Duke Clinical Research Institute

From Thought Leadership to Clinical Practice

SURVEILLANCE AND ALERT-BASED MULTIPARAMETER MONITORING TO REDUCE WORSENING HEART FAILURE EVENTS - SCALE-HF 1

A prospective, multicenter study designed to evaluate how the Bodyport Cardiac Scale and biomarkers change with worsening heart failure

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Duke Clinical Research Institute

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LIST OF TABLES AND FIGURES

ABBREVIATIONS

Table 1. List of Abbreviations

BCG	Ballistocardiograph
CFR	Code of Federal Regulations
DCRI	Duke Clinical Research Institute
ECG	Electrocardiograph
GCP	Good Clinical Practice
HF	Heart Failure
HFrEF	Heart failure with reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
IPG	Impedance plethysmograph
LVEF	Left Ventricular Ejection Fraction
US	United States

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)
- International Council on Harmonisation (ICH) E6

I agree to ensure that all staff members involved in the conduct of this trial are informed about their obligations in meeting the above commitments.

Principal Investigator: Adam DeVore, MD, MHS

Signed: _____ Date: _____

PROTOCOL SUMMARY

Title:	SurveillanCe and Alert-based multiparameter monitoring to reducE worsening Heart Failure events – **SCALE-HF 1**
Summary:	The overarching goal of this prospective, multicenter study is to utilize data from the Bodyport Cardiac Scale to develop an algorithm that allows for the early detection of worsening heart failure (HF). The Bodyport Cardiac Scale is capable of measuring key HF parameters of congestion and cardiac perfusion on a regular basis in a patient's home. These data will be combined into a model or composite index that may be used to identify patients at increased risk for decompensation, inform the reason for their decline, and offer the possibility to remotely optimize therapy to prevent further worsening HF. The SCALE-HF program will consist of multiple phases. For SCALE-HF 1, patients will be prospectively enrolled and utilize the Bodyport Cardiac Scale on a daily basis. Patients and clinicians will be blinded to the results other than data readily available from other devices such as body weight. There will be no attempt to influence clinical practice. Patients will be followed remotely for suspected clinical events.
Objectives:	The primary objective of this study is to utilize data from the Bodyport Cardiac Scale to develop a model that allows for the early detection of worsening HF.
Endpoints:	The primary endpoint of the study will be worsening HF. Worsening HF will be defined as an urgent, unscheduled clinic or emergency department visit or hospital admission with a primary diagnosis of HF in which the patient exhibited new or worsening symptoms of HF on presentation, had objective evidence of new or worsening HF, and received initiation or intensification of treatment for HF.
Design	This study is intended to enroll a broad population of patients. Patients may be consented and enrolled remotely, in clinic, or prior to hospital discharge. Training on device use will be provided and daily utilization will be requested. Device sensor data will be uploaded remotely and analyzed on a continuous basis. Treating clinicians will be blinded to the investigational sensor data. Follow-up will occur remotely at 6 weeks, 3 months and then every 3 months until the end of the study. Patients may also be contacted by the site and/or study team for suspected device malfunction or nonadherence with the Bodyport Cardiac Scale. At each interview, participants will be asked to report possible clinical events. Sites may also be queried to report possible clinical events. All patients will consent to release of medical records regarding HF history and suspected clinical events. Based on site- and participant-reported events, medical billing data and medical records for possible clinical events will be collected. Possible clinical events will be reviewed and adjudicated

	by a clinical events committee using standardized definitions. The committee members will be blinded to sensor and algorithm data.
Population:	Approximately 300 male and female participants in the US, 18 years of age or older, irrespective of left ventricular ejection fraction with symptomatic HF will be enrolled. Patients must be able to stand independently on the Bodyport Cardiac Scale. We will exclude patients with a weight > 170 kg, prior heart transplant or currently listed for heart transplant, current LVAD, current inotropes, and end-stage renal disease requiring chronic dialysis.
Sites Enrolling Participants:	Approximately 5 US sites
Duration of Study	Approximately 1 year (6 months enrollment and approximately 6 months follow up)
Study Product	Bodyport Cardiac Scale

