power of 86% and the endpoint considering the specificity a power of 98%. If the prevalence differs at least 22 events of clinically relevant hemorrhage within 48 hours following thyroid surgery need to be observed.

DURATION OF STUDY PERIOD	Total study duration: Enrolment of 12 months. All patients will be followed for 1 month, thus, last Follow-up (FU) will be obtained about 13 months after first patient in. Total study duration of 14 months is expected. Individual study duration: Study duration of each study patient will be about 1 month.

2. Abbreviations

ADE	Adverse device effect
AE	Adverse event
AUC	Area under the curve
CI	Chief Investigator
CRO	Contract Research Organisation
DD	Device deficiency
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
e-CRF	Electronic case report form
ERC	Endpoint Review Committee
e-TMS	Electronic trial management system
EOS	Global end of study
EQ-5D-5L	Patient questionnaire; standardised measure of health-related quality of life
EU MDR	EU Medical Device Regulation 2017/745
FAS	Full analysis set
FPI	First patient in
FU	Follow-up
GAD-7	Patient questionnaire; Generalizied Anxiety Disorder Scale-7
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
ICH	International Conference on Harmonisation
ITD	Intention-to-diagnose
IP	Investigational product (investigational medical device)
LPI	Last patient in
PI	Local Principal investigator
ROC	Receiver Operating Characteristic
Rx	Randomisation
RBMP	Risk based monitoring plan
SAE	Serious adverse event

SADE	Serious adverse device effect
SAP	Statistical analysis plan
SC	Steering Committee
SOC	Standard of care
SOP	Standard Operating Procedure
WOC	Withdrawal of consent

3. Introduction

The investigational product (IP) in focus is a purely diagnostic device without any therapeutic effect per se and without influence on treatment procedures but on timing and precision of treatment decisions, only. Thus, a diagnostic test design is used to first evaluate the diagnostic accuracy based on pre-defined cut-off values in patients with unknown disease status (phase III according [1]), subsequently followed by phase IV which aims to determine patients' benefit of the test-treatment combination. The two study phases will be combined into one phase III/IV seamless design in which a confirmatory phase III **diagnostic accuracy study (stage 1)** and a subsequent phase IV cluster-randomised **test treatment study (stage 2)** are connected to each other and data from the diagnostic accuracy study will also be used for the randomized test treatment study [2]. Further details are described in section 5 of this document.

This study protocol document primarily outlines the first stage of the seamless design which is the diagnostic accuracy study (stage 1). Thus, the term "this study" or "this trial" is used throughout this document with relation to the stage 1 study. However, key points of the subsequent phase IV randomized test-treatment study (stage 2) are already defined in this document, too.

3.1 Background Information

After thyroid surgery, 0.6 to 4% of patients develop post-operative bleeding [3]. A recent opinion paper from British experts determines the average frequency at 2% [4], a recent meta-analysis found the rate of post-operative hemorrhage to be 1.48 % in 424,563 patients [5]. Only 40% of these complications occur within 8 hours [6] after of surgery while 90% of post-operative bleeding occurs within the first 48 hours [6]. In most cases, these are rapidly progressing complications that require immediate intervention, as the bleeding is caused by arterial bleeding sources [3, 6, 7, 8], recently shown by the correlation of increased cervical pressure and decrease in cerebral perfusion and cerebral oxygenation in an animal experimental series [9]. Although bleeding that occurs later must also be treated surgically, it usually progresses less rapidly. The risk factors for post-operative bleeding are male gender, arterial hypertension, subtotal resection procedures, the drugs acetylsalicylic acid and clopidogrel, other oral anticoagulants (NOAKs, coumarines etc.) and high blood loss during the procedure. However, available study data are too limited for being usable to reliably predict the risk of post-operative bleeding. There is also no evidence that early post-operatively bleeding is less severe than bleeding that occurs later in the course after the operation [10].

Although for thyroid surgery post-operative bleeding is significantly less common than recurrent nerve palsy or iatrogenic hypoparathyroidism [11], it is always a potentially fatal complication. Up to 0.6% of patients with post-surgical bleeding die, while others suffer from hypoxic brain damage [7]. The cause of death or of hypoxic brain damage in these patients is a lack of oxygen assumed to be caused by a cervical compartment syndrome. Thyroid surgery patients are mostly female (75%) and young. This makes serious complications such as post-surgical bleeding with its risk for additional morbidity and life-threatening consequences particularly tragic. Already 14.7% of women < 30 years of age and 33.4% of women between 31 and 45 years of age suffer from thyroid pathologies. More than 80% of thyroid surgeries are performed for benign diseases [12]. Such severe surgical complications with a potentially life-threatening outcome are therefore dispropor-

tionate to surgery for a benign disease in predominantly young patients. With an operation frequency of approximately 65,000 to 75,000 patients per year in Germany [13] about 1,300 to 1,500 patients suffer this complication and are at risk of serious damage.

At the congress of the Surgical Working Group Endocrine Surgery 2012 in Regensburg, a survey revealed that 75% of thyroid surgeons consider post-operative bleeding as the most serious complication in thyroid surgery. Nevertheless, not a single experimental *in vivo* study on this problem has been made public by then - maybe because the mechanism was thought to be revealed. Many authors have already described this complication in their articles. They report that bleeding at the surgical site may originate from the upper or lower arterial blood vessels of the thyroid gland or from the pre-thyroid straight neck muscles [11]. Bleeding from the jugular vein or other neck veins has also been described. According to this description, breathing becomes increasingly difficult as the neck fills with blood and the swelling of the neck increases. This is assumed to be compounded by oedema of the mucous membranes and displacement or compression of the trachea, which then leads to respiratory arrest [11,14]. While the term "compressive hematoma" is commonly used in medical literature, there are only a few thyroid surgeons who question it [15].

This mechanistic idea was experimentally tested. In an *ex-vivo* study on the trachea of recently deceased patients in the forensic medicine department of the LMU in Munich, the theory that the trachea would completely collapse under pressures of up to 100 or even 130 mmHg that might be achievable in vivo was contradicted [16], although some minor luminal narrowing was observed. At unphysiological excessive pressures, not to be expected in a living person, reaching 250 mmHg *in vitro*, only 2 of 30 tracheas collapsed.

Tests with intubated, spontaneously breathing pigs under general anaesthesia [18] insured that neither swelling of the mucous membranes nor collapse of the trachea impaired the air supply. Still, under the simulated post-thyroidectomy bleeding, respiratory arrest was observed in all animals, which was reversible after lowering the intracervical pressure. The phenomenon could be repeated 6 times in each of the 12 animals. These results suggest that not the collapse of the airways but rather a reversible and repeatable pressure-dependent neurological reflex caused the respiratory arrest. Alternatively, a cervical compartment phenomenon with reduced brain blood flow could have caused the respiratory arrest. Animal studies in a porcine model with additional functional MRIs showed decreased brainstem activity under post-surgical bleeding with increasing pressure in the neck accompanied by respiratory arrest, and an increase in brainstem activity to the baseline level after pressure relief with resumption of spontaneous breathing. This observation could also be explained by a compartment phenomenon [18].

Using the same animal model in simulated post thyroidectomy hemorrhage with extended monitoring it was demonstrated that hemorrhage caused a compartment syndrome of the neck [9].

As more blood is accumulating at the surgical site, the cervical compartment pressure increases. Already at 12 mmHg the venous drainage of blood from the brain is impaired, causing the oxygen saturation of the brain to drop significantly as measured with cerebral near-infrared spectroscopy [9]. This leads to a reduction of the respiratory drive and, with a time delay, to a drop in oxygen saturation measured in peripheral tissues. Further bleeding from arterial sources leads to a further increase of compartment pressure in the neck finally almost reaching the mean arterial blood pressure. As diastolic arterial pressure values are exceeded, arterial perfusion pressure drops in the ophthalmic artery similar to effects of carotid artery stenosis of at least 70 % with a further drop of oxygen saturation in the brain. As bleeding continues, arterial brain perfusion continues to drop and together with venous congestion brain circulation arrests followed by respiratory arrest, a further drop of oxygen saturation of the peripheral tissues and death.

In a clinical study with post-operative pressure measurements [19] it could be demonstrated that post-surgical bleeding leads to a continuous increase in pressure in the neck without interruption as it is observed when coughing and pressing. The authors suggested that pressure alert starting with 10 mmHg would be beneficial in a clinical setting to provide early life-saving interventions.

Current medical guidelines [20] suggest post-operative intermittent monitoring of vital parameters and wound conditions including clinical signs of respiratory insufficiency during initial 36 to 48 hours following thyroidec-

tomy procedures. The first 8 hours after surgery require special care because the risk for the rare but potentially fatal hemorrhage (1-2%) is highest during that period. Monitoring is to be carried out in a recovery room or ward (ICU is not specified) by specifically trained medical staff in order to insure timely surgical revision in case of hemorrhage.

3.2 Study Rationale

Systematic invasive pressure measurement in the thyroid compartment after surgery might detect a continuous increase in pressure which is often caused by a growing haematoma, indicating serious post-surgery bleeding at a much earlier time compared to state of the art diagnostic workflow. In routine clinical care, detection of serious hemorrhage depends on the patients alerting symptoms even if post-operative intermittent monitoring of vital parameters and wound conditions is performed according to current medical guidelines and local instructions. Device-based, continuous hemorrhage detection within 36 to 48 hours after surgery would allow to objectively measure an increase in cervical pressure before symptoms occur. The IP cannot prevent bleeding complications, but early detection of post-operative hemorrhage is important to avoid additional morbidity and potential mortality. Thus, the risk of serious complications like hypoxic brain damage and death caused by post-operative hemorrhage is minimized. In addition, the intervention team would be able to fine-tune necessary actions during the rescue procedure based on objective pressure values, e.g. the decision to open cutaneous sutures immediately or later in the operation theatre, and therefore reduce additional perioperative morbidity and increase patients' safety.

The IP claims to measure pressure in the cervical compartment following thyroid surgery reliably, accurately, and safely, and can monitor pressure continuously. Therefore, the device might be able to detect clinically relevant hemorrhage within 48 hours following thyroid surgery earlier and with better predictive values compared to detection in current routine clinical care. Within this study, the diagnostic accuracy of the IP will be assessed.

3.3 Benefit-risk Assessment

3.3.1 General risk assessment of the HEDOS trial

- The study is purely diagnostic without any pre-defined therapeutic intervention in the study protocol. No random assignment to therapies is performed in this one-arm diagnostic accuracy trial.
- The indication for thyroid surgery and the consent of the patient to this therapeutic approach are decided in routine clinical care prior to any HEDOS trial activities in the corresponding patient.
- All medical therapies are at the discretion of the treating physician according to applicable medical guidelines and local treatment policies. Treatments and procedures will be decided by the treating physician based on the individual medical status of each study patient without guidance by the study protocol.
- All medical devices - with the exception of the IP diagnostic device - and drugs which may be used within the study will be marketed products to be used in line with market authorisation as given in their Instruction For Use (IFU) or Summary of Product Characteristics (SmPC) and represent standard of care (SOC). This also applies to the medical procedures within the trial. Thus, adverse events resulting from therapies within the study are expected to occur in similar clinical manifestations and at comparable rates as the known adverse events of the approved therapies in routine clinical care.
- The IP is only used as an external small box fixed at the upper arm of the patient by a soft silicone bracelet. A sterile disposable compartment pressure probe is placed in the surgical area at the end of the routine thyroid surgical procedure just before wound closure and subsequently connected to the device (in case of surgery on both sides two pressure sensors have to be used but both connected to just one external device box). Potential risks of this equipment are local infections at the suture or in the surgical area comparable to the risks of wound drainage often used after thyroid surgical procedures in routine

clinical care. However, pressure sensor catheter and the suture are protected by adequate dressing and the sensor will be removed completely within 48 hours after wound closure without reopening the suture.

