

## **Artificial Intelligence or Human Hand? A Pilot Study Evaluating Inferior Vena Cava Imaging for Hydration Status – The THAP2 Study**

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Research legislation: Ordinance on human research with the exception of Clinical trials (HRO) [i].

Type of Research Project: Research project involving human subjects

Risk Categorization: A acc. to ordinance HRO Art.7

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## PROTOCOL SIGNATURE FORM

Study Title      *Artificial Intelligence or Human Hand? A Pilot Study*  
                         *Evaluating Inferior Vena Cava Imaging for Hydration Status*

The project leader has approved the protocol version 2 dated 21.01.2026 and confirms hereby to conduct the project according to the protocol, the Swiss legal requirements [i, ii], current version of the World Medical Association Declaration of Helsinki [iii] and the principles and procedures for integrity in scientific research involving human beings [iv].

The project leader has received the ICF and consider it appropriate for use.

### Project leader/Sponsor:

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Name: Dr. med. sc. Laura Potasso

Date:      Signature: 

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## GLOSSARY OF ABBREVIATIONS

<i>AI</i>	<i>Artificial Intelligence</i>
<i>BASEC</i>	<i>Business Administration System for Ethical Committees</i>
<i>BS</i>	<i>Beginner Sonographer</i>
<i>CI</i>	<i>Collapsibility Index</i>
<i>CVP</i>	<i>Central Venous Pressure</i>
<i>eCRF</i>	<i>Electronic Case Report Form</i>
<i>ES</i>	<i>Experienced Sonographer</i>
<i>FAS</i>	<i>Full analysis set</i>
<i>HRA</i>	<i>Human Research Act</i>
<i>HRO</i>	<i>Human Research Ordinance</i>
<i>ICC</i>	<i>Intraclass Correlation Coefficient</i>
<i>IQR</i>	<i>Interquartile Range</i>
<i>IVC</i>	<i>Inferior Vena Cava</i>
<i>IVC CI</i>	<i>Collapsibility Index of Inferior Vena Cava</i>
<i>IVC max</i>	<i>Maximal Diameter of Inferior Vena Cava</i>
<i>PLR</i>	<i>Passive Leg Raise</i>
<i>RI</i>	<i>Right Intercostal</i>
<i>SC</i>	<i>Subcostal</i>
<i>US</i>	<i>Ultrasound</i>
<i>VAS</i>	<i>Visual Analogue Scale</i>

# 1 BACKGROUND AND PROJECT RATIONALE

Disturbances of water homeostasis are observed in various diseases and are associated with increased morbidity and mortality (1). Rapid and accurate identification of hydration status, specifically identifying hypervolemia (excess body water) or hypovolemia (reduced body water) is crucial for the diagnosis and treatment of numerous conditions.

Assessment of hydration status, however, can be challenging. Clinical parameters such as skin turgor, examination of mucous membranes, clinical assessment of jugular vein distension, peripheral edema, or pulmonary rales lack sensitivity and specificity in the identification of both hypervolemia and hypovolemia (1–3). Invasive measurements, such as right heart catheterization and direct central venous pressure (CVP) measurement via a central venous catheter, provide reproducible and reliable results (4,5); however, these procedures require advanced training, may cause significant adverse effects for the patient (e.g., bleeding, infection, thrombosis), and are not universally available (6,7). Therefore, non-invasive methods are needed, and ultrasound (US) has been identified as a promising tool due to its cost-effectiveness, absence of radiation, wide availability, and capability for dynamic assessments (8–12).

Many anatomical sites and structures have been evaluated for hydration status assessment by ultrasound. Due to its large size and its significant contribution to venous return to the heart, the inferior vena cava (IVC) is well studied and can be used as a surrogate of CVP (13,14). The IVC is typically visualized longitudinally at its entrance into the right atrium from a subcostal (SC) view (15,16). However, if this is not possible due to superimposed bowel gas, abdominal wounds/surgeries or the individual's body habitus, the right intercostal (RI) view can be used alternatively (17,18).