SCHEMATIC OF SCALE-HF STUDIES

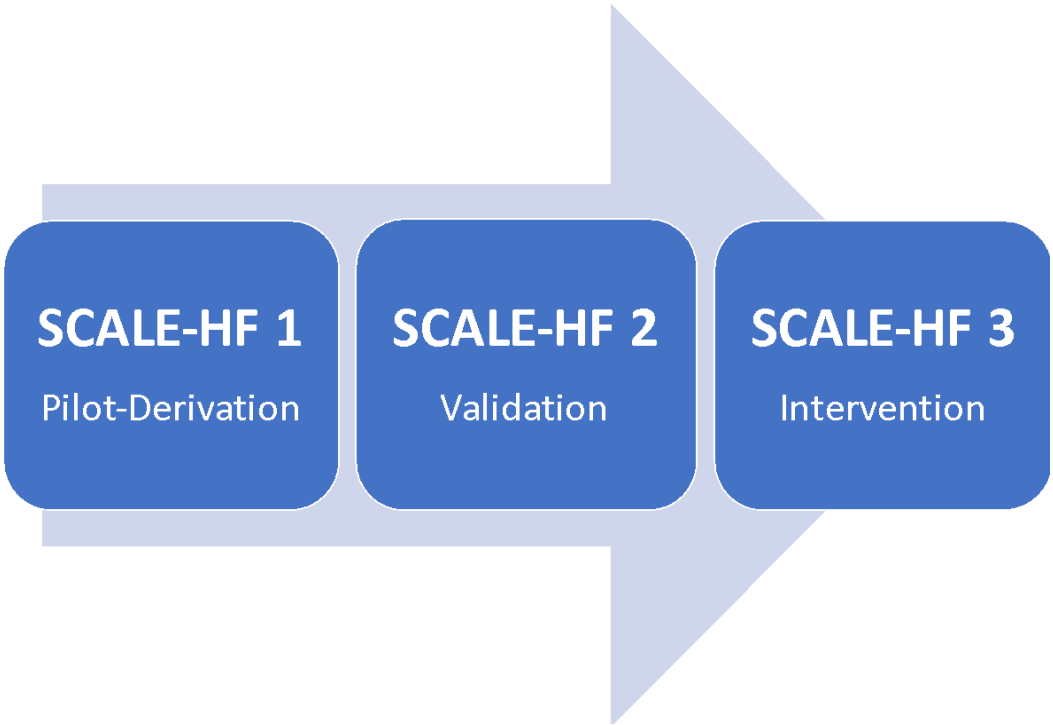

Figure 1. SCALE-HF Overall Design. Scale-HF 1 will be the first in a series of studies that aims to evaluate the use of the Bodyport Cardiac Scale to rapidly identify early worsening HF in order to allow for clinical interventions to prevent disease progression.

1. KEY ROLES

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2. BACKGROUND AND TRIAL RATIONALE

2.1 BACKGROUND INFORMATION

Heart failure (HF) is a major health, social and economic problem worldwide.[1] The incidence and prevalence of HF are increasing,[2] in part due to an aging population and rising burden of comorbidities.[3] Efforts to decrease mortality, decrease hospitalization rates and improve the well-being of patients with HF were modestly successful over the last decade with the introduction of medical therapies and care strategies.[4] However, despite advances in medical and device therapies, the number of hospitalizations for HF and associated readmissions remains high and represents an increasingly unsustainable financial burden.[5] As a result, reducing HF readmission rates has become a priority in many of the developed countries. In the US alone, the costs related to HF are expected to reach $70 billion by 2030, an increase of 130% on current costs.[6-8]

Achieving and maintaining an euvolemic status is a key goal in the management of HF. Thus, close observation of, and rapid response to changes in early physiological indicators are essential in achieving or maintaining euvolemia. Clinical signs and symptoms of HF decompensation are preceded by an increase in filling pressures, autonomic adaptation and resultant cardiac function and total fluid content changes.

The Bodyport Cardiac Scale provides an innovative and noninvasive approach to obtain clinically relevant hemodynamic parameters. The Bodyport Cardiac Scale is a physical platform in which the user stands with bare feet. The scale captures a number of physiological parameters including weight, electrocardiogram, impedance plethysmography and ballistocardiography to derive a proprietary

algorithm to monitor for cardiac decompensation through a preceding change in heart rate, cardiac output, stroke volume, cardiac time intervals, body weight and other biomarkers. Bodyport Cardiac Scale biomarkers are transmitted to a HIPAA-compliant cloud via an integrated cellular LTE-M modem for storage and visualization in a web-based application. The simplicity of the Bodyport Cardiac Scale enables patients to use the system at home, allowing patients to be monitored remotely and make treatment decisions with their medical team without the need for an in-person visit.