- The measurements of the IP are kept secret until the end of the trial and, therefore, do not affect treatment decisions.
- The HEDOS trial is therefore considered to generally represent a low structural risk profile by design with respect to additional adverse events compared to routine clinical care.

3.3.2 Assessment of the individual risk of study patients

- The individual risk of study patients by applied therapies within the trial is equal to the risk in routine clinical care since all therapies and treatment decisions will be in line with applicable medical guidelines and routine clinical care policies. Medical devices and drugs used within HEDOS - except for the diagnostic IP - are marketed products used in line with market authorisation, based on individual therapy decisions of the treating physician, and represent SOC. This also applies to all medical procedures performed within the trial.
- Additional individual risk may be added by the disposable compartment pressure probe(s) placed in the surgical area before wound closure. However, previous use of this equipment together with adequate dressing and complete removal within 48 hours after wound closure [19] did not lead to any local infection. The catheter is comparable to drains placed in routine clinical care in some hospitals in the surgical area.
- Thus, the additional individual risk for patients participating in this diagnostic study is deemed negligible.

3.3.3 General benefit of study patients

All patients participating in the HEDOS trial will have the benefit of careful standardised monitoring of their treatment and follow-up procedures by their study physicians as in routine clinical care but in addition undergo quality management by the CRO, the sponsor and the Steering Committee (SC) of the trial.

3.3.4 Individual benefit of study patients

Individual benefit of study patients compared to routine clinical care is not expected.

4. Study Objectives

The primary study objective of the trial is to evaluate the diagnostic accuracy, i.e. sensitivity and specificity, of the diagnostic IP in detecting clinically relevant hemorrhage within 48 hours following thyroid surgery using 12mmHg of pressure as binary cut-off. In addition, a three-level decision system based on two different pressure cut-offs (10 and 20 mmHg) will be established and validated assessing sensitivity and specificity.

A surgical intervention triggered by suspicion of a post-operative hemorrhage detected in routine clinical care which is intraoperatively confirmed as needed is considered as gold standard.

Secondarily, the safety of the use of the diagnostic IP is assessed.

Primary and secondary objectives are validated in a patient cohort most widely representing the routine clinical care population.

4.1 Primary Endpoint Parameters

There is a first co-primary endpoint pair and a hierarchically subordinated third endpoint. The third endpoint is only evaluated in a confirmative way if the first pair of endpoints leads to a significant result. The primary endpoints are defined as follows:

EP1. Sensitivity and specificity (co-primary) of the IP for detection of clinically relevant hemorrhage within 48 hours following thyroid surgery using 12 mmHg of pressure as cut-off compared to detection in routine clinical care.

EP2. Area under the Receiver Operating Characteristic (ROC) curve for detection of clinically relevant hemorrhage within 48 hours following thyroid surgery by the IP in a three-level decision system using 10 and 20 mmHg of pressure as cut-offs compared to detection in routine clinical care.

Clinically relevant hemorrhage following thyroid surgery" (=true disease) is defined as surgical intervention triggered by suspicion of a post-operative hemorrhage detected in routine clinical care which is intraoperatively confirmed as needed (gold standard of routine clinical care detection).

The three-level decision system referred to in EP2, EP4 and EP5 is detailed in section 5.

If sensor measurement in some study patients is stopped earlier than 48h after thyroid surgery, e.g. because of device problems or sensor removal, data will be censored at the time of last measurements available.

If sensor measurement in some study patients continues more than 48 hours after thyroid surgery data will be analysed until last data available.

4.2 Secondary Endpoint Parameters

Secondary endpoint parameters are defined as:

EP3. Safety of the use of the diagnostic IP by means of adverse events within 1 month following thyroid surgery.

EP4. Sensitivity and specificity of the IP for detection of clinically relevant hemorrhage within 48 hours following thyroid surgery in a three-level decision system using 10 and 20 mmHg of pressure as cut-offs compared to detection in routine clinical care.

EP5. Positive and negative predictive values of the IP for detection of clinically relevant hemorrhage within 48 hours following thyroid surgery using the two-level and the three-level decision system compared to detection in routine clinical care.

Clinically relevant hemorrhage and serious adverse events will be adjudicated by an independent Endpoint Review Committee (ERC) according to standardised definitions [7] given in the ERC charter. Outcome death in follow-up will be assessed as equivalent endpoint to clinically relevant hemorrhage.

Parameters relevant for endpoints within the test treatment study (stage 2) are collected within HEDOS study (diagnostic accuracy study, stage 1), too, e.g. clinical symptoms triggering surgical intervention of a suspected post-operative hemorrhage detected in routine clinical care, time to clinical or technical alerts, surgical interventions which did not show post-operative hemorrhage needing intervention.

5. Study Design

In general, the development of a diagnostic test is structured in four phases [1]. In phase I, the functionality and safety of the diagnostic test is examined. In phase II, the diagnostic test is applied to individuals with known disease status to define the cut-off value. Phase III evaluates the diagnostic accuracy based on the pre-defined cut-off value in patients with unknown disease status. Phase IV aims to determine patients' benefit of the test-treatment combination. Hence, the last two phases of the development process are combined. Two single studies are planned to be combined into a phase III/IV seamless design in which a confirmatory phase III **diagnostic accuracy study (stage 1)** and a subsequent phase IV **cluster randomised test treatment study (stage 2)** are connected to each other and data from the diagnostic accuracy study will also be used for the randomized test treatment study.

HEDOS represents stage 1 of the seamless design and is planned as a prospective, single-arm, multi-centre, blinded, observational, diagnostic accuracy study with a diagnostic medical product. The occurrence of a

post-operative hemorrhage with need for intervention, detected in routine clinical care, is considered as gold standard. It will be conducted in Germany and Austria with about 50 clinical sites participating. The study has a planned number of n=1,470 enrolled and measured patients within a follow-up period of 1 month after end of index thyroid surgical procedure. It is expected to observe about 22 cases of clinically relevant hemorrhage within 48 hours following thyroid surgery within the trial.

It is expected that patient recruitment is completed after about 12 months from the time the first patient is enrolled. The clinical phase of the trial will end about 1 month after the last patient has been enrolled and measured.

Further, a blinded sample size re-calculation based on the incidence of bleeding events measured by the gold standard procedure within the stage 1 study is planned (see section 12.3 for further details).

The randomized test-treatment study in stage 2 will be planned as a multi-center, confirmatory, prospective, parallel-group phase IV diagnostic cluster randomized test-treatment trial comparing the effectiveness of the IP detector vs. routine clinical care monitoring in a consecutive sample of patients undergoing a thyroid surgery. In the first step, all study sites will be randomized to either apply the IP detector (intervention group) on patients undergoing thyroid surgery or to perform routine clinical care monitoring (control group).

Hereby, the control group information is augmented with information coming from the phase III trial in stage 1 [21, 22, 23]. Since these patients are monitored in a routine clinical way and further receive treatment according to current routine clinical care standards anyway, serious heterogeneity with the control arm of the stage 2 study is not expected. Thus, the focus of patient enrolment will mainly be on recruiting study sites and their eligible patients into the intervention group.

It is expected that results of the diagnostic accuracy study (stage 1) will gain new insights into incidence proportion, time course, and strength levels of hemorrhage following thyroid surgery as detected by means of continuous pressure monitoring compared to detection by clinical symptoms, only. The rate of potentially relevant but subclinical hemorrhage without triggering symptoms is unknown yet. This is also applying for the time course and final stages of subclinical but potentially harmful hemorrhage.

Hence, after completion of stage 1 of the seamless design and after market approval of the medical device an unblinded interim analysis is carried out estimating the diagnostic accuracy of the detector and the incidence of alerts in both arms. Thereafter, based on this incidence a sample-size re-estimation is performed in order to derive the required sample size in the standard monitoring arm of stage 2.

The subsequent test treatment study (stage 2) uses the three-level decision system derived from the diagnostic accuracy study (stage 1):

- green phase representing safe conditions without any indication for clinical intervention,
- yellow phase alerting distinctive increase in pressure measures which indicates necessity of intensified monitoring of the patient and stand-by of the surgery team but without clear indication of clinical intervention,
- red phase with serious pressure increase above alert level indicating the need of instantaneous clinical intervention.

The relevant primary endpoint for the test treatment study (stage 2) will therefore be defined by the total incidence proportion of first alerts, technical (three-level decision system) and clinical (clinical symptoms triggering surgical intervention), because both will lead to improvement of clinical outcome of post-surgery patients: either by instantaneous clinical intervention or by intensified monitoring and stand-by of the surgery team providing a prepared subsequent instantaneous clinical intervention.

Figure 1 shows the seamless design graphically.

The subsequent stage 2 study will be described in detail in a separate study protocol with reference to this document, to be finalised after the results of the first study are available.

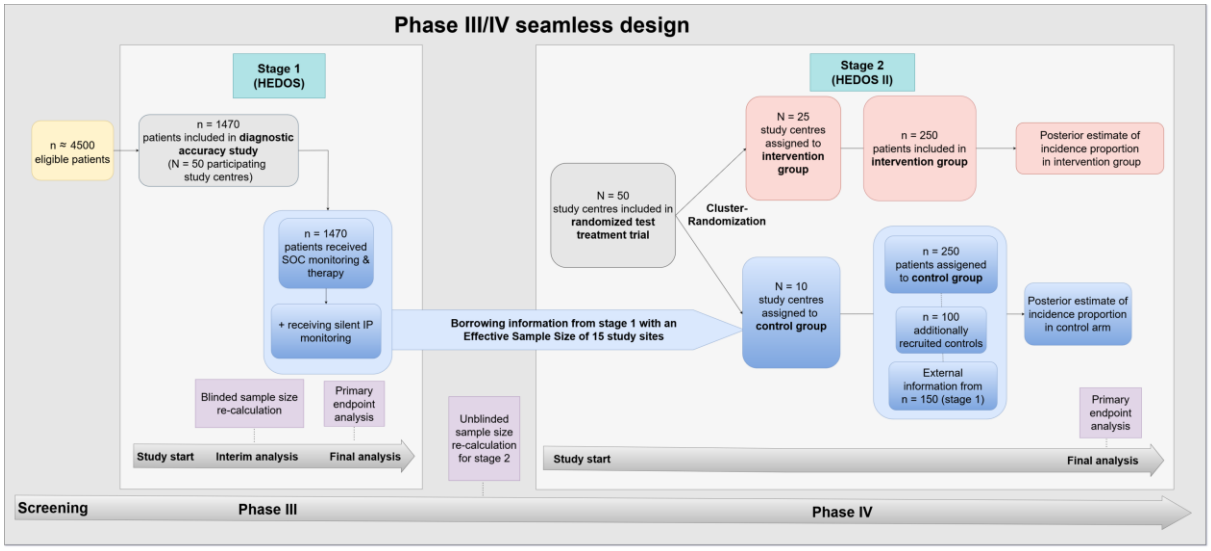

Figure 1: The confirmatory diagnostic accuracy phase III study and the phase IV randomized test-treatment study are connected via the seamless design. The Effective Sample Size represents the stage 2 prior informativeness in terms of the hypothetical number of stage 1 study centres available for information borrowing [24]. The sample sizes in stage 2 displayed here are exemplary and serve to illustrate the design. The final numbers are calculated in the final analysis of stage 1.

5.1 Flow Chart

The work flow of study procedures in this trial was designed to be as close to routine clinical care as possible to represent daily routine clinical care in an optimal way.

