CLINICAL INVESTIGATION PLAN (CIP)

Generation of prediction equations to analyze body composition of the elderly based on Bioelectrical Impedance Analysis (BIA)

BCA-12 (clinical investigation code)

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seca gmbh & co. kg
Hammer Steindamm 3-25
22089 Hamburg | Germany
(sponsor)

DECLARATION OF SPONSOR

This Investigation Plan (CIP) was subject of critical review and has been approved by the sponsor and its representatives. The information it contains is consistent with:

- ⇨ the Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects; last revision Fortaleza, Brazil, October 2013
- ⇨ the DIN EN ISO 14155
- ⇨ Guideline for good clinical practice E6(R1)
- ⇨ the German Medical Device Act, MPKPV
- ⇨ §20 German Medical Device Act

The investigator will be supplied with details of any significant or new findings, including AE's, relating to the administration of the medical device.

Sponsor:

seca gmbh & co. kg
Hammer Steindamm 3-25
22089 Hamburg | Germany

Hamburg 21.01.2019
place, date

Frederik Vogel
CEO Development & Manufacturing

Hamburg 23.1.2019
place, date

Robert M. Vogel
CEO Sales & Marketing

Hamburg 18.1.2019
place, date

Björn Jensen
R&D, Statistician

DECLARATION OF PRINCIPAL INVESTIGATOR

I confirm that I have read the Investigation Plan (CIP), Investigator's Brochure (IB), informed consent of the subject, and referenced documents of the CIP entitled:

Investigation Plan Title:	Generation of prediction equations to analyze body composition of the elderly based on Bioelectrical Impedance Analysis (BIA)
Investigation Plan No.:	BCA-12

I agree that the documentation contains all of the necessary information to conduct this study. I will conduct this study as outlined herein, in accordance with

- ⇨ the Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects; last revision Fortaleza, Brazil, October 2013
- ⇨ the DIN EN ISO 14155
- ⇨ Guideline for good clinical practice E6(R1)
- ⇨ the German Medical Device Act, MPKPV
- ⇨ §20 German Medical Device Act

The study will be started only in the case that a favorable opinion of the responsible Ethical Committee (EC), the Bundesamt für Strahlenschutz (BfS) and a successful request for waiving the authorization of the clinical trial to the Competent Authority (CA) has been obtained.

I will provide all study personnel under my supervision with copies of the CIP and any amendments of those, and access to all information provided by seca gmbh & co. kg. I will discuss the material with them to ensure that they are fully informed about the medical device and the study.

Institut für Humanernährung und Lebensmittelkunde
Abteilung Humanernährung
Düsternbrooker Weg 17
24105 Kiel | Germany

Kiel, 6.2.2019

place, date

Prof. Dr. Dr. Anja Bosy-Westphal
Principle Clinical Investigator

Sponsor:	seca gmbh & co. kg Hammer Steindamm 3-25 22089 Hamburg | Germany
Clinical investigation site:	Christian-Albrechts-Universität zu Kiel Institute for Human Nutrition and Food Science Department of Human Nutrition Düsternbrooker Weg 17 24105 Kiel | Germany
Principal investigator:	Prof. Dr. Dr. Anja Bosy-Westphal Christian-Albrechts-Universität zu Kiel Institute for Human Nutrition and Food Science Department of Human Nutrition Düsternbrooker Weg 17 24105 Kiel | Germany
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Commissioner for data protection:	Daniela Geißler Christian-Albrechts-Universität zu Kiel Christian-Albrechts-Platz 4 24118 Kiel
Statistics / data management:	Björn Jensen seca gmbh & co. kg Hammer Steindamm 9-25 22089 Hamburg | Germany
Project management / clinical affairs:	Kristin Klückmann seca gmbh & co. kg Hammer Steindamm 9-25 22089 Hamburg | Germany
Medical devices:	seca mBCA 515, 555 and 525 (medical Body Composition Analyzer)
Regulatory status:	The seca mbca are non-invasive medical devices class IIa in accordance with rule 10 of the MDD 93/42/EEC Annex IX. While the seca mBCA 515 and 525 are CE approved (CE 0123), the mBCA 555 will be applied without CE mark.

Regulatory information:	This Investigation Protocol (CIP) will be conducted in accordance with: - the Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects; last revision Fortaleza, Brazil, October 2013 - the DIN EN ISO 14155 - Guideline for good clinical practice E6(R1) - the German Medical Device Act, MPKPV - §20 German Medical Device Act The study will be started only in the case that a favorable opinion of the responsible Ethical Committee (EC), the Bundesamt für Strahlenschutz (BfS) and a successful request for waiving the authorization of the clinical trial to the Competent Authority (CA) has been obtained.

STUDY SYNOPSIS

Title of study:	Generation of prediction equations to analyze body composition of the elderly based on Bioelectrical Impedance Analysis (BIA)
Study code:	BCA-12
Study purpose:	The study is based on the clinical trial BCA-01 (AZ 111/11) "Generation of prediction equations to analyze body composition of obese adults based on Bioelectrical Impedance Analysis (BIA)" and implicates an extension of the study collective.
Objectives:	The objective of the study is to develop prediction equations for calculating Fat-Free Mass FFM, Total Body Water TBW, Extracellular Water ECW, Visceral Adipose Tissue VAT, total Skeletal Muscle Mass SMM and segmental SMM in a group of elderly. The prediction equations are based on linear regression analysis between the gold standard reference methods Air Displacement Plethysmography ADP, Dual-energy X-ray Absorptiometry DXA, Magnet Resonance Imaging MRI, Deuterium dilution method (D2O) and Sodium Bromide dilution method (NaBr) on the one hand and bioelectrical impedance measurements on the other hand. Multi-frequency bioimpedance is measured for all body segments: right arm, left arm, right leg, left leg, trunk, right body side and left body side using the seca mBCA 515 and 555 in standing position and the seca mBCA 525 in standing and lying position.
Study design:	Population based cross-sectional observational study
Study population:	150 elderlies (>60 years): community dwelling or living in old nursing homes
Entry criteria:	**Inclusion criteria** male and female subjects older than 60 years, stable medication (no changes during the past 6 months) subjects need to be able to sign the informed consent and privacy policy

Exclusion criteria
acute disease
intake of diuretics
wearing of support stockings
edema diagnosed by inspection and palpation of lower limbs
paralysis e.g. after a stroke
neurodegenerative diseases e.g. ALS
tumors in treatment
amputation
electronic implants e.g. pacemaker
under the skin applied injection systems (e.g. insulin pumps or pain pumps)
probands who cannot provide an ICF by themselves
probands who might be dependent from the sponsor or the investigation site
current alcohol abuse
active prostheses
electronic life-support systems, e.g. artificial heart, artificial lung
portable electronic medical devices, e.g. ECG devices or infusion pumps
metallic implants
cochlea implants und heart valves prothesis (e.g. Starr-Edwards-Prothesis)
vessel clips in the brain or medulla applied before 1995
defeatable pumps
catheter
iron or metallic parts in the body (e.g. shard of metal)
dental braces
magnetic tooth implants
not removeable piercings
extensive tattoos

Study treatments:

Treatment will not be executed.