2.2 RATIONALE

Despite recent advancements in medical therapy, many patients with HF continue to have a high burden of symptoms and are at increased risk for adverse outcomes. As noted above, management of worsening HF also represents a major economic burden on the public health system. Worsening HF is characterized by the need for rehospitalization or urgent outpatient treatment for acute HF in order to control symptoms, preserve end organ function, and prevent further disease progression including death. There remains an urgent need to detect early worsening HF in order to allow for clinical interventions to prevent disease progression.

2.3 POTENTIAL RISKS

The known risks to participants in the trial will be minimal, as SCALE-HF 1 will be limited to data collection. Risk is involved to the extent that privacy and confidentiality may be compromised. However, every reasonable effort will be made to limit breaches of privacy and confidentiality.

3. OBJECTIVES AND ENDPOINTS

3.1 PRIMARY OBJECTIVES

The primary objective of this study is to utilize data from the Bodyport Cardiac Scale to develop an algorithm that allows for the early detection of worsening HF.

3.1 SECONDARY OBJECTIVES

The secondary objectives of this study are to compare data from the Bodyport Cardiac Scale to:

- Data obtained from approved implantable devices and sensors
- Data obtained from other markers of congestion including invasive hemodynamics, biomarkers, and blood volume analysis

3.2 ENDPOINTS

The primary endpoint of the study will be worsening HF.

Worsening HF will be defined as an urgent, unscheduled clinic (requiring IV diuretics) or emergency department visit or hospital admission with a primary diagnosis of HF in which the patient exhibited new or worsening symptoms of HF on presentation, had objective evidence of new or worsening HF, and received initiation or intensification of treatment for HF.

Information will also be collected on death and any mortality events will be classified as cardiovascular or non-cardiovascular. We will also collect data on arrhythmic events requiring hospitalizations or a defibrillator shock where the collected data allows such an assessment.

4. STUDY DESIGN

4.1 OVERALL STUDY DESIGN

SCALE-HF 1 is a prospective, multicenter study. The overarching goal is to enroll a broad population of patients with HF and follow them remotely for clinical events. Patients will be identified by participating sites and may be consented and enrolled remotely, in clinic, or prior to hospital discharge. Follow-up visits will be remote and occur at 6 weeks, 3 months and then every 3 months until the end of the study. Follow-up information will be collected by sites and may be supplemented by a centralized telephone call center (and email) via trained personnel at the Duke Clinical Research Institute. Participants may also be contacted by the site and/or study team at other timepoints for study issues such as suspected device malfunction or nonadherence with the Bodyport Cardiac Scale.

Patients eligible for the study will have HF and a prior history of hospitalization for acute decompensated HF. A history of clinical HF will be confirmed by site investigators. To ensure that a broad population of patients is enrolled, there will be limited additional inclusion and exclusion criteria. The participant population is described in more detail in Section 5 below.

All patients will consent for longitudinal follow-up. This will include remote follow-up visits as well as access to clinical records to evaluate for future clinical events. The remote follow-up visits will place a minimal burden on patients and sites and be limited to assessments for suspected clinical events. All patients will consent to release of medical records regarding HF history and suspected clinical events. Based on site- and participant-reported events, medical records for possible clinical events will be collected. Possible clinical events will be reviewed and adjudicated by a clinical events committee using standardized definitions. The committee members will be blinded to sensor and algorithm data.

Training on device use will be provided to patients and daily utilization of the Bodyport Cardiac Scale will be requested. Device sensor data will be uploaded remotely and analyzed on an ongoing basis throughout the study. Patients, study teams, and treating clinicians will be blinded to the investigational sensor data other than basic information that is currently available through other devices including weight, heart rate and leg edema status. There will be no attempt to utilize the study data to influence clinical practice.