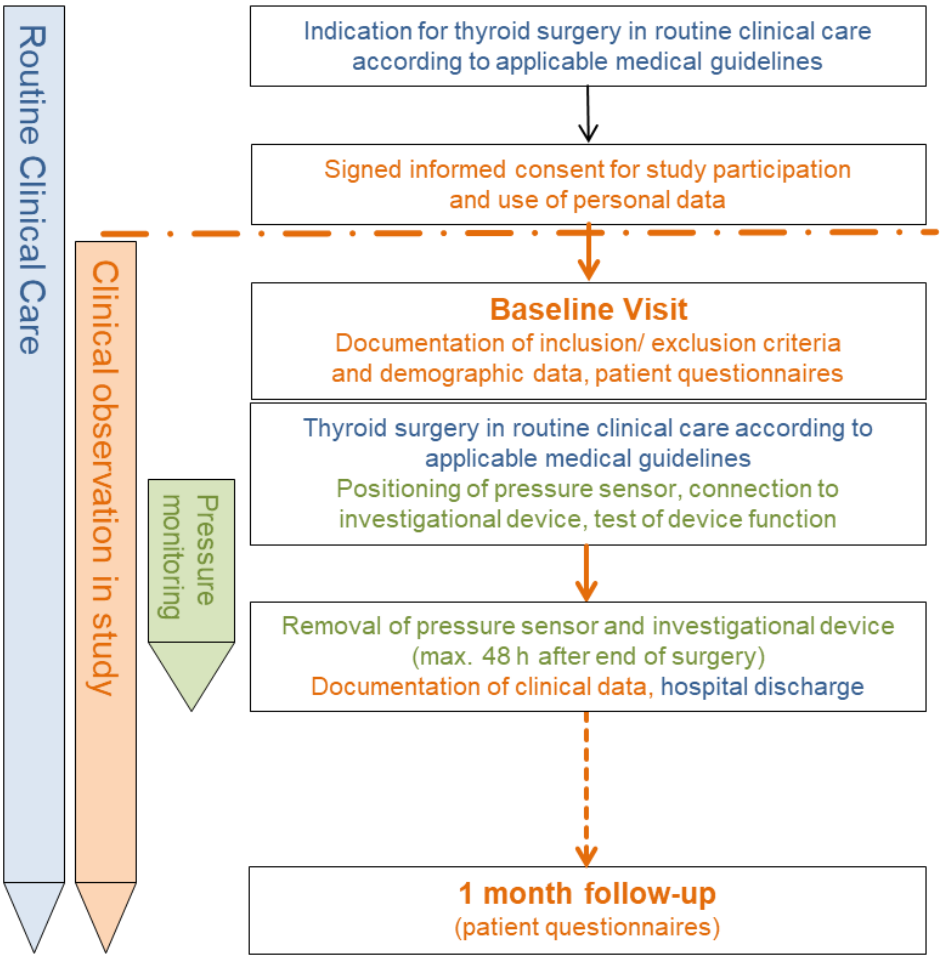

Figure 2: Study flow chart

All enrolled and measured patients will be followed for 1 month after end of index thyroid surgical procedure or until withdrawal of consent.

6. Selection of Patients

6.1 Informed Consent

A signed informed consent form, written in accordance with country-specific applicable data privacy acts, the Declaration of Helsinki (Appendix V) and applicable laws for research using medical devices, and approved by the responsible Ethics Committee (EC), will be obtained from every patient prior to any study-related procedure. It will be explicitly explained to patients eligible for the HEDOS study that their data might also be used within HEDOS II. All clinical data needed to evaluate the potential eligibility of a patient before study inclusion (pre-screening), e. g. recent laboratory results or other technical parameters, are to be performed during routine clinical care and are therefore not considered to be part of study related procedures.

An investigator will explain the nature, purpose and risks of the study and provide the patient with a copy of the patient information sheet. The patient will be given sufficient time to consider the study's implications before deciding to participate. In addition, it will be explained that the patient is free to leave the trial at any time without any disadvantage or loss of therapy quality.

Should there be any modifications to the protocol, such that this would directly affect the patient's participation in the study, e.g. a change in any procedure, an addendum to the informed consent form specifying the modification must be compiled and the patients who already gave informed consent must agree to sign this addendum indicating that they consent to further participate in the modified study.

A signed copy of the patient's informed consent form and any signed addendum to the informed consent form must be maintained in the study file on site. The patient's permanent medical records at the site should indicate the patient's study participation.

6.2 Study Population

6.2.1 Number of patients and definition of status

HEDOS will enrol and measure presumably 1,470 eligible adult patients and follow each of them for 1 month, assuming that 22 events of clinically relevant hemorrhage within 48 hours following thyroid surgery will be observed.

A patient is considered as **enrolled** into the trial according to regulatory requirements as soon as he has **signed** the informed consent form. Documentation of any patient data in the e-CRF is permitted only after the patient signs the informed consent form. All enrolled patients will be reported and will be part of the **safety population**. Enrolled patients who are subsequently not measured with thyroid surgery as defined in the study protocol will not count to the number of enrolled patients needed, and will be replaced as soon as absence of thyroid surgery has been determined and documented in the clinical files of the patient.

A patient is considered as **screened** as soon as inclusion and exclusion and other eligibility criteria have been checked and documented in the e-CRF after the patient signed the informed consent form. Screened patients who are subsequently not measured with thyroid surgery as defined in the study protocol will not count to the number of enrolled patients needed, and will be replaced as soon as absence of thyroid surgery has been determined and documented in the clinical files of the patient. These patients will be followed until date of determination of absence of thyroid surgery. If a screened patient is scheduled for index thyroid surgery after global end of the study or after termination of study participation of the corresponding study site his study participation will end at the corresponding date of administrative termination.

A patient is considered as **measured** in the trial as soon as he is **enrolled and thyroid surgery** as defined in the study protocol was performed. All measured patients will be part of the ITD population. Measured patients will be followed according to study protocol.

The day of **enrolment** is **day 1 of study participation**, the **day of index thyroid surgery** as defined in the study protocol is **day 1 of follow-up** for primary and secondary endpoints of an individual study patient.

6.2.2 Inclusion criteria

I1. Age ≥18 years.

I2. Indication for thyroid surgery (e.g. total thyroidectomy, subtotal resection, partial resection or lobectomy) in routine clinical care according to applicable medical guidelines using all adequate surgical approaches.

I3. Signed informed consent.

All inclusion criteria have to be documented for source data review in the permanent clinical files of the patient at the site.

6.2.3 Exclusion criteria

E1. Intended use of drains.

6.2.4 Randomisation (Rx)

For this type of purely diagnostic trials no randomisation (Rx) into treatment groups is required (within-subject design). All patients passing in- and exclusion criteria and subsequent index thyroid surgery will receive the diagnostic IP and will be assessed.

7. Therapy

Within this purely diagnostic trial by study protocol no medical treatment is defined other than thyroid surgery as inclusion criterion. Indication for thyroid surgery, type of surgery performed (e.g. total thyroidectomy, subtotal resection, partial resection or lobectomy) and procedures before, during and after surgery are at the discretion of the treating physician in routine clinical care according to applicable medical guidelines and local policies, and are not defined in the study protocol. Therapies provided to study patients will be documented as required in the e-CRF.

7.1 Investigational medical product (IP)

The IP used within this study is ISAR-M THYRO®, a diagnostic device of class IIb according to EU regulation 2017/745 for early detection of hemorrhage following thyroid surgery. The device uses a sterile disposable compartment pressure probe to be placed in the operating field at the end of thyroid surgery before wound closure. It will be connected to a wearable, external device fixed as a small box at the upper arm of the patient by a soft silicone bracelet. In case of surgery on both neck sides two pressure sensors have to be used but both connected to just one external device box.

The IP system consists of the following technical components:

- Thyro I KID (REF: TH-020101): The Key Instrument of pressure Detection (KID) is a sterile, disposable compartment pressure probe to be used with reusable parts of the IP system. It is an invasive probe with air chamber and connector for pressure absorption in surgery cavities. The upper end of the pressure probe (soft air chamber) is inserted into the thyroid compartment before closing the surgical wound. The sensor connector is plugged into a socket of the SON.
- Thyro I SON (REF: TH-010201): The Smart OperatioN (SON) is a unit for recording and displaying the sensor data, acoustic and visual alarm, storage of monitoring data and data transmission to the external

monitoring master (MOM) via wireless communication. The SON is to be attached to the patient's upper arm using an accessory belt (REF: TH-010301). One or two KIDs shall be connected to the SON.

- Thyro I MOM (REF: TH-010401): The MOnitoring Master (MOM) is a medical device app (CRI_1.0.1, version number V3.4A) pre-installed at a handheld with a protective cover to display patient files, trend analyzes, statistics and with acoustic and visual alarming function. It has a wireless connection to the SON for data exchange and for control and alarming nearby the patient.
- Thyro I DOCK (REF: TH-010501): The Device Of Charging Key (DOCK) is the storage and charging unit for both, the MOM and the SON. The unit will be located at medical staff. The DOCK is connected to the power by an AC-DC reliable green medical adaptor (REF: TH-010601).

The IP will be used within the study for continuous measurement of pressure values and their digital documentation with alerts and pressure display off. Potential risks of this equipment are local infections at the suture or in the surgical area. However, pressure sensor catheter and suture are protected by adequate dressing and the sensor will be removed completely about 48 hours after wound closure without reopening the suture.

The IP (without market approval) shall be kept in a locked location with limited and controlled access only for authorized persons at the study site. It will only be used for patients enrolled into the study.

7.1.1 Intended use of the IP

The system is installed at the end of the operation and runs for up to 48 hours. The use of the system allows timely re-operation and haemostasis even in the symptom-free stage and allows a data based decision for a necessary rescue operation. The IP is light weighted, battery operated and can be carried by the patient on the body.

In the study version of the IP all pressure values measured by the pressure probe are recorded and analyzed. If the specified pressure points are exceeded, this event is stored in a log file, but is not used to trigger an alert that can be detected by the user. This means that there is no pressure display on SON or MOM, no trend display on the MOM and no pressure alert on both devices. In addition, no pressure alert messages are emitted via SMS.

Based on the saved pressure file and the event log file, the compartment pressure history can be analyzed retrospectively over the entire duration of the observation and the correctness of the recorded pressure alerts can be traced and checked.

7.1.2 Technical and functional features of the IP

A detailed description is given in Appendix VI.

7.1.3 Information on traceability and use of the IP

For accountability of technical components of the IP system, the following information will be documented and traced by the study sites in the e-CRF:

a) information on all components ever received at the study site (identification by serial or lot numbers, expiry date if applicable, quantity, and date of receipt),

b) information on usage of the IP including, if applicable, identification of corresponding study patient, and date or dates of use and date of return from study patient,

c) where applicable, information of the disposal of IP as per instructions of the sponsor,

d) information on return of unused, expired, or malfunctioning IPs.

Summary reports on accountability and use are available within the e-CRF for individual study sites.

In addition to documentation by the study sites, the sponsor will document and trace IP devices ever shipped to study sites or returned from them.

7.2 Unblinding

The HEDOS trial is a single-arm study without blinded treatment or procedure groups. Thus, unblinding procedures for investigators are not applicable. The measurements of the IP are not visible to investigators and will be kept secret until the end of the trial.

7.3 Auxiliary Medical Therapies

All medical therapies used within HEDOS comprise marketed products used in line with market authorisation and represent SOC, therefore no auxiliary medical therapy is defined.

7.4 Concomitant Medication

All patients will be provided with medical care and accepted evidence-based medication in accordance with applicable recent guidelines. Concomitant medication will be documented by generic name in the e-CRF.