Study conduct:

Each subject will undergo the following examinations:
1 height measurement
1 body composition measurements in standing position with the seca mBCA 515
1 body composition measurements in standing position with the seca mBCA 555
1 body composition measurements in standing position with the seca mBCA 525
1 body composition measurements in supine position with the seca mBCA 525
1 DXA measurement
1 whole body MRI scan
1 ADP measurement
2 blood drawings
3 hand grip strength measurements

Study statistics:

The biometric sample size calculation for the previous study BCA-01 (AZ 111/11) was carried out by the Coordination Centre for Clinical Studies (KKS) of the Charité, Augustenburger Platz 1, 13353 Berlin, Germany under the direction of Gerald Splettstoesser. The study BCA-01 included subjects from 18 to 65 years.

For target variable measurement resistance of the left body side (RI 50 kHz) was chosen. This provides, according to preliminary tests done by the investigator, the best approach to gain the most relevant

medical results for formula generation. The precision (confidence interval width for μ) of all other variables was varied in a way that maximum (superior sample size) will always to be found in the resistance measurement of the left body side (RI 50 kHz) being crucial for formula generation.
The resulting sample size to generate a formula was N = 124 in the study BCA-01.

This number of 124 subjects is the basis for the calculation of the sample size in the current study BCA-12 for formula generation in older people.

The smaller age range that shall be examined in comparison to study BCA-01 is opposed to a greater change in body composition with high age. So no adaptation of sample size for these reasons is planned.

To achieve an overlap in the age range with the previous study BCA-01 additional 26 subjects between 60 and 65 years shall be examined.

The resulting sample size to generate a formula for elderly is N = 150.

This number allows a homogenous age distribution from 60 - 80 years. Older subjects will be examined as far as they can be recruited.

The prediction equations shall be developed by stepwise multiple regression analysis.

ABBREVIATIONS AND DEFINITION OF TERMS

ADP	Air Displacement Plethysmography
ADI	Acceptable Daily Intake
AE	Adverse Event
BCA	Body Composition Analysis
BfArM	Federal Institute for Drugs and Medical Devices
BfS	Federal Office for Radiation Protection
BIA	Bioelectrical Impedance Analysis
BM	Bone Mass
BMI	Body Mass Index
CI	Clinical Investigation, synonym term is "clinical study" or "study"
CIP	Clinical Investigation Plan, synonym term is "study protocol" or "protocol"
CRF	Case Report Form
D_2O	Deuterium
DIN	German Industrial Norm
DXA	Dual-Energy X-Ray Absorptiometry
ECW	Extra Cellular Water
FM	Fat Mass
FFM	Fat Free Mass
ICF	Informed Consent Form
ICW	Intra Cellular Water
IRMS	Isotopic Ratio Mass Spectrometry
KKS	Coordination Center for Clinical Studies
LST	Lean Soft Tissue
mBCA	medical Body Composition Analyzer
MDD	Medical Device Directive
MPKPV	Medical Device Clinical Investigation Regulation
MRI	Magnet Resonance Imaging
NaBr	Sodium Bromide
NOEL	No-Observed Effect Level
R	Resistance
SAE	Serious Adverse Events
SMM	Skeletal Muscle Mass
TBW	Total Body Water
UV	Ultra Violet
V	Volume
VAT	Visceral Adipose Tissue
XRF	X-Ray Fluorescence Spectroscopy
Z	Impedance

CIP REVISION HISTORY

Revision number	Revision date	Explanation	Comment
1.0	05-12-17	First revision	
1.1	29-01-18	Handgrip strength measurement has been added for quality assessment of muscle mass	Changes in chapter 2.7 Procedure
1.2	07-05-18	According to the feedback from the ethical committee on April 17, 2018 and a meeting between Anja Bosy-Westphal and the ethical committee on April 24, 2018 the following changes were made: • Radiologist and commissioner for data security were added on page 4 • MRI specific exclusion criteria were added • Exclusion criteria "heart or kidney insufficiency" was changed to "intake of diuretics" to avoid internistic pre-examinations • Time column was added to the examination schedule • Statistical method for data analysis was added	Changes affect the synopsis, chapter 1.8 Requirements on study population, chapter 2.7 Procedure and chapter 3. Study statistics
1.3	23-10-18	After consulting the laboratories in Jülich and Boston we agreed to reduce the dosages for D2O and NaBr as follows: • Before: 0,4g D2O per kg body weight and 0,05g NaBr per kg body weight • Now: 0,1g D2O per kg body weight and 0,04g NaBr per kg body weight	Changes affect chapter 2.3 Reference Methods (page 19)
1.4	16-01.2019	New mBCA 555 is included	Changes affect chapters: 1.3 Regulatory Information (page 13); 2.2 Model for standing bioimpedance measurement: mBCA 555 (page 17); 2.8 Procedure (pages 23-24)

CONTENT

1. INVESTIGATIONAL PLAN

1.1 Bioelectrical Impedance Analysis

The use of bioelectrical impedance analysis (BIA) is widespread both in healthy subjects and patients. BIA allows the determination of the fat-free mass (FFM), skeletal muscle mass (SMM), fat mass (FM), extracellular water (ECW) and total body water (TBW) when using appropriate population, age or pathology-specific BIA equations and established procedures. BIA equations are based on validation studies where BIA is compared with reference methods such as Air Displacement Plethysmography (ADP), Dual-Energy X-Ray Absorptiometry (DXA), Magnetic Resonance Imaging (MRI) and isotope dilution. [1]

1.2 Study Rationale

The study is based on the clinical trial BCA-01 (AZ 111/11) "Generation of prediction equations to analyze body composition of obese adults based on Bioelectrical Impedance Analysis (BIA)" and implicates an extension of the study collective.

1.3 Regulatory Information

The seca mbca are non-invasive medical devices class IIa in accordance with rule 10 of the MDD 93/42/EEC Annex IX. While the seca mBCA 515 and 525 are CE approved (CE 0123), the mBCA 555 will be applied without CE mark.

This Clinical Investigation (CI) will be conducted in accordance with

- ⇨ the Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects; last revision Fortaleza, Brazil, October 2013
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The study will be started only in the case that a favorable opinion of the responsible Ethical Committee (EC), the Bundesamt für Strahlenschutz (BfS) and a successful request for waiving the authorization of the clinical trial to the Competent Authority (CA) has been obtained.

1.4 Study Objective

The objective of the study is to develop prediction equations for calculating Fat-Free Mass (FFM), Total Body Water (TBW), Extracellular Water (ECW), Visceral Adipose Tissue (VAT), total Skeletal Muscle Mass (SMM) and segmental SMM in a sub-group of elderly persons. The prediction equations are based on linear regression analysis between the gold standard reference methods Air Displacement Plethysmography (ADP), Dual-energy X-ray Absorptiometry (DXA), Magnet Resonance Imaging (MRI), Deuterium dilution method (D_2O) and Sodium Bromide dilution method (NaBr) on the one hand and bioelectrical impedance measurements on the other hand.
Multi-frequency bioimpedance is measured for all body segments: right arm, left arm, right leg, left leg, trunk, right body side and left body side using the seca mBCA 515 and 555 in standing position and the seca mBCA 525 in lying position.

1.5 Study Design

The study BCA-12 is a cross-sectional observational study.

1.6 Study Schedule

As soon as the study BCA-12 is approved by the local ethical committee of the Christian-Albrechts-University Kiel, the BfArm and the BfS the subject recruitment will start. The measurement period of subjects is estimated with one year. The measurement duration per subject is 2 days.

1.7 Requirements on study procedure

Please refer to chapter 2.7 Procedure in this document.