4.2 SCHEDULE OF EVENTS

Table 2. SCALE-HF 1 Schedule of Events

	Baseline Visit	Follow-up Visits
Eligibility criteria	X	
Informed consent	X	
Demographics [a]	X	
Laboratory evaluations [b]	X	
Electrocardiogram	X	

Relevant medical history [c]	X	
Implantable device data [d]		X
HF outcomes [e]		X
Arrhythmic events requiring hospitalizations [f]		X

[a] Includes date of birth, sex, race, ethnicity
[b] Includes most recent basic metabolic panel (sodium, potassium, blood urea nitrogen, serum creatinine) and natriuretic peptide levels, B-type natriuretic peptide (BNP) or N-terminal pro-BNP. Where available will collect right heart cath data.
[c] Includes heart failure history including last assessment of left ventricular ejection fraction
[d] Patients with cardiac implantable electronic devices including pulmonary artery sensors and implantable cardioverter defibrillators will provide routine interrogation data
[e] Hospital readmissions and all-cause mortality.
[f] Hospitalization event or treatment for ventricular arrhythmia (shock by defibrillator)

5. STUDY POPULATION

5.1 INCLUSION CRITERIA

Participants eligible for inclusion in this study must fulfill all of the following criteria:

1. Provide informed consent before trial enrollment
2. Age ≥ 18 years
3. A diagnosis of symptomatic HF including a worsening HF event in the preceding 12 months. Worsening HF events will be determined by local clinician-investigators and will typically include the following: a) HF symptoms (eg, dyspnea, fatigue); b) HF signs (eg, elevated jugular venous pressure, peripheral edema), or laboratory/imaging evidence of HF (eg, pulmonary congestion on chest x-ray, elevated natriuretic peptide levels) during the event, and treatments targeting acute HF (eg, intravenous diuretics, vasodilators, or inotropes).

5.2 EXCLUSION CRITERIA

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the trial population will be representative of all eligible participants.

1. Weight > 170 kg
2. Use of chronic inotropic therapy
3. Prior heart transplant or currently listed for heart transplant
4. Current or planned left ventricular assistance device
5. Chronic kidney disease requiring chronic dialysis
6. Unknown left ventricular ejection fraction (LVEF). The LVEF should be based on the most recent local measurement using echocardiography, multigated acquisition scan, computed tomography scanning, magnetic resonance imaging, or ventricular angiography. Patients with preserved and reduced LVEF will be permitted in the study though enrollment may be capped to ensure no

more than approximately 2/3 of the total enrollment includes patients with preserved or reduced LVEF.

7. Terminal illness other than HF, such as malignancy, or with a life expectancy of less than 1 year as determined by the enrolling clinician-investigator
8. Unable to participate in longitudinal follow-up including daily use of the Bodyport Cardiac Scale. Patients must be able and willing to stand independently on the Bodyport Cardiac Scale daily.

6. STUDY VISITS AND ACTIVITIES

6.1 SCREENING AND ENROLLMENT

Patients will be identified from outpatient clinic logs as well as current admission panels. Patients previously included in clinical trials will also be screened for candidacy. Eligible candidates will be enrolled from an outpatient setting or an inpatient setting. Enrollment will be capped to ensure that no more than approximately 2/3 of the total enrollment will be at the time of hospital discharge or from the outpatient setting.

Prior to screening activities, each patient will be given an opportunity to ask questions and to understand the details of study participation, including risks and benefits. This consent process will be documented in the patients' source documents and evidenced by the patient signing the informed consent form (ICF). All patients will consent to release of medical records regarding HF history and suspected clinical events. Informed consent will be obtained either in person or via e-consent according to respective institutional policies.

After signing the ICF, each patient will be assigned a unique identifier number that will be used on all documentation.

Screening data will be collected after informed consent is signed. The Screening evaluations include:

- Informed Consent
- Inclusion/Exclusion Criteria
- Demographics
- Medical history
- Most recent physical examination, biomarkers (NT-proBNP, basic metabolic panel) and vital signs measurements
- Current medications
- Recent laboratory data including renal function and natriuretic peptide values

If measurement of any of the above assessments does not occur in the normal course of patient care, clinical practice should not be changed to accommodate collection of additional data.

Following enrollment, the patient will be provided with the study device and receive training in person or remotely on its use from study coordinators or company representatives.

1. Outpatient- Enrollment can occur in person or remotely. Scale will be provided upon clinic visit or shipped to patient directly after the appointment

2. Inpatient- Patient is enrolled prior to discharge. Scale will be provided prior to discharge or shipped by Bodyport Inc. to patient directly after the discharged

6.2 SURVEILLANCE/FOLLOW UP

Follow-up will occur remotely at 6 weeks, 3 months and then every 3 months until the end of the study. Follow-up will occur via telephone interviews by trained personnel by individual participating sites. This approach will ensure the consistency and quality of data collection and minimize loss to follow-up. At each interview, participants will be asked to report any encountered clinical events.