7.5 Post-study Treatment

Within this purely diagnostic trial no post-study treatment is defined. Any medical therapy within or after the individual end of participation in this trial represents the individual decision of the treating physician and has to be in line with current medical guidelines and local policies. No therapies are specified in this study protocol.

8. Adverse Event (AE) recording

Within this purely diagnostic trial no medical treatment is defined other than thyroid surgery. The diagnostic IP is used as external tool outside the body. The catheter-based pressure sensor is introduced during the surgical procedure into the surgical field just before wound closure. Results of clinical studies with comparable catheter-based pressure sensors yield very low to negligible rates of adverse events caused by the sensor. All other medical devices and medication used in HEDOS comprise only marketed products used in line with market authorisation and SOC as described in applicable medical guidelines. Thus, adverse events are expected to occur in similar clinical manifestations and at a comparable rate as the known adverse events of the applied thyroid surgery in routine clinical care. The trial is therefore assessed as representing a low structural risk.

8.1 Adverse Events (AEs)

Is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, in the context of a clinical investigation whether or not related to the IP. This definition includes events that are anticipated as well as unanticipated events and those occurring in the context of a clinical investigation related to the IP or the procedures involved. For users or other persons, this definition is restricted to events related to IPs.

Any surgery procedure or other intervention irrespective of its relation to the IP or the index thyroid surgery is an AE and has to be documented.

A newly diagnosed concomitant disease is also considered an AE.

All AEs occurring from enrolment until end of follow-up of each study patient will be documented by study site personnel in the e-CRF immediately after study site personnel's awareness of the event, and will subsequently be assessed by the sponsor and reported to authorities involved.

8.2 Serious Adverse Events (SAEs)

A SAE is any untoward medical occurrence that

- led to death,
- led to serious deterioration in the health of the subject, that either resulted in
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - hospitalisation or prolongation of patient hospitalisation, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
  - a chronic disease,
- led to foetal distress, foetal death or a congenital abnormality or birth defect.

More than one of the above criteria can be applicable to each event.

These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

NOTE:

The following overnight hospitalisations are not considered SAEs:

- Not urgent hospitalisation for
  - a condition existing before signing consent, or
  - a procedure required by the study protocol without serious deterioration in health.
- Elective inpatient hospitalisation (e.g. surgery) verifiably planned before signing consent.
- Any overnight hospital stay required only for diagnostic procedure (e.g. in a sleep laboratory).

8.3 Device Related Adverse Events

This study uses a diagnostic IP, only. Causal relationship of adverse events has to be assessed in relation to the IP, only. It will be assessed and reported by the sponsor.

However, classification of adverse events as related to other medical devices or therapies used within the trial will follow the definitions as given for routine clinical care. Treating physicians have to report adverse events related to other medical devices or therapies to the corresponding manufacturer of the device. Reporting duties of manufacturers of other than the IP device used within this diagnostic trial have to follow routine procedures relevant for marketed medical devices.

8.3.1 Adverse Device Effect (ADE)

An adverse event related to the use of an IP. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the IP. It also includes any event resulting from use error or from intentional misuse of the IP.

8.3.2 Serious Adverse Device Effect (SADE)

An adverse device effect that has resulted in any of the consequences to the characteristic of a serious adverse event. According to EU MDR Article 80 any serious adverse event that has a causal relationship with

the IP, the comparator or the investigation procedure or where such causal relationship is reasonably possible will be reported without delay to all involved authorities.

8.3.3 Device Deficiency (DD)

Device deficiencies are defined as inadequacy of an IP with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequacy of information provided by the manufacturer, including labelling. All device deficiencies shall be documented and appropriately managed by the sponsor.

Device deficiencies that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate also have to be recorded in the e-CRF and reported without delay to all involved authorities.

8.4 Recording and Reporting of SAEs by investigators

The investigator should specify and report in the e-CRF the nature of the sign or symptom leading to the SAE, the date of onset of the sign or symptom, the date of resolution of the specific event (not of the underlying disease), the intensity, interventions performed (if any), the relationship to the IP or the index thyroid surgery itself, and the outcome.

Following the patient's written consent to participate in the study, all SAEs, whether related or unrelated to the IP or the index thyroid surgery itself, must be reported expeditiously by the investigator to the sponsor through the SAE section of the e-CRF **within 24 hours of becoming aware of the event** and will subsequently be assessed by the sponsor and reported to authorities involved. An SAE form within the e-CRF should be completed for any event where doubt exists regarding its status of seriousness. As a minimum, the investigator has to fill out the following items of the internet-based SAE form:

- Type of event
- Description
- Date of onset
- Criteria for seriousness
- Causal relationship to study therapy.

As soon as further information regarding the event is available (e.g. discharge letter), the investigator should complete the documentation in the e-CRF and sign it electronically. Copies of the discharge letter, of all reports regarding examinations carried out and/or diagnostic findings should be digitally provided to the CRO. For laboratory results, the laboratory normal ranges should be included. All documents should be digitally provided to the CRO after adequate blinding of patient identifiers, only.

Follow-up of any **SAE that is fatal or life threatening** should be digitally provided immediately but no later than **within two additional calendar days of becoming aware of the event**.

Any SAE recording (initial report and follow-up information on e.g. changes of an ongoing SAE's intensity or relationship to the IP or outcome) is done through the SAE section of the e-CRF. An automated e-mail notification system within the e-trial management system will inform sponsor and CRO instantaneously, thus, no extra SAE form needs to be send but sponsor and CRO will receive an automated digital notification on the SAE at the same time of the data being documented or changes of relevant SAE data being made in the e-CRF.

8.4.1 Definition of Intensity

Be aware that intensity of an adverse event and its seriousness are independent definitions, e.g. an adverse event might be serious but mild in intensity or vice versa.

Intensity	Definition
Mild	Patient is aware of signs and symptoms but they are easily tolerated
Moderate	Signs/symptoms cause sufficient discomfort to interfere with usual activities
Severe	Patient is incapable to work or perform usual activities

8.4.2 Definition of Causality

The sponsor and the investigators will use the following definitions to assess the relationship of SAEs to the IP or the investigation procedure.

Not related:

Relationship to the device or procedures can be excluded when:

- the event has no temporal relationship with the use of the IP, or the procedures related to application of the IP;
- the SAE does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the SAE;
- the event involves a body-site or an organ that cannot be affected by the device or procedure;
- the SAE can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the IP used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.

Possible

The relationship with the use of the IP or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

Probable

The relationship with the use of the IP or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

Causal relationship

The SAE is associated with the IP or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with IP use/application or procedures;
- the event involves a body-site or organ that
  - the IP or procedures are applied to;
  - the IP or procedures have an effect on;

- the SAE follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the SAE (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the IP used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the SAE.

The sponsor and the investigators will distinguish between the SAEs related to the IP and those related to the procedures (any procedure specific to the clinical investigation). If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.

8.5 Adverse Event Follow-up Procedures

The investigator should take all appropriate measures to ensure the safety of the patients and should therefore follow-up the outcome of any SAE (clinical signs, laboratory values etc.) until the return to normal or consolidation of the patient's condition. Thus, an SAE, i.e. the event primarily fulfilling criteria of seriousness, may end even if the underlying disease is still ongoing.

In case of any SAE, the patient must be followed until clinical recovery is completed and/or laboratory results have returned to normal, or until progression has been stabilised. This may imply that follow-up will continue after termination of the trial, and that additional investigation may be requested by the CRO. This may mean that the CRO will ask the investigator for further clinical reports and documents, even if these are generated after the end of the patient's participation in the trial, if this is needed to finally assess the outcome of a SAE and of the patient's safety with respect to this SAE.

8.6 Recording and Reporting of events to authorities

In general, AEs, SAEs and device deficiency will be assessed by the sponsor and reported to authorities involved.

Reportable events to authorities in accordance with EU MDR Article 80 are:

a) any serious adverse event that has a causal relationship with the IP, the comparator or the investigation procedure or where such causal relationship is reasonably possible;

b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;

c) any new findings in relation to any event referred to in points a) and b).

For all **reportable events which indicate an imminent risk** of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it, the sponsor will report to authorities immediately, but not later than **2 calendar days** after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.

This includes events that are of significant and unexpected nature such that they become alerting as a potential public health hazard. It also includes the possibility of multiple deaths occurring at short intervals.

Any other reportable events or a new finding/update to it, will be reported by the sponsor to involved authorities immediately, but not later than **7 calendar days** following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

The sponsor will report in line with EU guidelines (e.g. using SAE collection table of the MDCG guideline "Guidance on safety reporting in clinical investigations") and/or national guidelines (e.g. reporting forms of individual SAEs of the German BfArM), if applicable. The quarterly SAE summary will also be reported.

Routine clinical requirements for physicians of reporting deficiencies of non-IP devices or drug reactions to the corresponding manufacturer as defined in applicable regulatory documents for routine clinical care reporting are not touched by this procedural study definition.

9. Study Schedule

All data and assessments described in the following sections have to be documented as defined in the e-CRF, even if not described in detail in the study protocol.

9.1 Visit Schedule

The timing of study visits and assessments are outlined in Table 1. The term “visit” in the context of study procedures is related to both, clinical visits at the site as well as to documentation forms in the e-CRF.

Assessments and procedures	**Baseline**	**1 month FU**[1, 3]
Signed informed consent form	x	
Check of inclusion & exclusion criteria	x	
Medical history assessment	x	
Physical examination	x	
Clinical routine laboratory parameters[2]	x	
Documentation of concomitant medication	x	
Thyroid surgery[5]	x	
Generalised Anxiety Disorder questionnaire (GAD-7)	x	x
General Health Questionnaire (EQ-5D-5L)	x	x
Assessment of adverse events[4]	x	x

Table 1: Study visit schedules and procedures

[1] Time window ± 7 days related to visit schedules as displayed in the e-CRF
[2] Blood sample not older than 2 weeks at the date of baseline visit
[3] By means of patient questionnaires sent to and replied by the patient
[4] Including provision of external medical documents
[5] Within 3 months after patient’s informed consent

9.2 Baseline Visit

9.2.1 Pre-operative enrolment

Enrolment of eligible patients might be performed at a patient’s visit in hospital up to 3 months prior to thyroid surgery. In any case, prior to any data documentation in e-CRF and prior to any trial related procedure, a signed informed consent form has to be obtained from every patient to be enrolled in HEDOS and kept on

file locally. The date of written informed consent will be documented in e-CRF (= date of enrolment), even if weeks prior to thyroid surgery. It represents day 1 of the study participation of each individual patient.

The date of the baseline visit is the date of documenting in- and exclusion criteria (= screening process). Other clinical assessments may also be documented on this date even if their date of origin is prior to baseline visit but within the permitted time window. The date of the baseline visit must not be prior to the date of enrolment.

At the baseline visit, the investigator or designee will:

- Obtain patients' informed consent (investigator, may be prior to baseline visit) and document it (investigator or designee).
- Document all inclusion and exclusion criteria.
- Assess patient's medical history.
- Perform physical examination, record vital signs and document routine clinical laboratory parameters.
- Document concomitant medication.
- Document index thyroid surgery including placement of sensor(s) and data on IP used.
- Document and assess any adverse event from enrolment until hospital discharge.
- Ask the patient to complete the EQ-5D-5L and the GAD-7 questionnaires prior to thyroid surgery.

A patient meets eligibility criteria of the study if he passed all inclusion and exclusion criteria as described in the sections above.

9.2.2 Thyroid surgery

Index thyroid surgery should preferably be performed during the same hospital stay as the baseline visit. However, if a patient provided signed informed consent at an outpatient visit prior to the index thyroid surgery stay, mandatory data obtained at both patient visits will be documented in the baseline visit.

Index thyroid surgery should in any case be performed within 3 months after the patient gave informed consent for study participation (= date of enrolment).