1.8 Requirements on study population

Only subjects who meet the following inclusion and exclusion criteria shall be included in the study BCA-12:

Inclusion criteria:
- male and female subjects older than 60 years,
- subjects need to be able to sign the informed consent form

Exclusion criteria:
- acute disease
- intake of diuretics
- wearing of support stockings
- edema diagnosed by inspection and palpation of lower limbs
- paralysis e.g. after a stroke
- neurodegenerative diseases e.g. ALS
- tumors in treatment
- amputation
- electronic implants e.g. pacemaker
- under the skin applied injection systems (e.g. insulin pumps or pain pumps)
- probands who cannot provide an ICF by themselves
- probands who might be dependent from the sponsor or the investigation site
- current alcohol abuse
- active prostheses
- electronic life-support systems, e.g. artificial heart, artificial lung
- portable electronic medical devices, e.g. ECG devices or infusion pumps
- metallic implants
- cochlea implants und heart valves prothesis (e.g. Starr-Edwards-Prothesis)
- vessel clips in the brain or medulla applied before 1995
- defeatable pumps
- catheter
- iron or metallic parts in the body (e.g. shard of metal)
- dental braces
- magnetic tooth implants
- not removeable piercings
- extensive tattoos

1.9 Subject Discontinuation Criteria

All subjects have the right to withdraw consent without prejudice at any time during the study. If a subject withdraws consent, the investigator should make a reasonable effort to determine the cause for withdrawal of consent. For these subjects, as well as for subjects who require permanent discontinuation from examination with the medical device, the investigator should make a reasonable effort to complete all required study procedures. All information should be documented in the subject's source data documents and on the Case Report Form (CRF). A subject who discontinues treatment will not be replaced. The subject's participation in this study should be permanently discontinued as a result of:

- formal withdrawal of informed consent
- investigator concludes that it is in the subject's best interest to discontinue study procedures
- presence of other medical conditions that prohibit continuation of study procedures
- subject is willingly or inadvertently non-compliant to any of the CIP procedures in the opinion of the investigator

1.10 Study Discontinuation Criteria

Study is discontinued only if irreversible failure of devices for measurement of body composition cannot be compensated.

2. INVESTIGATIONAL DEVICES

The seca medical Body Composition Analyzer (mBCA) is mainly used in hospitals, medical practices and inpatient care facilities in accordance with national regulations.
The mBCA records weight, height and bioelectrical impedance measurements and automatically calculates parameters such as fat-free mass (FFM) which can be derived from them. The results are displayed in graphical form and assist the attending physician with the following medical issues:

- determining energy expenditure and energy reserves as a basis for nutritional advice
- assessing metabolic activity and the success of a training program, e.g. within the framework of rehabilitation or physiotherapy
- determining a patient's fluids status

The mBCA is not intended for use on children.

2.1 Model for standing bioimpedance measurement: mBCA 515

ation

Technical Data

General:
- Dimensions (W×H×D): 976 × 1,251 × 828 mm
- Display type: 8.4" touch-screen display, can be swiveled 180° to the left and right
- Power supply: Power adapter
- Voltage: 100 V – 240 V
- Interfaces: seca 360° wireless, USB 2.0, Ethernet
- Microsoft® Windows® compatible printer via seca 115 PC software

Bioelectrical Impedance Analysis:
- Measurement method: 8-point Bioelectrical Impedance Analysis
- Type of electrode: Stainless steel, three pairs of hand electrodes, two pairs of foot electrodes
- Measurement frequencies: 1; 1.5; 2; 3; 5; 7.5; 10; 15; 20; 30; 50; 75; 100; 150; 200; 300; 500; 750; 1,000 kHz
- Measurements: Impedance (Z), Resistance (R), Reactance (Xc), Phase angle (φ)
- Measurement range Impedance: 10 Ω to 1,000 Ω
- Measurement segments: Right arm, left arm, right leg, left leg, right half of body, left half of body, torso
- Measurement current: 100 µA
- Measurement time: max. 90 seconds for 19 frequencies

The seca mBCA 515 has an integrated calibrated scale with a maximum load of 300kg. More information about the technical data for the scale and technical modifications can be found at the instruction for use for doctors and assistants at chapter 13.

PC software seca analytics 115:
The device mBCA 515 does not have "on-board" subject or user management. To manage subject files and user accounts, the device must be connected to a PC on which the seca 115 PC software is installed. Subject files can be created directly on the device to manage measured results. The subject files are stored in the database of the seca analytics 115 PC software supplied.

Recording weight and height:
The device uses an electronic scale. Weight is recorded across 4 load cells. Height is recorded via wireless transmission from the seca 274 length measuring device.

Bioimpedance measurement:
Bioimpedance is measured according to the 8-point method. The flow of the low alternating current and the measurement of impedance are performed for each side of the body using a pair of foot electrodes and a pair of hand electrodes. The hand electrodes are attached at different heights so that persons with different heights can adopt the ideal position on the device for a bioimpedance measurement.

2.2 Model for standing bioimpedance measurement: mBCA 555

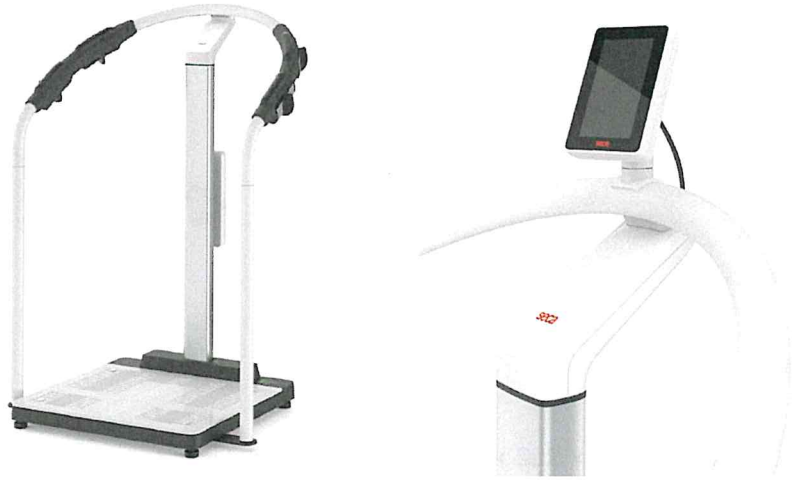


Figure 1: mBCA 555 (left: without display)

Technical Data

General:

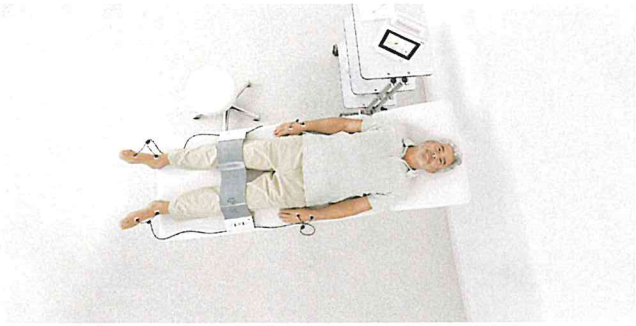
- Dimensions (W×H×D): 840 × 1,280 × 655 mm
- Display type: 4,3 inch TFT touch screen with a 16:9 format, can be swiveled 180° to the left and right
- Power supply: Power adapter
- Voltage: 100 V – 240 V
- Interfaces: seca 360° wireless, WiFi, Ethernet
- Medical device class IIa