Routine data collection at each follow up timepoint will include:

- Possible clinical event including those that occur outside of the enrolling health system such as hospitalization, emergency room visit or clinic visit with IV diuretic administration

Based on participant-reported events, clinical data for rehospitalizations, emergency department visits, and worsening heart failure related clinic visits will be obtained and submitted for review. As an additional mechanism to safeguard against under-reporting of events, sites will conduct medical record queries at 6 weeks, 3 months and then every 3 months until the end of the study enrollment to screen for hospitalizations or procedures.

Patients may also be contacted by the site and/or study team including the sponsor and coordinating center for suspected device malfunction or nonadherence with the Bodyport Cardiac Scale. Nonadherence is defined as device non-use for 3 days or more. Patients will be potentially contacted using email, phone calls or text messaging to provide reminders to use the scale. Should non-use continue beyond 4 days the patient may be contacted by a phone call to explore potential problems with the technology or explore whether an event might have occurred.

Upon study discontinuation the patients are asked to return the scale to the company and are provided with a return shipping label.

7. COMPENSATION

Participants will not receive any compensation for participating in this study.

8. COSTS

Participants will not incur any additional costs due to study participation. Patients or their insurance company will be required to pay for all expenses related to regular care such as outpatient visits and other hospital care.

9. SAFETY MONITORING

No safety related concerns are expected with the non-invasive scale. No safety specific / adverse endpoints are defined

10. STATISTICAL METHODS AND DATA ANALYSIS

10.1 STATISTICAL AND ANALYTICAL PLANS

The Bodyport Cardiac Scale captures various physiological signals including an electrocardiograph, an impedance plethysmograph, and a ballistocardiograph. These raw signals will be filtered and interpolated prior to feature extraction and model validation. Regions with motion artifacts or noise will be identified and removed. Ensemble average waveforms will be constructed from the real-time signals. Specific characteristic features will be identified on the averaged waveforms. Temporal and amplitude-based biomarkers will be extracted from the identified features within and across each averaged waveform. These features and biomarkers will be assessed longitudinally by constructing trends consisting of multiple measurements and identifying statistically significant changes over time. Some of the key features being explored in this study are: weight, heart rate, heart rate variability, peripheral impedance, body fluid, balance, stroke volume, cardiac output, pre-ejection period, left ventricular ejection time, as well as the amplitude and timing of characteristic features on the IPG, ECG, and BCG signals. A focus on these specific features is driven by prior research demonstrating clinical relevance to cardiovascular function and heart failure status.

During analysis, various methods will be implemented to select signal features that demonstrate a meaningful association with HFEs. Those features most strongly correlated to HFEs will be combined into a model and associated alert algorithm. The development of the model may use a combination of techniques, including multivariate regression and machine learning (e.g. support vector machines, clustering, decision trees, Bayesian networks). Models will be evaluated and optimized based on their sensitivity and specificity to detect heart failure events.

10.2 INTERIM ANALYSIS

Throughout the study, enrollment rates, heart failure event prevalence, and adherence will be analyzed.

Additionally, at 100 enrolled patients with approximately 90 day follow up, an interim analysis may be performed. Data will be shared with Bodyport for statistical analysis and possible publication. Bodyport will use the scale biomarker data to validate a model that reflects changes in patient status. The model will use intra-patient biomarker trends to detect meaningful deviations from a patient's baseline state.

10.3 SAMPLE SIZE

Data derived from this study will add to the model development aims of the Bodyport Cardiac Scale. This study is statistically powered to detect approximately 75 primary endpoints which will approximate to about 300 enrolled patients. An event rate of 75 equates to an approximate rate of 25% at 6 months. Given that this study is a development study however additional events may be required to derive the predictive algorithm.

10.4 Adjudication Committee

The Adjudication Committee consists of trained clinicians, who will, when an event occurs, review the medical records to confirm that the event meets the criteria of the trial endpoints.

11. PROCEDURES AND INSTRUCTIONS

11.1 PROTOCOL AMENDMENTS AND OTHER CHANGES IN STUDY CONDUCT

PROTOCOL AMENDMENTS

Any substantive changes will be made as formal amendments to the protocol and will be submitted for appropriate review by an institutional review board (IRB).