Any event during the hospital stay for index thyroid surgery which fulfils criteria of an adverse event has to be adequately documented in the eCRF.

The baseline visit ends with hospital discharge.

9.3 Follow-up

The day of index thyroid surgery is day 1 of follow-up on primary and secondary endpoints.

Each patient will be followed until one month after day of index thyroid surgery (± 7 days related to visit schedules as displayed in the e-CRF) or until withdrawal of consent (WOC) or death.

9.3.1 Clinical follow-up after 1 month using patient questionnaires

One month after day of index thyroid surgery (± 7 days related to visit schedules as displayed in the e-CRF) or triggered by documentation of withdrawal of consent (WOC), three questionnaires will be sent to the patients by their corresponding study sites together with toll-free envelopes for reply. Patients will be asked to:

- Complete the EQ-5D-5L and the GAD-7 questionnaires
- Document clinical events in a FU questionnaire which are suspicious as AEs.

In case of missing reply after one written reminder by the study site, the patient will be contacted by the study site by phone in order to obtain the required information.

In case a patient reports a clinical event, which is suspicious as SAE, the responsible study site will contact the patient's family doctor, and / or the hospital where the patient was treated, and ask for supporting documents (i.e. hospital discharge letter, diagnostic reports) as applicable. The study site is responsible for completion of the reported event data in the e-CRF.

9.4 Patient Withdrawal from the Study

Individual study participation is only prematurely terminated in case of patient's death or explicit wish (withdrawal of consent). Premature termination of study participation of a study patient is not possible by decision of an investigator.

If a patient expresses his **Withdrawal Of Consent (WOC)** to any further study participation, completion of FU documentation in e-CRF is mandatory. If WOC is expressed during a personal site visit, site staff should document AEs since last assessment, ask the patient to complete the EQ-5D-5L and the GAD-7 questionnaires and send them to CRI. If withdrawal of consent is expressed not during a personal site visit, site staff should inform the patient that final questionnaires will subsequently be send to him by mail and should ask the patient to complete and send them to CRI.

9.5 Blood Samples

Routine laboratory parameters obtained within routine clinical care are part of the standard work-up of the patient's status before study participation and therefore not considered as part of study related procedures. If these parameters can be assessed from a blood sample not older than 14 days at the date of baseline visit, blood sampling and analysis do not have to be repeated within the study baseline visit.

All blood parameters will be determined at local laboratory provided their analytical laboratories are certified. In the e-CRF laboratory values and information whether the value is assumed to be clinically normal or abnormal will be documented. Standard normal values of the corresponding laboratory will not be documented because the assessment of clinical abnormality is more relevant in this trial compared to formal rating against normal values (e.g. in case of chronic diseases).

10. Duration of Study Participation

The following definitions apply only to the diagnostic accuracy study HEDOS, that for HEDOS II will be defined in the corresponding study protocol.

10.1 Overall Duration of the Study

Enrolment of patients is expected to be accomplished after about 12 months. Last Follow-up assessment will be reached about 1 month after enrolment of the last patient. Thus, total study duration of about 12 months + 1 month = 13 months plus 1 month for final data cleaning is expected. The total study duration is expected to be about 14 months.

Global end of study (EOS) is defined as the date of the last clinical follow-up on outcome after 1 month performed in a study patient (= last patient last visit). This date will be approved by the sponsor and announced to the sites by the CRO.

10.2 Individual Duration of the Study

The follow-up time for each patient will be about 1 month. Every patient will be followed according to study protocol until about one month after index thyroid surgery, withdrawal of consent or death.

11. Stopping and Discontinuation Criteria

When the study is terminated, the nature of termination will be documented (scheduled end/premature termination with justification). Termination of the study will be communicated in writing according to the legal requirement, premature termination in line with rules for expedited reporting. The decision to stop the study will be reached jointly by sponsor and SC.

11.1 Discontinuation Criteria related to the Study

Following a recommendation of the SC, the sponsor may decide discontinuation of the study due to efficacy criteria or safety concerns. Discontinuation of the study can also be decided if patients cannot be recruited in sufficient numbers within a certain time period.

Furthermore, the sponsor in collaboration with the Chief Investigator (CI) has the right to close local study sites for enrolment of further patients if major protocol deviations occur, if the site does in general not adequately comply with the study protocol or decisions of the committees or the CI or if the site remains inactive for several months. Such decisions will always be taken on a case-by-case basis.

11.2 Discontinuation Criteria related to the Patient

- The investigator is not able to decide about the discontinuation of study participation of any patient enrolled. In this case, after enrolment and index thyroid surgery the patient will continue to be followed according to study protocol until about 1 month after index thyroid surgery, withdrawal of consent or death.
- Study patients will be advised in the informed consent forms that they have the right to withdraw from study participation at any time without giving reasons. However, the investigator should try to find out the reason for patient's withdrawal of consent and document it in the e-CRF.
- In case that a protocol deviation is noticed, the patient will stay in the trial and will be followed according to protocol.
- In case that an AE/SAE occurs which is not death, the patient will stay in the trial and will be followed according to protocol.

Reasonable effort should be made to contact any patient lost to follow-up during the course of the study in order to complete assessments and retrieve any outstanding data. The responsible investigator will take all acceptable measures to retrieve information on outcome of all patients enrolled in the trial.

12. Statistics and Methods

A general description of the statistical methods to be used to analyse the diagnostic accuracy study (stage 1 of the seamless design) is outlined below. The subsequent stage 2 study of the seamless design will be described in detail in a separate study protocol with reference to this document, to be finalised after the results of the first study are available. A more detailed statistical analysis plan (SAP) is provided in a separate document for both stages together.

Statistical analyses will be performed using SAS and R, the version used will be specified in the SAP. The SAP will accommodate protocol amendments or unexpected issues in study execution or data that affect planned analyses, and will provide more details on the analytic approaches, coding guidelines, censoring of time-to-event variables, and output tables and figures.

12.1 Statistical Methods

12.1.1 Description of Baseline characteristics

A descriptive analysis of parameters assessed at baseline will be performed. Categorical variables are summarised by absolute and relative frequencies. Continuous variables are summarised by mean and standard deviation (SD) or by median, quartiles and/or interquartile range (IQR), as appropriate. The number of available observations and the number of missing observations are reported separately for the diagnostic groups (clinically relevant hemorrhage present vs. not present).

12.1.2 Analysis of the primary endpoint

Analyses of the co-primary endpoints in the stage 1 diagnostic study are based on the population of all enrolled patients with subsequent index thyroid surgery. This corresponds to the intention to diagnose (ITD) principle, whereas missing or inconclusive values are imputed by false positive or false negative results, respectively [25]. In accordance with the ICH E9 guidelines, the analysis population of all these patients is defined as the “Full Analysis Set” (FAS).

In the first pair of primary hypotheses, sensitivity and specificity are considered as co-primary endpoints. They are combined via the Intersection-Union Test. The global null hypothesis can only be rejected if both individual null hypotheses of sensitivity and specificity are rejected. The corresponding first global alternative hypothesis states that the IP exceeds a pre-defined minimum sensitivity of 80% and specificity of 65%. The second primary global hypothesis considers the three-level decision system. Due to the hierarchical order of primary hypotheses, the second primary global hypothesis can only be evaluated in a confirmative way if the first global primary hypothesis leads to a significant result. The hierarchical order of hypotheses requires no adjustment of the type I error rate.

The analysis of the first global primary hypothesis contains the estimation of the resulting sensitivity and specificity of the IP according to the defined cut-off value of 12 mmHg. For the estimation, a mixed binary logistic regression model is used [26]: The binary test result represents the dependent variable, the true disease status is included as fixed effect. Additionally, a random-intercept is estimated for each centre. Sensitivity is estimated via the calculation of the marginal mean for a diseased individual (=surgical intervention performed which confirmed post-operative hemorrhage needing intervention). False-positive rate, which is the counter probability of the specificity, is estimated via the calculation of the marginal mean for a non-diseased individual. Two-sided 95%-logit confidence intervals with p-values are reported.

If the mixed binary logistic regression model does not converge, a non-parametric multi-factorial approach is used to estimate sensitivity and specificity [27]. With this approach, separate estimates of sensitivity and specificity, respectively, are calculated for each centre and finally weighted averaged. Two-sided 95%-logit confidence intervals for the averaged sensitivity and specificity and p-values based on Analysis-of-Variance-type-statistics are reported.

The first primary null hypothesis can be rejected if the lower limit of both confidence intervals lies above the according pre-defined minimum threshold (0.8 for sensitivity and 0.65 for specificity).

The analysis of the third primary endpoint regarding the area under the receiver-operating characteristic curve (AUC) of the three-level decision rule is performed in analogy to the analysis of the first co-primary pair. The according null hypothesis can be rejected if the lower limit of the confidence interval lies above the according pre-defined minimum threshold of 0.7.

Further details will be specified in the SAP.

12.1.3 Analysis of the secondary endpoints

The positive and negative predictive values are reported descriptively with 95%-logit confidence intervals. Their calculation follows from the analysis method chosen for the primary endpoints. To estimate predictive

values with the mixed binary logistic regression model, the true disease status represents the dependent variable. The test results are included as fixed effects and again a random-intercept is estimated for each centre. Positive predictive value is estimated via the calculation of the marginal mean for a test positive result. False-negative rate, which is the counter probability of the negative predictive value, is estimated via the calculation of the marginal mean for a non-diseased individual. Two-sided 95%-logit confidence intervals with p-values are reported.

Other secondary endpoints, including safety endpoints, will be analysed descriptively.

12.1.4 Safety analysis

Safety analysis will be performed in the safety population, i.e. all patients enrolled (= all patients giving signed informed consent), irrespective of whether index thyroid surgery has been performed according to study protocol. Safety analysis will cover relevant aspects of safety reporting to regulatory bodies according to EU MDR Article 80.

12.1.5 Subgroup analysis

Subgroup analyses for primary and secondary endpoints are based on the same analysis sets and ITD scope as in the main analyses of these endpoints. The subgroup analyses are presented descriptively without formal hypotheses testing and will be performed post-hoc.

12.2 Sample Size and Power Calculations

Initial sample size calculation for the stage 1 study is performed for the first primary hypothesis considering sensitivity and specificity as co-primary endpoints. This hypothesis states the superiority considering sensitivity and specificity of the IP against pre-defined minimum thresholds. The optimal sample size calculation for a single-arm confirmatory diagnostic accuracy study is applied [28].

The sensitivity of the IP is assumed to be 99%, the specificity is assumed to be 95%. The pre-defined minimum sensitivity equals 80%, the minimum specificity is 65%. A higher minimum sensitivity than minimum specificity is chosen as false negative results are much more relevant for the patient than false positive results. The assumed prevalence of clinically relevant hemorrhage within 48 hours following thyroid surgery is 1.5%. The two-sided significance level is set to 5% for the endpoint considering sensitivity and the endpoint considering specificity, respectively. An overall power of 80% is aimed. This leads to a total sample size of 1,470 patients enrolled and measured which is based on the assumed prevalence of 1.5%. Due to the optimal sample size calculation, the endpoint considering the sensitivity reaches a power of 86% and the endpoint considering the specificity a power of 98%. If the prevalence differs at least 22 events of clinically relevant hemorrhage within 48 hours following thyroid surgery need to be observed. Consecutive patient recruitment without any selection is important to receive valid estimates of predictive values as secondary endpoints.

The sample size calculations are performed with R version 4.0.2.