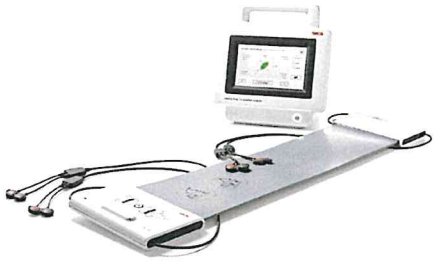
Bioelectrical Impedance Analysis:

- Measurement method: 8-point Bioelectrical Impedance Analysis
- Type of electrode: Stainless steel, four pairs of hand electrodes, two pairs of foot electrodes
- Measurement frequencies: 1, 2, 5, 10, 20, 50, 100, 200 and 500 kHz
- Measurements: Impedance (Z), Resistance (R), Reactance (Xc), Phase angle (φ)
- Measurement range Impedance: 10 Ω to 1,000 Ω
- Measurement segments: Right arm, left arm, right leg, left leg, right half of body, left half of body, torso
- Measurement current: 100 µA
- Measurement time: 30 seconds

The seca mBCA 555 has an integrated calibrated scale with a maximum load of 300kg. More information about the mBCA 555 can be found in the investigator´s brochure.

2.3 Model for supine bioimpedance measurement: mBCA 525





Technical data

General:
- Dimensions (W×H×D): 252 × 262 × 230 mm / 9.0 x 10,3 x 9,1 “
- Weight: 3 kg / 6,6 lbs
- Display type: 7" touch-screen display
- Power supply: Power adapter, rechargeable battery
- Voltage: 100 V – 240 V
- Power frequency: 50 Hz – 60 Hz
- Interfaces: WiFi, seca 360° wireless, USB 2.0, Ethernet
- Microsoft® Windows® compatible printer via seca 115 PC software

Device components:
The device consists of a monitor and a measuring mat. The monitor is for administering patient and user data and for preparing and evaluating bioimpedance measurements. The device is equipped with a touchscreen display. The monitor has a storage compartment with a magnetic catch for storing the measuring mat. The measuring mat is placed on the patient's legs for a bioimpedance measurement. Measured results are transmitted to the monitor unit by WiFi. The electrode cables of the measuring mat are equipped with connections for push-button electrodes.

Bioelectrical Impedance Analysis:
- Measurement method: 8-point Bioelectrical Impedance Analysis
- Type of electrode: adhesive electrodes (PVC free)
- Measurement frequencies: 1; 2; 5; 10; 20; 50; 100; 200; 500; kHz
- Measurements: Impedance (Z), Resistance (R), Reactance (Xc), Phase angle (φ)
- Measurement range Impedance: 10 Ω to 1,000 Ω
- Measurement segments: Right arm, left arm, right leg, left leg, right half of body, left half of body, torso
- Measurement current: 100 µA
- Measurement time: 30 seconds

Recording weight and height:
The subject´s weight and height is recorded manually.

Bioimpedance measurement:
The bioimpedance measurement is carried out with the subject lying down, using the 8-point method. The electrode cables are connected to two pairs of electrodes for each half of the body. The electrodes are affixed to the patient's hands and feet.

Management of patient files:
subject files can be created directly on the device to manage measured results. The subject files are stored in the patient database of the device or in the seca analytics 115 PC software.

Subject files can be managed and edited using the mBCA 525 or the seca 115 PC software.

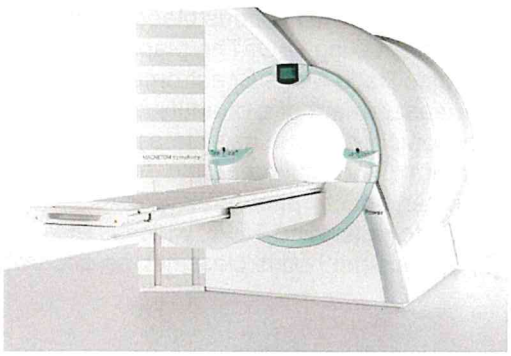
The two devices mBCA 515 and 525 differ in two ways. One difference is the measurement position. The mBCA 515 measures the subject in standing position, while measurements with the mBCA 525 are conducted in supine position. Since fluids in the body shift, when the patient lies down, the measurements differ between these two positions. Another difference between the two devices is the placement of the electrodes. The mBCA 515 measures for example parts of the hands that are not included in measurements with the mBCA 525. These differences lead to different measurements too. To be able to distinguish these two effects in the analysis, an additional measurement with the mBCA 525 in standing position shall be made.

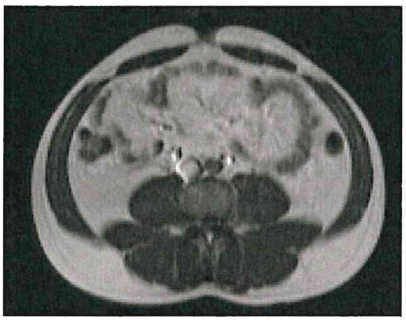
2.4 Reference Methods

The following reference methods are used to cross-validate the results of the mBCA 525 and 515:

Magnetic Resonance Imaging (MRI)

MRI is a special radiology technique designed to image internal structures of the body using magnetism, radio waves. MRI uses a tube scanner surrounded by a giant circular magnet. The patient is placed on a moveable bed that is inserted into the magnet. The magnet creates a strong magnetic field that aligns the protons of hydrogen atoms, which are then exposed to a beam of radio waves. This spins the various protons of the body, and they produce a faint signal that is detected by the receiver portion of the MRI scanner. A computer processes the receiver information and an image is produced. The image and resolution is quite detailed compared to other technology and can detect tiny changes of structures within the body, particularly in the soft tissue, brain and spinal cord, abdomen and joints. The whole-body scan takes about 15 minutes.



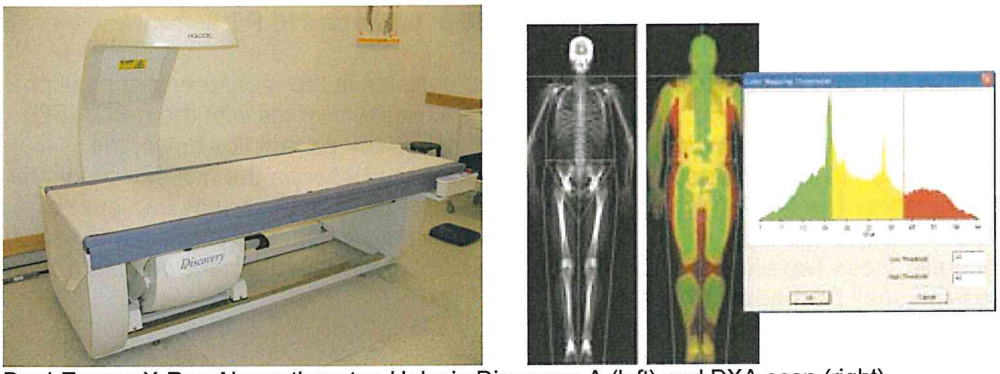


Magnetic Resonance Imaging: MAGNETOM manufactured by SIEMENS (left) and MRI scan (right)

In Body Composition, MRI is used as gold standard to calculate the volume of different body compartments as SMM or adipose tissue. Different body compartments are segmented manually by a trained observer based on grey level differences within the MRI scan. The measured area (cm^2) is then multiplied with the slice thickness to generate the tissue volume (cm^3). By further multiplication with the specific tissue density the mass of the body compartment is calculated.