Any change or addition to this protocol requires a written protocol amendment that must be approved by Bodyport Inc. and the Investigator before implementation. Amendments affecting the scope of the investigation, or the scientific quality of the study require additional approval by the IRB. Examples of amendments requiring such approval are:

1. A significant change in the study design (e.g., duration of follow up)
2. A change in patient inclusion and exclusion criteria

Protocol changes affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval, but the IRB must be kept informed of such administrative changes.

11.2 RECORDING OF DATA, DOCUMENTATION, AND RETENTION OF DOCUMENTS

Data will be stored and evaluated in such a way as to guarantee subject confidentiality in accordance with the legal stipulations applying to confidentiality of data. All study records must be available for inspection by the Sponsor, its authorized representatives, and regulatory authorities.

Data on subjects collected on CRFs during the study will be documented in an anonymous fashion and the subject will only be identified by the study number and by initials if also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, both Bodyport Inc. and the Investigator are bound to keep this information confidential.

The Investigator must maintain source documents for each subject in the study, consisting of all demographic and medical information, and must keep a copy of the signed ICF. The subject's clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include but are not limited to the subject's hospital/clinic records, physicians' and nurses' notes, appointment book, original laboratory reports, ECG, pathology and special assessment reports and signed ICFs. All information on the CRFs must be traceable to these source documents in the subject's file. Data without a written or electronic record will be defined before study start and will be recorded directly on the CRFs, which will be documented as being the source data.

Essential documents defined in the ICH Guidance on Good Clinical Practice (ICH E6) and listed below, must be retained by the Investigator for as long as needed to comply with national and international regulations. The Sponsor will notify the Investigator(s)/institution(s) when the study-related records are no longer required. The Investigator agrees to adhere to the document retention procedures by signing the protocol.

Essential documents include:

1. IRB approvals for the study protocol and all amendments
2. All source documents and laboratory records
3. CRF copies
4. Subjects' ICFs (with study number and title of study)

11.3 AUDITING PROCEDURES

Investigator understands that source documents for this study must be made available to appropriately qualified personnel from the Sponsor or its designees, to the IRB, and/or to health authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents. The Sponsor conducts audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of GCP. A regulatory authority may also wish to conduct an inspection (during the study or even after its completion). If an inspection is requested by a regulatory authority, the Investigator must immediately inform the Sponsor that this request has been made.

11.4 PUBLICATION OF RESULTS

An integrated clinical and statistical report will be prepared at the completion of the treatment period. However, it is intended that the results of the study will be included on http://clinicaltrials.gov and published and/or presented at scientific meetings.

11.5 DISCLOSURES AND CONFIDENTIALITY

By signing this protocol, the Investigator agrees to keep all information provided by Bodyp ort, Inc. in strict confidence and to request similar confidentiality from his/her staff and the IRB. The information provided by Bodyport Inc. to the Investigator may not be disclosed to others without direct written authorization from Bodyport Inc., except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.
The Investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. The Investigator should keep a subject enrollment log relating codes to the names of subjects. The Investigator should maintain documents not for submission to the Sponsor, (e.g., subjects' signed consent forms), in strict confidence.

Data use agreements or contracts will be executed with each participating site in addition to the applicable institutional approvals prior to any participating site investigator sending patient/subject data for this study.

12. ETHICS AND GOOD CLINICAL PRACTICE

This study must be carried out in compliance with the protocol and:

- ICH Guidance on Good Clinical Practice (ICH E6)
- World Medical Association, Declaration of Helsinki

12.1 INSTITUTIONAL REVIEW BOARD AND ETHICS

Each participating institution will submit this protocol and their ICF for IRB approval prior to starting the study. The Investigators will not begin any study subject activities until approval from the IRB has been documented and provided as a letter to the Investigator. Before implementation, the Investigators will submit to and receive documented approval from the IRB of any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB approval, with the exception of those necessary to reduce immediate risk to study subjects.

12.2 INFORMED CONSENT

The Investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. No subject can enter the study before his/her informed consent has been obtained. The ICF must be submitted by the Investigator for IRB approval.

12.3 DECLARATION OF HELSINKI

The Investigator must conduct the study in accordance with the principles of the current version of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/en/30publications/10policies/b3/index.html

13. STUDY DISCONTINUATION

All sites reserve the right to discontinue the study at any time. The Sponsor reserves the right to terminate the study in its entirety or at a specific study center at any time and as specified in the clinical study agreement.

14. REFERENCES

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