12.3 Interim Analyses

A blinded adaptive design to re-estimate the sample size for the stage 1 study is planned. The interim analysis to re-estimate the prevalence and the sample size is performed after 50% enrolled and measured study patients. Using the optimal sample size calculation (Stark and Zapf 2020), the sample size will be re-estimated based on the estimated prevalence. If the re-estimated sample size is larger than the size of the internal pilot study, recruitment continues until the re-estimated sample size is reached. The maximum sample size is set to 4,500 patients enrolled and measured.

Due to the blinded character of the adaptive design, no adjustment of the type I error rate is necessary [29].

12.4 Patient Selection for Analyses

A patient is considered as enrolled into the current trial according to regulatory requirements as soon as the signed the informed consent form. All enrolled patients will be part of the safety population.

A patient is considered as measured as soon as he is enrolled, screened, index thyroid surgery as defined in the study protocol was performed, and pressure monitoring by the IP was started. All measured patients will be part of FAS and will be followed according to study protocol.

Refer to section 6.2.1 for additional details.

13. Access to Source Data / Documents

13.1 Source Data

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents.

13.2 Source Documents

Source documents are defined as original documents, data and records (e.g. hospital records, clinical and office charts, electronic patient records, laboratory notes, memoranda, patient diaries or evaluation check lists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, records kept at pharmacy, at the laboratories and at medico technical departments) involved in this clinical study.

In case of data that are result of patient reporting and will not be documented in clinical routine, the e-CRF is the source document, if the patients answer is documented there without prior documentation.

13.3 Direct Access

Direct access is defined as the permission to examine, analyse, verify and reproduce any records and reports that are important for evaluation of a clinical study. Any party with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and sponsor proprietary information.

The investigator agrees that representatives or the designees of the sponsor such as monitors and auditors, and appropriate regulatory agencies will be given direct access to the regular clinical files of the patient.

14. Quality Control and Quality Assurance

14.1 Quality Control

Quality control is defined as the operational techniques and activities, such as monitoring, undertaken within the quality assurance system to verify that the requirements for quality of the study related activities have been fulfilled. Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

14.2 Initiation Visit

At each site an initiation visit will be performed by a representative of the CRO before enrolment of the first patient at this site.

14.3 Study Monitoring

The investigators and study sites involved in the clinical trial are obliged by current regulations and by contract to permit clinical trial-related monitoring, audits and regulatory inspections, if applicable, including provision of direct access to source data and documents.

A Risk Based Monitoring Plan (RBMP) will establish the guidelines for conducting quality management (e. g. on-site monitoring visits, off-site central monitoring, and other tasks of quality control). The RBMP will identify the requirement to perform an ongoing review of any e-CRF item (automated, by means of statistics and by research professionals, e. g. manual queries), the amount of source data verification and review, the frequency of on-site monitoring visits and actions to be taken based on the result of central and on-site monitoring. Thus, frequency of on-site visits and amount of source data verification is dynamic and dependent on performance and quality of each study site. Authorised, qualified representatives of the designated CRO will accomplish the monitoring of the study sites during the trial.

It is important that the investigator and relevant personnel are available during the monitoring visits and that an appropriate location and sufficient amount of time is devoted to the process. During the monitoring visit a PC with internet connection should be available to the monitor for direct connection to the internet database of the study and to all the data of the patients if stored in the data system of the hospital.

The main duty of the monitor is to help the sponsor and the investigator to maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the trial. At regular intervals during the study, the local site will be contacted through monitoring visits, letters/ emails or telephone calls by a monitor to review the progress of the study.

14.4 Close Out Visit

Independent close-out visits are not planned. The sponsor is responsible for return of IP devices and related equipment from participating study sites. In case of special requests by the sponsor, a separate close out visit may be performed at the end of the trial participation of a study site. The close out visit may be combined with the last monitoring visit.

14.5 Quality Assurance

Quality Assurance is defined as the planned and systematic actions that are established to ensure that the study is performed and the data are generated, documented (recorded) and reported in compliance with Good Clinical Practice (GCP) as defined in ISO 14155 and the applicable regulatory requirements.

The investigator should permit auditing by or on behalf of the sponsor and inspection by applicable regulatory authorities. The investigator shall take appropriate measures required by the sponsor to take corrective actions for all problems found during the audit or inspections.

14.5.1 Inspections

An Inspection is defined as the act by a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authorities to be related to the clinical study and that may be located at the site of the study, or at the sponsors and/or clinical research organisation facilities or at any other establishments deemed appropriate by the regulatory authorities.

14.5.2 Audits

An audit is a systematic and independent review of study related activities and documents to determine whether the validated study related activities were conducted and the data were recorded, analysed and accurately reported according to the protocol, designated Standard Operating Procedures (SOPs), GCP as defined in ISO 14155:2020 and the applicable regulatory requirements. An independent audit at the study site may take place at any time during or after the study.

15. Ethical and Legal Consideration

This is a trial with a non-marketed diagnostic medical product as IP which meets relevant ethical and regulatory standards (e.g. EU MDR, related national acts, GCP as defined in ISO 14155:2020). The trial will be conducted in accordance with the principles laid down in the Declaration of Helsinki in its version of October 2013 (Fortaleza) (Appendix V).

Before initiating the study, approval of the corresponding Ethics Committees will be obtained.

15.1 Ethical Consideration

15.1.1 Ethics Committee (EC)

Provided this is not contradictory to national law, the principal investigator is responsible for submitting an application to the appropriate EC. Furthermore, the principal investigator is required to forward to the sponsor or the CRO a copy of the written and dated approval or favourable opinion of the local EC. The CRO will provide substantial support for any EC submission. The sponsor is responsible to assure that approval of the local EC is obtained prior to study start in the respective study site in accordance with local requirements.

During the trial, any modification to trial application or substantial amendment to clinical trial protocol should be submitted to regulatory bodies and ECs involved. They will also be informed of any event likely to affect the safety of patients or the continued conduct of the trial, in particular of any change in safety aspects.

15.1.2 Steering Committee (SC)

The trial SC will consist of a small group of medical experts (representatives of study sites and independent experts) and an expert biostatistician (refer to Appendix I). The functions of the SC are the following:

- Overall responsibility for the execution and scientific reporting of the trial.
- Advice on the scientific and clinical aspects of the study protocol and related documents.
- Together with the sponsor responsibility for the conduct of the study according to the guidelines of GCP as defined in ISO 14155:2020 and applicable medical guidelines including the monitoring of patient recruitment.
- Reassessment of benefit-risk ratio if deemed necessary.
- Decisions on continuation or termination of the study.

A SC charter providing operating procedures and responsibilities will be discussed and enacted at the latest during the second meeting. Meeting frequency will be defined by the committee and may vary depending on tasks. Meetings may be conference calls or face-to-face meetings. Minutes of each meeting will be provided.

15.1.3 Endpoint Review Committee (ERC)

The ERC will consist of clinical experts and will centrally adjudicate SAEs as primary and secondary outcome parameters if based on clinical events. Adjudication will primarily be performed as a continuous online-process within the e-TMS, depending on the number of documented and cleaned SAEs. In addition, meetings may be performed, either face-to-face or conference calls, if needed. Minutes of each meeting will be provided.

An ERC charter providing operating procedures and responsibilities will be discussed and enacted latest at the ERC kick-off meeting prior to start of adjudication.

15.1.4 Data and Safety Monitoring Board (DSMB)

This diagnostic accuracy study (stage 1) has no pre-defined treatment and no blinded therapies. The primary outcome parameter is sensitivity and specificity of detection of clinically relevant hemorrhage within 48 hours following thyroid surgery. The IP is only of diagnostic character. One component of the IP (the catheter-based pressure sensor) will be inserted into the surgical wound before closure but no blinding of the procedures is performed. Thus, the function of a DSMB with access to unblinded data necessary for assessment of the safety status of a blinded therapy study can be ensured in the context of this diagnostic study without blinded therapies by ERC and SC.

15.2 Legal Consideration

The study will be performed in Germany and Austria as medical device study with a diagnostic IP in accordance with EU MDR and related national acts as well as ISO 14155:2020 and EU General Data Protection Regulation (2016/679, GDPR).

In general, no therapy procedures will be defined by the study protocol with the exception of the index thyroid surgery. Thyroid surgery procedures for the individual study patient will be decided and performed by the treating physician in line with applicable medical guidelines and local policies in routine clinical care based on the clinical situation of the individual study patient.

All other medical therapies applied within this trial are at the discretion of the treating physician and will be utilised as routine clinical care therapies with marketed products used in line with their corresponding market authorisation and represent SOC as defined in current medical guidelines. This also applies to all medical procedures within the trial.

No additional invasive or stressful diagnostic or therapeutic procedures will be performed compared to routine clinical care of the patient population in focus.

Approval of the study from regulatory authorities and ethics committees will be obtained before first patient in.

15.3 Modification of Protocol

Any substantial amendment to the clinical trial protocol requires written approval/favourable opinion by responsible regulatory bodies and ECs prior to its implementation, unless there are overriding safety reasons that require immediate action. In some instances, an amendment may require a change to the informed consent form. In this case, the investigator must receive approval/favourable opinion of the responsible EC concerning the revised informed consent form prior to implementation of the change.

15.4 Financing and Insurance

The trial is completely funded by the sponsor. The costs necessary to perform the study will be agreed upon with each investigator and will be documented in a separate financial agreement which will be signed by the investigator and the CRO on behalf of the sponsor, prior to the study commencing.

A patient insurance within this study on top of insurance in place by treating institutions and manufacturers of medical devices used within this study according to routine clinical has been effected.

15.5 Investigators' Information on investigational medical product

Investigators will be informed and trained on the diagnostic IP and its use within the index thyroid surgery by the sponsor. Each training will be certified. In general, other medical therapies and medical procedures are not affected by the diagnostic IP.

In case of new information related to the diagnostic IP or its handling gathered within the course of the study the sponsor is responsible for timely information of the investigators and the patients, if necessary.

15.6 Personal Data and Data Protection

All data obtained in the context of the clinical trial are subject to data protection. This applies to patients' data as well as to investigators' personal data which may be included in any database of the sponsor or the CRO. Data protection processes and responsibilities according to EU General Data Protection Regulation (GDPR) are defined in an agreement on joint control of data between study sites and the sponsor as well as in an agreement of contract data processing between the sponsor and the CRO.

The study sites are responsible that patient documents (e.g. copies of reports on special findings) transmitted to the CRO or the sponsor contain no names or other directly identifying data, but only the year of birth and a relevant patient study number given by the e-TMS. The storage of data for statistical analysis shall likewise be performed only under the patient's study number.

15.7 Data Handling and Record Keeping

15.7.1 Completion of Case Report Forms

All medical data in this trial are to be recorded directly in e-CRFs provided by the CRO. Documentation on paper will be restricted to exceptional circumstances, only, which have to be approved in writing by the CRO. The investigator must ensure the accuracy, completeness and timeliness (and legibility in case of documentation on paper) of data.

15.7.2 Archiving

The principal investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents. The principal investigator has to retain the study documents (i.e. investigator site file) after the completion or discontinuation of the study for the time period as required by national legislation. This especially applies to patient's signed informed consent forms and the patient identification list.

The principal investigator must notify the sponsor prior to destroying any essential study documents within the specified period following completion or discontinuation of the trial.

15.8 Confidentiality

All information disclosed or provided by the sponsor (or any company / institution acting on his behalf), or produced during the trial, including, but not limited to, the clinical trial protocol, the e-CRFs and the results obtained during the course of the trial, is confidential. The principal investigator or any person under his/her authority agrees to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the sponsor. The investigators shall be bound by the same obligation as the principal investigator. The principal investigator shall inform the investigators of the confidential nature of the trial. Both, the principal investigator and the investigators shall use the information solely for the purposes of the trial, to the exclusion of any use for their own or for a third party's account.