Dual-Energy X-Ray Absorptiometry (DXA)

Dual-Energy X-Ray Absorptiometry commonly referred to as DEXA or DXA, is a technique originally developed for the determination of Bone Mineral content in the detection and treatment of osteoporosis.



Dual-Energy X-Ray Absorptiometry: Hologic Discovery A (left) and DXA scan (right)

More recently, application of the technique has been expanded to include the analysis of Fat Mass (FM) and Lean Soft Tissue (LST), in addition to Bone Mass (BM). DXA is a two compartment method, but estimations allow the calculation of three compartments (FM, LST and BM).
The radiation exposure of a DXA Scan is around 7 to 10 µSv and much lower than an x-ray scan of the chest with around 100 µSv.

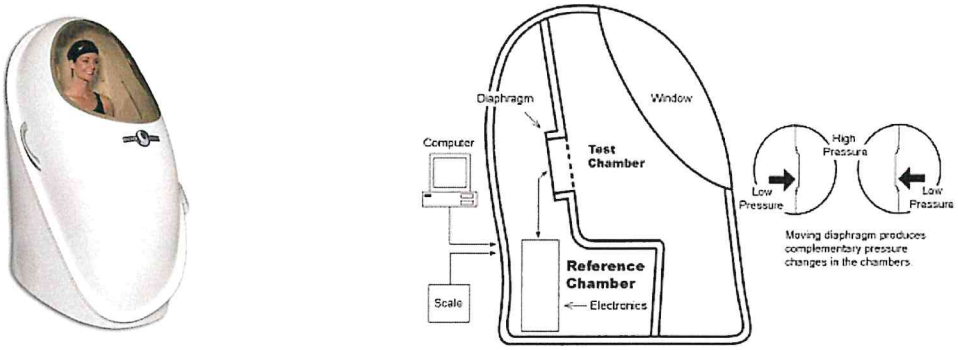
Dilution methods (D_2O, NaBr)

To calculate TBW and ECW dilution methods are regarded as gold standard. These methods involve orally administering a defined amount of a tracer in accordance with the subject's weight and determining the dilution of the tracer in the plasma after a 4 hour equilibration phase. The stable isotope of Hydrogen Deuterium (D_2O) is used to determine TBW. The salt Sodium Bromide (NaBr) of which only very small amounts pass through the cell membrane is used to determine ECW.

A D_2O dose of 100 mg per kg body weight mixed with tap water is administered orally in the morning fasting and after a 2 hour fluid abstention. The distribution of the stable isotope in the TBW is completed after 4 hours. During this period, the subject remains fasting. Two venous blood samples of 10 ml whole blood are taken immediately before and four hours after taking D_2O. The plasma samples are analyzed using Fourier Transformation Spectroscopy, Isoptopic Ratio Mass Spectrometry (IRMS) or Photospectrometry. Spectroscopy is used to comprise any measurement of a quantity as a function of either wavelength or frequency. Spectrometry is the spectroscopic technique used to assess the concentration or amount of a given chemical species such as atomic, molecular or ionic. In this case, the instrument that performs such measurements is a spectrometer, spectrophotometer, or spectrograph. Deuterium dilution is a reliable, unstressful method to determine TBW, which is also suitable for pregnant of breastfeeding women and children [2, 3]. This method is classified as accurate and safe for the patient, but not fast for the user.

Orally administered NaBr is resorbed quickly and completely and almost exclusively distributes in the extracellular compartment [4]. Blood samples of 10 ml are taken immediately before and 4 hours after oral application of 40 mg NaBr per kg body weight. The serum sample after ultrafiltration can be analyzed using Anion Exchange Chromatography and UV Detection at 200 nm according to Miller et al. 1989. Alternatively, the serum can be analyzed by X-Ray Fluorescence Spectroscopy (XRF). XRF is the emission of characteristic "secondary" or fluorescent X-rays from a material that has been excited by bombarding with high-energy X-rays or gamma rays [5]. In general, this analysis is performed without opening the vial, therefore preserving the full amount of specimen for the next analysis as D_2O. Historically, bromide salts were used as anticonvulsants and sedatives. The oral NaBr dose for measuring ECW is below the pharmacologically effective dose (more than 1 to 6 g per day), however. The No-Observed Effect Level (NOEL) for NaBr is 100 mg per kg per day and the Acceptable Daily Intake (ADI) for NaBr from food and drinking water is 1 mg per kg per day [6]. On 82 healthy subjects in an age range of 12 to 65 years (BMI of 15.3 to 48 kg/m2), no adverse reactions were observed after taking NaBr doses of 30-60 mg per kg per day [7]. The route of elimination is renal (half-life of 11 to 12 days). As dilution methods require a certain effort these techniques are used for scientific purposes only.

Air Displacement Plethysmography (ADP)



Air Displacement Plethysmography: BOD POD® device, manufactured by COSMED S.r.l., Rome, Italy (left) and measurement principle (right)

FM and FFM are measured using Air Displacement Plethysmography (ADP). ADP is performed by the BOD POD® device (Cosmed S.r.l., Rome, Italy). Participants wear tight-fitting underwear and a swim cap. Two repeated measurements of body volume are performed, averaged and corrected for predicted body surface area and thoracic gas volume using BOD POD® software (version 4.5.0). Percentage fat mass (FM) is calculated from body density using the equation by Siri et al. (Siri, W.E. Body composition from fluid spaces and density: Analysis of methods. 1961. Nutrition 1993, 9, 480–491). Fat free mass (FFM) is calculated as body weight minus FM.

2.5 mBCA Device Accountability

The mBCA 515 and 525 devices are delivered and installed by the sponsor. The responsible staff at the Clinical Investigation Site stores the product in a secure, limited access area under normal temperature and humidity conditions. After completion of the CI the devices are to be returned to the sponsor.

2.6 Recruitment

Subjects are recruited at local pharmacies, sport clubs and notice boards of local coliseums using information flyer. The subjects will be recruited from the investigational sites subject pool and public advertisement. Potential participants of the study are asked by the investigator to join the investigation.

A subject will only be admitted to the study if all inclusion and none of the exclusion criteria are met. Potential subjects will be screened for study eligibility. A subject is considered enrolled after:

- Written Informed Consent is obtained
- Meeting Inclusion and Exclusion criteria

2.7 Consent

An investigator will explain to the subjects the nature, significance and implications of the study prior to any Clinical Investigation related examination. The investigator will explain all methods, rules of conduct and any restrictions which may apply. Possible effects and side effects will be discussed. Subjects will be informed that they are free to withdraw from the study at any time, without giving any reason for doing so. They must be able to understand the full implications of their decision.

All participants will sign an informed consent form as evidence of consent.

The subject information sheet and the informed consent form of each participant will be filed in the Investigator Site File. A second original (or copy) of the signed consent form and a copy of the information sheet will be handed to the subjects after signature and before enrollment.