15.9 Responsibilities

The sponsor of this trial is responsible for taking all reasonable steps to ensure the proper conduct of the trial with regard to ethical aspects, clinical trial protocol compliance, integrity and validity of the data recording.

16. Final Report and Publication Policy, Property Rights

The sponsor will be responsible for preparing the final study report that is to be signed by the SC. The sponsor will communicate the results of the trial to the investigators as well as to responsible regulatory bodies and ECs.

The SC will be primarily responsible for the creation, review and submission of publications and presentations relating to the major aspects of the study within a timely fashion after completion of the study. All analyses will be the responsibility of the SC. Manuscripts for publication will be drafted by members of the SC or other interested investigators. All manuscripts will be subject to coordinated submission and review prior to submission. Coordination will be done by SC.

All relevant measures for transparency of clinical trials, and especially the recommendations of the editors of the major medical journals, will be met. The publication rules are regulated separately and described in detail in a publication policy that is confirmed by the SC and the sponsor.

All information and documents provided by the sponsor or its representatives are and remain the sole property of the sponsor. The investigators shall not mention any information for any other intellectual property rights. All results, data, documents and inventions, which arise directly or indirectly from the trial in any form, shall be the immediate and exclusive property of the sponsor.

17. Definitions and Classification

17.1 Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the EC-approved protocol (acc. to ICH guideline E3 - questions and answers, 2012).

17.2 Important Protocol Deviation

Important protocol deviations are any protocol deviations that may significantly impact the completeness, accuracy, and/or of the study data or that may significantly affect a subject's rights, safety, or well-being. For example, important protocol deviations may include enrolling subjects in violation of key eligibility criteria designed to reliability ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial. Protocol violation and important protocol deviation are sometimes used interchangeably to refer to a significant departure from protocol requirements (acc. to ICH guideline E3 - questions and answers, 2012). Study-specific definitions of important protocol deviations may be given by the SC.

Patients with important protocol deviations will be excluded from the per-protocol analysis. Details are given in the SAP.

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19. Signatures

The undersigned have read this protocol and agreed to conduct this study in accordance with all stipulations of the protocol, with current EU and national regulations, with the principles of good clinical practice, and in accordance with the Declaration of Helsinki.

Date	**Signature**
08/08/2023	PD Dr. Markus Albertsmeier, Chief Investigator
	Olivia Fedunik-Brehm, SC member and sponsor representative
	Professor Peter E. Goretzki, SC member
	Professor Philipp Riss, SC member
	Dr Ulrich Wirth, SC member
	Professor Antonia Zapf, SC member and study statistician
	Professor Andreas Zielke, SC member
	Local principal investigator
	(Name local principal investigator; printed)

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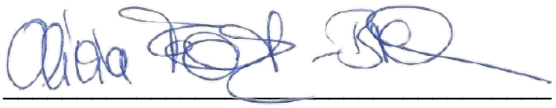
Date	**Signature**
_____	_____ PD Dr. Markus Albertsmeier, Chief Investigator
07.08.2023	 Olivia Fedunik-Brehm, SC member and sponsor representative
_____	_____ Professor Peter E. Goretzki, SC member
_____	_____ Professor Philipp Riss, SC member
_____	_____ Dr Ulrich Wirth, SC member
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Date	Signature
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_____	_____ Olivia Fedunik-Brehm, SC member and sponsor representative
23.8.2023	_____ Professor Peter E. Goretzki, SC member
_____	_____ Professor Philipp Riss, SC member
_____	_____ Dr Ulrich Wirth, SC member
_____	_____ Professor Antonia Zapf, SC member and study statistician
_____	_____ Professor Andreas Zielke, SC member
_____	_____ Local principal investigator
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_____	_____ Olivia Fedunik-Brehm, SC member and sponsor representative
_____	_____ Professor Peter E. Goretzki, SC member
25.8.2023	_____ Professor Philipp Riss, SC member
_____	_____ Dr Ulrich Wirth, SC member
_____	_____ Professor Antonia Zapf, SC member and study statistician
_____	_____ Professor Andreas Zielke, SC member
_____	_____ Local principal investigator
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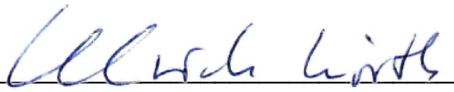
_____	_____ Professor Peter E. Goretzki, SC member
_____	_____ Professor Philipp Riss, SC member
10.08.2023	 Dr Ulrich Wirth, SC member
_____	_____ Professor Antonia Zapf, SC member and study statistician
_____	_____ Professor Andreas Zielke, SC member
_____	_____ Local principal investigator
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_____	_____ Olivia Fedunik-Brehm, SC member and sponsor representative
_____	_____ Professor Peter E. Goretzki, SC member
_____	_____ Professor Philipp Riss, SC member
_____	_____ Dr Ulrich Wirth, SC member
8.8.2023	A. Zapf Professor Antonia Zapf, SC member and study statistician
_____	_____ Professor Andreas Zielke, SC member
_____	_____ Local principal investigator
	_____ (Name local principal investigator; printed)

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Date	Signature
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	Olivia Fedunik-Brehm, SC member and sponsor representative
	Professor Peter E. Goretzki, SC member
	Professor Philipp Riss, SC member
	Dr Ulrich Wirth, SC member
	Professor Antonia Zapf, SC member and study statistician
09/08/23	Professor Andreas Zielke, SC member
	Local principal investigator
	(Name local principal investigator; printed)

Appendix I. Members of the Steering Committee

(Sorted in alphabetic order)

- **Olivia Fedunik-Brehm**
  CEO, Representative of the sponsor (non-voting), ISAR-M GmbH, Bergfeldstraße 9, 83607 Holzkirchen, Germany; e-mail: olivia.fedunik-brehm@isar-m.com
- **Professor Dr. Peter E. Goretzki**
  Surgeon, Chirurgische Klinik Campus Charité Mitte / Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany; e-mail: peter.goretzki@charite.de
- **Professor Dr. Philipp Riss**
  Surgeon, Klinische Abteilung für Viszeralchirurgie, Medizinische Universität Wien, Währinger Gürtel 18-20, 1090 Wien, Austria, e-mail: philipp.riss@meduniwien.ac.at
- **Dr Ulrich Wirth**
  Surgeon, Klinik für Allgemein-, Viszeral-, Gefäß- und Transplantationschirurgie – Campus Großhadern, Marchioninistraße 15, D-81377 München, Germany; e-mail: ulrich.wirth@med.uni-muenchen.de
- **Professor Dr. Antonia Zapf**
  Statistician, Universitätsklinikum Hamburg-Eppendorf, Institut für Medizinische Biometrie und Epidemiologie, Martinistraße 52, 20246 Hamburg, Germany; e-mail: a.zapf@uke.de
- **Professor Dr. Andreas Zielke**
  Surgeon, Chirurgische Klinik, Diakonie-Klinikum, Rosenbergstraße 38, 70176 Stuttgart, Germany; e-mail: andreas.zielke@diak-stuttgart.de

Appendix II. Time Table

Section	Tasks	Date
Draft study planning	Draft Protocol	December 2020
Final study planning	Final protocol – First submission	February 2022
	Final protocol – Second submission	December 2022
Study preparation	E-TMS, e-CRF; other study relevant documentation	June 2021
	Start of site selection, site contacts, site evaluation	May 2021
	First EC submission	May 2021
	First submission to authorities	September 2021
	Second EC submission	October 2022
	Second submission to authorities	November 2022
Study initiation	Start of site contracting	August 2021
	Start of supply of sites with study materials, start of initiation visits	February 2022
	Start of recruitment period (FPI)	February 2023
	End of recruitment period (LPI)	January 2024
Study duration	End of follow-up of last patient	February 2024
	Median follow-up period of all patients	1 month
Database lock	End of final data cleaning	March 2024
Final analysis	Results to be presented to SC	April 2024

Appendix III. Patient questionnaires

Follow-up questionnaire on events

HEDOS-Studie: Patienten-Fragebogen zum Verlauf

Patienten ID: «PatientID», **Geschlecht:** «Geschlecht», **Geburtsjahr:** «Geb.Jahr» (Zentrums-ID «CID»)

Sehr geehrte Patientin, sehr geehrter Patient,

seit «Date_baseline» nehmen Sie als Patient(in) der Klinik/Praxis «Institution» («city») an der HEDOS-Studie teil, die Nachblutungen nach Schilddrüsen-Operationen mit einem neuen Diagnosegerät untersucht. Das Auftragsforschungsinstitut CRI in München wurde mit der Durchführung dieser Studie beauftragt.

Zu Beginn Ihrer Studienteilnahme wurden bereits Ihre medizinischen Daten durch Ihre Ärzte für diese Studie dokumentiert. Nun benötigen wir nach ihrer Schilddrüsen-Operation Informationen darüber, wie es Ihnen zur Zeit geht und wie es Ihnen zwischenzeitlich bezüglich Ihrer Gesundheit und auch Ihres Wohlbefindens ergangen ist. So ist es für die Auswertung der Studie auch wichtig zu erfahren, ob Sie seit Ihrer Entlassung nach der Schilddrüsen-Operation beim Arzt oder im Krankenhaus waren.

Wir bitten Sie daher, die folgenden **drei Fragebögen** vollständig auszufüllen und in dem beigefügten Rückumschlag an CRI in München zu schicken. Sie können den fertigen Rückumschlag ohne Briefmarke in einen Postbriefkasten ihrer Wahl einwerfen, denn das **Porto bezahlt CRI**.

WICHTIG: Aus Datenschutzgründen enthalten Ihre Fragebögen nur pseudonymisierte Daten, d.h. nur Ihre Patienten-Nummer im Rahmen der HEDOS-Studie sowie Ihr Geschlecht und Ihr Geburtsjahr. CRI kennt Ihren Namen und Ihre Anschrift nicht, daher haben Sie dieses Schreiben und die Fragebögen über Ihr Studienzentrum erhalten. Bitte notieren Sie aus diesem Grund auch keinen Namen auf den Fragebögen oder auf dem Briefumschlag und unterschreiben Sie bitte nicht.

Falls Ihnen Fragen unverständlich vorkommen oder Sie Schwierigkeiten beim Ausfüllen bzw. Fragen zur HEDOS-Studie haben, wenden Sie sich bitte an Ihr Studienzentrum. Die Telefonnummer finden Sie auf Ihrer Patienteninformation.

Wir bedanken uns sehr für Ihre Mithilfe!

Mit freundlichen Grüßen

Ihr HEDOS-Studienteam

HEDOS-Studie: Patienten-Fragebogen zum Verlauf

Patienten ID: «PatientID», **Geschlecht**: «Geschlecht», **Geburtsjahr**: «Geb.Jahr» (Zentrums-ID «CID»)

Fragebogen vom Patienten ausgefüllt am (Datum): _ _ /_ _ / _ _ _ _ *(Tag / Monat / Jahr)*

1. Waren Sie seit Ihrer Entlassung nach der Schilddrüsen-Operation für mindestens eine Nacht im Krankenhaus?

   ☐ Nein

   ☐ Ja ➔ Bitte nennen Sie nachfolgend jeweils Datum, Grund der Krankenhausaufnahme und Name der Klinik

   A. Datum _ _ . _ _ . _ _ _ _ *(Tag / Monat / Jahr)*

   Grund _____

   Name der Klinik _____

   B. Datum _ _ . _ _ . _ _ _ _ *(Tag / Monat / Jahr)*

   Grund _____

   Name der Klinik _____

2. Waren Sie seit Ihrer Entlassung nach der Schilddrüsen-Operation bei einem niedergelassenen Arzt / in einer Arztpraxis?