2.8 Procedure

	Examination schedule	responsible	time in minutes
preparation			
1.	pre-treatment discussion	investigator	
2.	read Informed Consent Form	subject	
3.	check inclusion and exclusion criteria	investigator	
4.	sign Informed Consent Form incl. Consent for processing personal data	subject	
5.	if all criteria are fulfilled undress subject	subject	
source data			5
6.	enter patient name and ID in source data doc.	investigator	
7.	enter date of examination, date of birth and gender in source data doc.	investigator	
8.	check if signed Informed Consent Form is available	investigator	
10.	check inclusion and exclusion criteria	investigator	
create subject file in PC software seca analytics 115			5
11.	start seca analytics 115	investigator	
12.	login as user named "BCA-12"	investigator	
13.	create new subject file	investigator	
14.	enter subject ID, gender, date of birth and select the ethnicity	investigator	
15.	save subject data	investigator	
mBCA 515 measurement in standing position			5
16.	start mBCA 515	investigator	
17.	go to patient tab	investigator	
18.	enter subject ID and click on search	investigator	
19.	select subject to be measured	investigator	
20.	go to weight & height tab	investigator	
21.	ask subject to take shoes off	investigator	
22.	measure subject height with seca 274 and send it wirelessly to the mBCA 515	investigator	
23.	ask subject to take socks off	investigator	
24.	step on mBCA 515 glassplattform	subject	
25.	weight is measured and BMI is calculated automatically	mBCA	
26.	click on BIA tab	investigator	
27.	State whether the subject meets the mBCA contraindications or not	investigator	
28.	**Yes:** the measurement is **not** performed.	investigator	
29.	**No:** the procedure continues. The dialog window for positioning the patient appears.	investigator	
30.	Ensure that the patient is standing on the device correctly:	investigator	

Test point	Characteristics
Hands	• Hands must be clean • Same pair of hand electrodes on left and right • Select the pair of hand electrodes such that arms are extended but not under strain • Finger spacers of the hand electrodes between the middle finger and ring finger on both sides
Feet	• Stand on device with bare feet • Feet must be clean • Heels on the rear foot electrodes • Balls of feet on the front foot electrodes
Position	• Upright position • Knees slightly bent • Do not move during the measurement

	Examination schedule	responsible	time in minutes
31.	If the patient is in correct contact with an electrode pair, the corresponding electrode indicator on the touchscreen display will be green. As soon as all the electrode indicators on the touchscreen display are green, a countdown to the start of measurement appears. Measurement starts automatically.	mBCA	
32.	Remaining measurement time is displayed.	mBCA	
33.	As soon as the measurement ends, the message End of measurement appears.	mBCA	
34.	Press the continue button	investigator	
35.	enter PAL value and waist circumference	investigator	
36.	Press the save button	investigator	
37.	check in seca analytics 115 if measurement data was saved	investigator	
38.	inform subject to put socks and shoes back on	investigator	
measurement with mBCA 555			3
37.	start PC software for mBCA 555	investigator	
38.	enter subject ID	investigator	
39.	select handrail position	investigator	
40.	step on mBCA 555 glassplattform	subject	
41.	Ensure that the patient is standing on the device correctly:	investigator	
42.	If the patient is in correct contact with an electrode pair, start the measurement with the PC software	investigator	
43.	As soon as the measurement ends, the message "BIA measurement: OK" appears --> measurement must be saved manually	investigator	
mBCA 525 measurement in standing position			5
44.	keep subject standing	investigator	
45.	start mBCA 525	investigator	
46.	login as user "BCA-12"	investigator	
47.	select subject file to be measured	investigator	
48.	enter weight, height, PAL and waist circumference	investigator	
49.	click on BIA tab	investigator	
50.	follow instructions on the monitor screen	investigator	
51.	save measurement data	investigator	
52.	check in seca analytics 115 if measurement data was saved	investigator	
mBCA 525 measurement in lying position			15
53.	make sure subject lays down for 10 min.	investigator	
54.	login as user "BCA-12"	investigator	
55.	select subject file to be measured	investigator	
56.	enter weight, height, PAL and waist circumference	investigator	
57.	click on BIA tab	investigator	
58.	follow instructions on the monitor screen	investigator	
59.	save measurement data	investigator	
60.	check in seca analytics 115 if measurement data was saved	investigator	

Test point	Characteristics
Hands	• Hands must be clean • Same pair of hand electrodes on left and right • Select the pair of hand electrodes such that arms are extended but not under strain • Finger spacers of the hand electrodes between the middle finger and ring finger on both sides
Feet	• Stand on device with bare feet • Feet must be clean • Heels on the rear foot electrodes • Balls of feet on the front foot electrodes
Position	• Upright position • Knees slightly bent • Do not move during the measurement

	Examination schedule	responsible	time in minutes
blood drawing			25
61.	take baseline blood sample (30ml)	investigator	
62.	calculate NaBr and D2O amount based on body weight	investigator	
63.	weigh D2O within a flask	investigator	
64.	add NaBr to the fluid and solve the dry chemical within the fluid D2O	investigator	
65.	ask subject to drink the solution quickly	investigator	
66.	inform subject not to drink within the next 4 hours	investigator	
67.	after 4h take the next blood sample (30ml)	investigator	
DXA measurement			30
68.	accompany the subject to the clinic of radiology (UKSH, Kiel)	investigator	
69.	starting QDR program on the DXA connected PC	investigator	
70.	click on daily quality control tab	investigator	
71.	measure the spine phantom for qualiy control	investigator	
72.	wait for "systemcheck successful" note	investigator	
73.	click ok tab	investigator	
74.	get undressed to underwear and remove all metall items (piercings etc)	subject	
75.	click measurement tab	investigator	
76.	click new patient tab	investigator	
77.	enter data (code, height, weight, date)	investigator	
78.	select whole body scan	investigator	
79.	position subject on measurement table	investigator	
80.	click measurement tab	investigator	
81.	after measurement is completed click analysis tab	investigator	
82.	click results tab	investigator	
83.	click finish tab	investigator	
84.	click report tab	investigator	
85.	print results	investigator	
ADP measurement			15
86.	start BODPOD software	investigator	
87.	get undressed to underwear and put on a bathing cap	subject	
88.	enter data to the software (code, height, gender, birthday)	investigator	
89.	measure weight using the connected scale	investigator	
90.	measure the volume of a standardized cylinder	investigator	
91.	inform the subject to enter the measurement chamber	investigator	
92.	close BODPOD door	investigator	
93.	measure subjects volume	investigator	
94.	click results tab	investigator	
95.	print results	investigator	
MRI measurement			30
96.	accompany the subject to the Department of Internal Medicine III (UKSH, Kiel)	investigator	
97.	subjects get undressed to underwear and remove all metall items (piercings etc	investigator	
98.	place subject on the MRI scanner table	investigator	
99.	place hearing conservation on subjects ears	investigator	
100.	conduct whole body MRI scan (15 Min)	investigator	
101.	MRI software is programmed by a trained radiological assisstent	radiological assisstent	
102.	after completed measurement assist subject by leaving the MRI measurement table	investigator	
103.	get dressed again	subject	
104.	save MRI data on a CD	investigator	
Handgrip strength*			10
105.	adjust dynamometer to subject	investigator	
106.	set dynamometer needle in 0-position	investigator	
107.	check subject position: relaxed; elbow 90° bent; shoulder, lower arm and wrist in neutral position	investigator	
108.	hold dynamometer relaxed in right or left hand	subject	
109.	press with maximal power	subject	
110.	write down measured value	investigator	
111.	reset dynamometer needle in 0-position	investigator	
112.	repeat procedure (102. to 105.) 2 times	investigator & subject	

**Handgrip strength is measured with a dynamometer manufactured by Saehan for quality assessment of muscle mass.*

3. STUDY STATISTICS

The biometric sample size calculation for the previous study BCA-01 (AZ 111/11) was carried out by the Coordination Centre for Clinical Studies (KKS) of the Charité, Augustenburger Platz 1, 13353 Berlin, Germany under the direction of Gerald Splettstoesser. The study BCA-01 included subjects from 18 to 65 years.

For target variable measurement resistance of the left body side (RI 50 kHz) was chosen. This provides, according to preliminary tests done by the investigator, the best approach to gain the most relevant medical results for formula generation. The precision (confidence interval width for μ) of all other variables was varied in a way that maximum (superior sample size) will always to be found in the resistance measurement of the left body side (RI 50 kHz) being crucial for formula generation.
The resulting sample size to generate a formula was N = 124 in the study BCA-01.

This number of 124 subjects is the basis for the calculation of the sample size in the current study BCA-12 for formula generation in older people.

The smaller age range that shall be examined in comparison to study BCA-01 is opposed to a greater change in body composition with high age. So no adaptation of sample size for these reasons is planned.
To achieve an overlap in the age range with the previous study BCA-01 additional 26 subjects between 60 and 65 years shall be examined.

The resulting sample size to generate a formula for elderly is N = 150.

This number allows a homogenous age distribution from 60 - 80 years. Older subjects will be examined as far as they can be recruited.

The prediction equations shall be developed by stepwise multiple regression analysis.

4. RISK MANAGEMENT

The risk management of the seca mBCA 515 and 525 was carried out in accordance with ISO 14971. The risk analysis was developed by a risk management team, which consists of members of the following sections:

- Research and development
- Quality Management
- Quality Assurance
- Product Management
- Sales
- Customer Service
- Safety Representative for Medical Devices
- Project Manager

4.1 Summary of risk analysis, including identification of residual risks

The risks or hazards that may occur during the course of the Clinical Investigation were evaluated and analyzed separately in following 2 sections:

- risks of the device
- risks during Clinical Investigation for the operator, subject and third persons

4.1.1 Risks of the mBCA

The risk management of the mBCA was performed according to EN ISO 14971. The risk analysis comprises a detailed analysis of potential risks that may affect the safety and performance of the mBCA. For each identified risk the manufacturer seca gmbh & co. kg defined the probability of occurrence and the potential of the consequences. The hazards were evaluated and risk reduction measures were implemented to reduce the risks. All hazards, that were rated as "not acceptable" could be rated as "acceptable" after risk reduction measures.
The remaining risk because of the weak measurement current for patients with electronic implants is low, but the patient group was still contraindicated.
The mBCA fulfill the requirements of EN 60601 and IEC 62133.
Detailed information can be found in the reference documents D1-D4.

4.1.2 Risks during the Clinical Investigation for the operator, subject and third persons

All examinations are part of a standard clinical routine and will be performed by skilled qualified personnel only (radiological assistants, nutritionists, physicians). Taking of blood samples could potentially lead to hematoma, peripheral nerve injury and fainting. An experienced physician is performing blood sampling to reduce these risks. A few minutes walking distance to reach the DXA and MRI facilities might bear the risk of commuting accidents (e.g. to twist one's ankle). Walking speed will kept slow to avoid falling. No additional risks of the others study-specific measures (dual-energy x-ray absorptiometry, dilution methods) are known at present.

4.2 Contra-indications for the investigational devices

Bioimpedance measurements may not be performed on persons exhibiting the following characteristics:
- electronic implants, e.g. cardiac pacemakers
- active prostheses

Bioimpedance measurements may not be performed on persons who are connected to one of the following devices:
- electronic life-support systems, e.g. artificial heart, artificial lung
- portable electronic medical devices, e.g. ECG devices or infusion pumps

Bioimpedance measurements may only be performed on persons exhibiting the following characteristics after discussion with the attending physician:
- cardiac arrhythmias
- pregnancy

4.3 Precautions and Warnings for the investigational devices

The following precautions and warnings should be considered when measuring the body composition with the seca mBCA:

Hazard to patient, damage to device
- Technical modifications may not be made to the device.
- The device does not contain any parts for servicing by the user. Please only have maintenance, technical checks and repairs performed by seca.

Risk of electric shock
- Never touch the power supply with wet hands.
- Make sure that the power cable is not crushed and cannot be damaged by sharp edges.

Hazard to patient (seca mBCA 515)

- Subject the device to a hygiene treatment after each measurement
- The mBCA 515 is not designed to be a rising aid. Assist people with limited mobility, e.g. when they are getting up from a wheelchair.
- Ensure that the weighing platform is dry before the patient steps onto it.
- Ensure that the patient does not step directly onto the edges of the weighing platform.
- Ensure that the patient steps onto the weighing platform slowly and safely.

Risk of infection
- Before and after every measurement, wash your hands to reduce the risk of cross-contamination and nosocomial infections.

Damage to device
- Make sure that fluids never get inside the device. These can destroy the electronics.
- Switch off the device before you disconnect the power pack from the power supply.
- Do not subject the device to shocks or vibrations.
- Do not place the device in direct sunlight and make sure that it is not placed in the direct proximity of a heat source. The excessive temperatures could damage the electronics.
- Use only chlorine and alcohol-free disinfectants which are explicitly suitable for acrylic sheet and other sensitive surfaces (active ingredient: quaternary ammonium compounds, for example).
- Do not use aggressive or abrasive cleaning agents.
- Do not use organic solvents (e.g. white spirit or petroleum spirit).

5. SAFETY ASSESSMENT

5.1 Definitions

Adverse Event
An adverse event (AE) is any untoward medical condition in a subject while participating in a clinical trial and which does not necessarily have to have a causal relationship with the use of the medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Symptoms or medically significant laboratory or instrumental abnormalities of a pre-existing disease, should not be considered as AE. Anticipated symptoms associated with tumor inflammation like fever, tumor pain, redness should not be considered as a medical device related AE. However, occurrences of new symptoms, as well as worsening of pre-existing conditions or events, drug interactions or the significant worsening of disease under investigation that is not recorded elsewhere in the CRF under specific efficacy assessment, are also considered as AEs.

Serious Adverse Event
A Serious Adverse Event (SAE) is defined as an AE, which falls into one or more of the categories listed below:

- ⇨ results in death
- ⇨ is life-threatening
- ⇨ requires in subject hospitalization or prolongation of existing hospitalization
- ⇨ results in persistent or significant disability/incapacity, where disability is defined as a substantial disruption of a person's ability to conduct normal life functions, either reported or defined as per judgment
- ⇨ is a congenital anomaly / birth defect

Complaint
A complaint is defined as an AE, which is not an untoward medical condition in a subject, but may comprise a technical defect or problem with the medical device.

5.2 Legal Aspects

For the documentation and reporting of AE and SAE the requirements as defined in the "*Medizinprodukte-Sicherheitsplan-Verordnung (MPSV)*" must be followed. This means, that both the investigator and the sponsor must immediately inform the BfArM about any SAE, independently from the causal relationship with the medical device or the medical procedure applied. The relevant reporting form, which must be used, is available on the homepage of the BfArM (www.bfarm.de) in section "*Medizinprodukte/Formular*" and will be provided to the investigator in advance.

5.3 Documentation

All AEs will be reported from the time subject signs informed consent through study completion or premature discontinuation and must be documented on the Adverse Event page of the CRF. If an AE is considered serious, both the Adverse Event page of the CRF and the SAE Report Form must be completed.

Any ongoing AE should be followed up until the earliest occurrence of one of the following:

- ⇨ AE is resolved
- ⇨ AE is stabilized if it has not been resolved within 30 days from the last measurement with the medical device. Documentation of stabilization must be recorded in the subject's source data documents.