   ☐ Nein

   ☐ Ja ➔ Bitte nennen Sie nachfolgend jeweils Datum, Grund und Fachrichtung des Arztes (z. B. Hausarzt, Orthopäde, Chirurg, Neurologe)

   A. Datum _ _ . _ _ . _ _ _ _ *(Tag / Monat / Jahr)*

   Grund _____

   Fachrichtung _____

   B. Datum _ _ . _ _ . _ _ _ _ *(Tag / Monat / Jahr)*

   Grund _____

   Fachrichtung _____

3. Wurde seit Ihrer Entlassung nach der Schilddrüsen-Operation eine neue chronische Erkrankung festgestellt?

   ☐ Nein

   ☐ Ja ➔ _____
   (bitte beschreiben)

HEDOS-Studie: Patienten-Fragebogen zum Verlauf

Patienten ID: «PatientID», **Geschlecht**: «Geschlecht», **Geburtsjahr**: «Geb.Jahr» (Zentrums-ID «CID»)

4. Sind seit Ihrer Entlassung irgendwelche Beschwerden oder Krankheitszeichen aufgetreten?
(z.B. Infektionen, Kopfschmerzen, Erbrechen etc., unabhängig von der Schilddrüsen-Operation)

☐ Nein

☐ Ja➔ Bitte nennen Sie nachfolgend nähere Angaben:

Beschreibung der Beschwerden: _____

Beginn: __ . __ . ____ *(Tag / Monat / Jahr)*

Intensität:
☐ Beschwerden sind gut tolerierbar
☐ Beschwerden behindern mich in meinem Alltag
☐ Ich kann nicht arbeiten oder meinen alltäglichen Aktivitäten nachgehen

Medikamentöse oder medizinische Behandlung dieser Beschwerden:
☐ Nein
☐ Ja, _____ *(bitte beschreiben)*

Aktueller Zustand:
☐ Beschwerden bestehen nicht mehr
Ende am __ . __ . ____ *(Tag / Monat / Jahr)*
☐ Beschwerden dauern heute noch an

Beschreibung der Beschwerden: _____

Beginn: __ . __ . ____ *(Tag / Monat / Jahr)*

Intensität:
☐ Beschwerden sind gut tolerierbar
☐ Beschwerden behindern mich in meinem Alltag
☐ Ich kann nicht arbeiten oder meinen alltäglichen Aktivitäten nachgehen

Medikamentöse oder medizinische Behandlung dieser Beschwerden:
☐ Nein
☐ Ja, _____ *(bitte beschreiben)*

Aktueller Zustand:
☐ Beschwerden bestehen nicht mehr
Ende am __ . __ . ____ *(Tag / Monat / Jahr)*
☐ Beschwerden dauern heute noch an

Beschreibung der Beschwerden: _____

Beginn: __ . __ . ____ *(Tag / Monat / Jahr)*

Intensität:
☐ Beschwerden sind gut tolerierbar
☐ Beschwerden behindern mich in meinem Alltag
☐ Ich kann nicht arbeiten oder meinen alltäglichen Aktivitäten nachgehen

Medikamentöse oder medizinische Behandlung dieser Beschwerden:
☐ Nein
☐ Ja, _____ *(bitte beschreiben)*

Aktueller Zustand:
☐ Beschwerden bestehen nicht mehr
Ende am __ . __ . ____ *(Tag / Monat / Jahr)*
☐ Beschwerden dauern heute noch an

EQ-5D-5L; Standardised measure of health-related quality of life developed by the EuroQol Group; version for Germany (deutsch)

Bitte kreuzen Sie unter jeder Überschrift DAS Kästchen an, das Ihre Gesundheit HEUTE am besten beschreibt.

BEWEGLICHKEIT / MOBILITÄT

- Ich habe keine Probleme herumzugehen ❑
- Ich habe leichte Probleme herumzugehen ❑
- Ich habe mäßige Probleme herumzugehen ❑
- Ich habe große Probleme herumzugehen ❑
- Ich bin nicht in der Lage herumzugehen ❑

FÜR SICH SELBST SORGEN

- Ich habe keine Probleme, mich selbst zu waschen oder anzuziehen ❑
- Ich habe leichte Probleme, mich selbst zu waschen oder anzuziehen ❑
- Ich habe mäßige Probleme, mich selbst zu waschen oder anzuziehen ❑
- Ich habe große Probleme, mich selbst zu waschen oder anzuziehen ❑
- Ich bin nicht in der Lage, mich selbst zu waschen oder anzuziehen ❑

ALLTÄGLICHE TÄTIGKEITEN *(z.B. Arbeit, Studium, Hausarbeit, Familien- oder Freizeitaktivitäten)*

- Ich habe keine Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑
- Ich habe leichte Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑
- Ich habe mäßige Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑
- Ich habe große Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑
- Ich bin nicht in der Lage, meinen alltäglichen Tätigkeiten nachzugehen ❑

SCHMERZEN / KÖRPERLICHE BESCHWERDEN

- Ich habe keine Schmerzen oder Beschwerden ❑
- Ich habe leichte Schmerzen oder Beschwerden ❑
- Ich habe mäßige Schmerzen oder Beschwerden ❑
- Ich habe starke Schmerzen oder Beschwerden ❑
- Ich habe extreme Schmerzen oder Beschwerden ❑

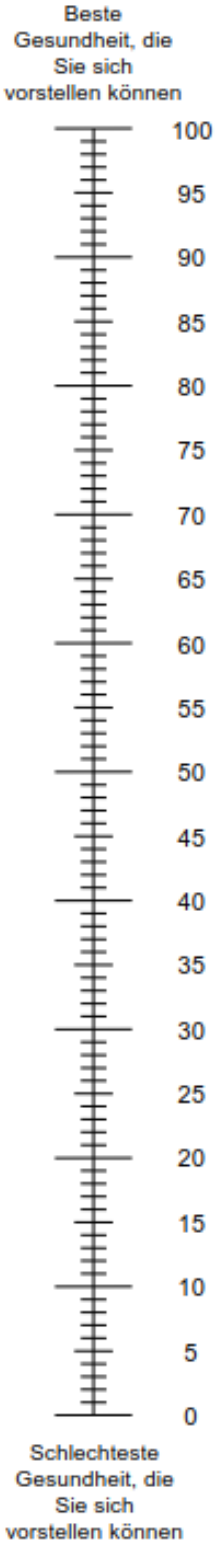
ANGST / NIEDERGESCHLAGENHEIT

- Ich bin nicht ängstlich oder deprimiert ❑
- Ich bin ein wenig ängstlich oder deprimiert ❑
- Ich bin mäßig ängstlich oder deprimiert ❑
- Ich bin sehr ängstlich oder deprimiert ❑
- Ich bin extrem ängstlich oder deprimiert ❑

2

- Wir wollen herausfinden, wie gut oder schlecht Ihre Gesundheit HEUTE ist.
- Diese Skala ist mit Zahlen von 0 bis 100 versehen.
- 100 ist die beste Gesundheit, die Sie sich vorstellen können. 0 (Null) ist die schlechteste Gesundheit, die Sie sich vorstellen können.
- Bitte kreuzen Sie den Punkt auf der Skala an, der Ihre Gesundheit HEUTE am besten beschreibt.
- Jetzt tragen Sie bitte die Zahl, die Sie auf der Skala angekreuzt haben, in das Kästchen unten ein.

IHRE GESUNDHEIT HEUTE = ☐



3

Generalised Anxiety Disorder Scale-7 (GAD-7), version for Germany (deutsch)

Wie oft fühlten Sie sich im Verlauf der letzten 2 Wochen durch die folgenden Beschwerden beeinträchtigt?	**Überhaupt nicht**	**An einzelnen Tagen**	**An mehr als der Hälfte der Tage**	**Beinahe jeden Tag**
a. Nervosität, Ängstlichkeit oder Anspannung	☐ 0	☐ 1	☐ 2	☐ 3
b. Nicht in der Lage sein, Sorgen zu stoppen oder zu kontrollieren	☐ 0	☐ 1	☐ 2	☐ 3
c. Übermäßige Sorgen bezüglich verschiedener Angelegenheiten	☐ 0	☐ 1	☐ 2	☐ 3
d. Schwierigkeiten zu entspannen	☐ 0	☐ 1	☐ 2	☐ 3
e. Rastlosigkeit, so dass Stillsitzen schwer fällt	☐ 0	☐ 1	☐ 2	☐ 3
f. Schnelle Verärgerung oder Gereiztheit	☐ 0	☐ 1	☐ 2	☐ 3
g. Gefühl der Angst, so als würde etwas Schlimmes passieren	☐ 0	☐ 1	☐ 2	☐ 3

Gesamtwert _____ = Addition ____ + ____ + ____

der Spaltensummen

Appendix IV. Definition of procedural terms

- **Patient's Enrolment**
  - Date of informed consent signed.
- **Start of Patient's Follow-up (FU)**
  - Date and time of index thyroid surgery.
- **Last Patient Last Visit (LPLV) = global End of Study (EOS)**
  - Last final visit of a study patient at the study site or last contact, equivalent to EOS. This date will be approved by sponsor.
- **Notification of EOS to regulatory bodies and ECs**
  - Within 15 days after EOS this milestone has to be notified to all involved regulatory bodies and ECs; in case of premature termination expedited reporting is mandatory.
- **Final Database Lock (FDBL)**
  - Final data cleaning and last endpoint assessment. This date will be approved by sponsor.
- **Final Report**
  - Within one year after EOS a final report according to applicable international standards has to be provided to all involved ECs.
- **Operational End of Study**
  - Date of all contracts closed and all administrative procedures finished.
- **End of Project (EOP)**
  - Might be months or years after operational end of study depending on how long support of the CRO is still required by the sponsor (e.g. for publications, sub-analyses, final report etc.).

Appendix V. Declaration of Helsinki (Version Fortaleza, October 2013)

Refer to **https://www.wma.net/wp-content/uploads/2016/11/DoH-Oct2013-JAMA.pdf**

Appendix VI. Technical and functional features of the ISAR-M THYRO system (IP)

Thyro I KID features	**Relevant and covered by the clinical study**
Insertion of disposable pressure probe(s) **KID** into the thyroid gland(s)	yes
Conversion of compartment pressure into air pressure in the pressure probe	yes
Conversion of air pressure values into a digital electrical signal in the sensor probe, which is connected to the pressure probe	yes
Thyro I SON features	
Positioning of a battery-operated device **SON** on the patient's upper arm for up to 48 h	yes
Display of pressure values on the screen of a mobile, battery operated device on demand	No (hidden in study)
Triggering an acoustic and optical alarm when set pressure thresholds are exceeded	No (hidden in study)
Optical and acoustic alarm output in case of other device errors	Yes
Storage of all alarms in a Log file including pressure alarms	Yes
Transfer of pressure values, alarms and log files to an external monitor unit via Bluetooth in real time	Yes
Thyro I MOM Features	
Display of pressure values on the display of the external unit **MOM** in real time	No (hidden in study)
Graphical representation and trend analysis of the pressure values on the external unit	No (hidden in study)
Optical and acoustic alarm output in case of pressure alarms on the external unit	No (hidden in study)
Optical and acoustic alarm output in case of other device errors on the external unit	Yes
Transmission of the alarm message in the event of pressure alarms via SMS to external smartphones in real time	No (hidden in study)
Transmission of the alarm message in case of device errors via SMS to external smartphones in real time	Yes
Transmission of pressure data and log files into a database from the external device via WLAN or GSM after each session	Yes
Thyro I DOCK Features	
Inductive charging of the patient device (SON) by an charging and storage device **DOCK**	Yes
Plug-in charging of the monitor unit (MOM) by the DOCK	Yes
Simultaneous charging of both battery-powered units SON and MOM by the DOCK	Yes