Complaints must be documented in the source documents and the CRFs providing more detailed information about the specific issues of the complaint (e.g. technical problem with the medical device).

5.4 Reporting

The investigator must report all SAEs immediately by E-Mail to the sponsors following E-Mail-Address: kristin.klueckmann@seca,com. The sponsor has to inform the BfArM immediately about any SAE. The SAE contact information for reporting SAEs or death as well as the reporting form is provided in the Investigator Site File.

A follow-up SAE form will be filled in by the investigators if important follow-up information (i.e., diagnosis, outcome, causality assessment, results of specific investigations) is made available after submission of the initial form. The follow-up SAE form will be sent to the sponsor. The investigator will submit, on request, copies of all these reports to the relevant EC. All AEs and complaints must be reported within the investigation plan report, after the CI was terminated and evaluated.

6. ETHICAL COMMITTEE / COMPETENT AUTHORITY / STANDARDS

6.1 Involved Ethical Committee (EC)

Prior to initiation of the study, the sponsor or authorized party will submit the study protocol, ICF, and any other documents that pertain to subject information to the EC. The favorable opinion from the Committee must be documented in a letter to the sponsor specifying the protocol number, protocol version, documents reviewed, and date the committee granted the approval.

The sponsor must submit and, where necessary, obtain approval from the EC for all subsequent protocol amendments and changes to the ICF. The investigator must immediately notify the competent

authority and EC from SAEs occurring at the site, as well as other AE reports received from the sponsor, in accordance with local procedures.

6.2 Competent Authority (CA)

In accordance with of the German Act on Medical Devices (MPG) the competent federal higher authority can waive the authorization in case of clinical trials of medical devices with a low safety risk. The medical device investigated in this clinical investigation meets the requirements as a device with a low safety risk. Prior to start of the study a request for waiving the authorization of the clinical trial will be submitted to the Competent Authority by the Sponsor.

6.3 Applicable standards

Please refer to chapter Regulatory Information in this document.

6.4 Subject privacy and confidentiality of data

Confidentiality of data shall be observed by all parties involved at all times throughout the CI. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. The principal investigator or institution shall provide direct access to source data during and after the CI for monitoring, audits EC review and regulatory authority inspections. As required, the principal investigator or institution shall obtain permission for direct access to source data documents from the subject, hospital administration and national regulatory authorities before starting the CI.
Case report forms (CRF) will be filled out, signed and dated by the clinical investigation site. CRF only contain pseudonymized data. Completed CRF pages will be collected by the Sponsor after data have been monitored according to the monitoring plan for data analyzes.

7. SUBJECT DATA

7.1 Informed Consent

Prior to the beginning of the study, the investigator must have the written EC approval for the informed consent form and any other information provided to the subject. Before undertaking any study-related procedures with subjects, the purpose and nature of the study as well as possible adverse effects must be explained to them in understandable terms for the subject, parents or legal representatives and written informed consent must be obtained from each participant. Each informed consent will be signed and personally dated by the subject. Each subject will receive a copy of the signed informed consent.

7.2 Case Report Form (CRF)

The study sites will collect at least the data required for transfer into the CRF on the source data. Next, site staff will transfer the study data from the source documents into the CRF. After completion each CRF page will be printed and signed by an investigator or authorized designee. In case of any changes to the CRF the applicable CRF page will be printed and signed again. After conduct of the source data verification the study monitor will collect the CRFs. A copy of the CRFs stays at the investigations site. CRFs must be completed for all subjects who sign ICF even if the subject fails to complete the study. No section of the CRF is to be left blank without an appropriate explanation by the investigator, since the lack of such explanation may necessitate discarding an otherwise usable observation. Data reported on CRFs should be consistent with source data documents when applicable, or the discrepancies should be explained. Any correction or deletions are to be made by crossing out with a single line (so it´s still legible), then initialing and dating by the investigator or other

authorized person. The use of correction fluids to "white-out" mistakes in data entry is not permitted. The investigator should ensure the accuracy, completeness, legibility, and timelines of the data reported to the sponsor in the CRFs and in all required reports. The CRF shall be signed and dated by the principal investigator or his/her authorized designees.

8. MONITORING / INSPECTIONS / AUDITS

8.1 Monitoring

The sponsor will assign a study monitor to maintain contact with the investigator and will visit the study site for the purpose of discussing and/or retrieving data in order to comply with DIN EN ISO 14155 guidelines. An initiation visit will be conducted by the sponsor and the study monitor to discuss the protocol and the obligations of both the sponsor and the investigator. The investigator must allow the study monitor to perform periodic, interim monitoring visits. The purpose of these visits is to review the CRFs at regular intervals throughout the study to verify adherence to the protocol, and the completeness, consistency and accuracy of the data being entered on them. The study monitor should have access to subjects' records needed to verify the entries on the CRFs for source data verification. The investigator should be available at some time during the interim monitoring visit to review the data and resolve any queries. The investigator agrees to co-operate with the study monitor to ensure that any problems detected in the course of these visits are resolved. The study monitor will perform a close-out visit at the conclusion of the investigator's involvement in the study.

8.2 Inspections / Audits

The Investigator will make all pertinent records available, including source data documentation, for inspection by the EC competent authorities and for auditing by the sponsor after appropriate notification. The verification of CRF data must be made available by direct inspection of source data documents. This information will be considered as confidential.

9. ADMINISTRATIVE PROCEDURES

9.1 Amendments

No change to the protocol may be made without the joint agreement of both the Investigator and the sponsor. Any amendment to the original protocol will be made by the sponsor. The written amendment must be submitted to the EC and the investigator must await the approval before implementing the changes. If in the judgment of the EC the investigator, and/or the sponsor, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written informed consent form will require similar modifications. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.

9.2 Publication policy

All unpublished documentation (including the protocol, CRF, and Investigator's Brochure) given to the investigator is strictly confidential. All recipients must agree not to disclose the information herein contained to any person without the prior written authorization of the sponsor. The investigator agrees that the sponsor maintains the right to use the results of this study in their original form and/or in a global report for submission to governmental and regulatory authorities of any country. The results of the study are intended to be published.

9.3 Study Report

The final study report will be prepared according to the DIN EN ISO 14155. The final study report will be prepared regardless of whether the study is completed or prematurely terminated. The sponsor and the Principal Investigator will sign the final report after review. The final report will be provided to the EC, the competent authority and upon re-quest, to all the investigators.

9.4 Confidentiality

All information provided to the Principal Investigator dealing with the medical device will be regarded as confidential.

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APPENDIX

Instruction for use
A1 BA_seca 515_BH_17-10-07-626-002b_11-2016S.pdf
A2 BA_seca_525_17-10-05-350-002_12-2015_B_EN.pdf
A3 BA_seca 514_515_mBCA_AH_17-10-07-627-005b_12-2016B.pdf

Declaration of Conformity
B1 DoC_17-10-09-289c_seca_515.pdf
B2 DoC_17-10-09-337_seca 525.pdf

Labels
C1 5141321004_20161101.pdf
C2 5157021009_20160915.pdf

Risk Management
D1 R1_525_Risikomanagement-Bericht_04022016_sign.pdf
D2 050712_Risikomanagement_Bericht_mbca.pdf
D3 Risikoanalyse_mBCA 515.pdf
D4 Risikoanalyse_mBCA_525_v10_09112015.pdf