For sonographic IVC assessment, two parameters are particularly relevant for evaluating hydration status: a) the maximum IVC diameter in the longitudinal view (IVC max), typically measured at end-expiration in spontaneously breathing individuals, and b) the IVC diameter variation with normal respiration, known as collapsibility index (IVC CI). Several studies have shown that the combination of IVC max >2.1 cm and IVC CI <50% correlates with elevated right atrial pressure, which is strongly correlated with elevated CVP and therefore suggests hypervolemia (14,19–23).

However, this combination can also be observed in non-hypervolemic states, including severe tricuspid insufficiency, chronic obstructive pulmonary disease, pericardial effusion, drug-induced vasoplegia, as well as in physiological conditions such as pregnancy and regular endurance sports among both professional and amateur athletes (24–27). The latter is understood as an adaptive, physiological response to chronic increased venous return and cardiac output (24,28).

In addition, a hypervolemic state as assessed by IVC US can transiently be elicited by a passive leg raise (PLR). PLR consists of moving an individual from a supine position to one in which the lower limbs are elevated to approximately 45° while the upper body remains horizontal. This positional change shifts approximately 150–300 mL of blood toward the IVC, transiently increasing its diameter (29).

Despite its advantages, IVC US is highly operator-dependent, and measurement accuracy varies with operator experience and IVC depth (30,31). Several US devices nowadays include artificial intelligence (AI)-guided IVC measurements using image processing algorithms and pattern recognition, offering the potential to facilitate and expedite examinations. These AI-tools enable automatic identification of measurement-points, such as IVC max measurement, and calculation of IVC CI (32). However, it remains unclear how well these AI-guided measurements correlate with those performed by human operators, and how useful AI tools are for inexperienced sonographers.

The goal of this project is to compare AI-guided sonographic IVC measurements with those of human operators (experienced sonographer, beginner sonographer) in two commonly used views (SR, RI) in healthy, euvoletic participants before and after PLR, which mimics hypervolemia, in order to assess the possible role of AI-guided sonographic IVC measurements by assessing its feasibility and reliability. The project involves vulnerable individuals (healthy volunteers), yet it presents a risk category A according to art. 7 of the Human Research Ordinance (HRO) as it implies only a minimal risk for the participants (ultrasound assessment, no radiation, no invasive measurements).

## 2 PROJECT OBJECTIVES AND DESIGN

### 2.1 Hypothesis and primary objective

The primary objective of this cross-sectional, observational study is to determine how many healthy, euvoletic participants are classified as hypervolemic based on the proposed cut-off values for IVC measurements in the SC view, when assessed by an experienced sonographer (ES), by a beginner sonographer (BS), and by an AI-guided system applied by the ES and BS before and after PLR.

The null hypothesis is that AI-guided IVC measurements and human operator measurements will classify the same participants as hypervolemic, with no differences related to experience level of the sonographer.

**Secondary objectives** will be

- Intra-rater agreement as described for the primary objective.
- Interrater agreement as described for the primary objective.
- Reliability and consistency of measurements performed by ES and BS with and without AI-guidance.
- Reliability and consistency of measurements calculated for pre-defined subgroups (age, sex, body mass index, fluid intake in liters on the day of assessment, number of hours per week of sport, IVC visualization depth).
- Feasibility analysis including the possibility of visualization of IVC, possibility of IVC recognition by AI and time until proper visualization for ES and BS.
- Tolerability analysis for participants using the Visual Analogue Scale (VAS).

### 2.2 Primary and secondary endpoints

The primary endpoint is to determine the percentage of healthy, euvoletic participants with IVC max >2.1 cm and IVC CI <50% in the SC view when assessed by an ES, by a BS, and by an AI-guided system applied by ES and BS before and after PLR.

**Secondary endpoints** will be

- (a) Intra-rater agreement: percentage of healthy, euvoletic participants with IVC max >2.1 cm and IVC CI <50% in the SC view, assessed by an AI-guided system vs ES and vs BS, before and after PLR.
- (b) Interrater agreement: percentage of healthy, euvoletic participants with IVC max >2.1 cm and IVC CI <50% in the SC view, assessed by an ES vs BS, before and after PLR.
- (c) ICC of IVC max and IVC CI assessed in the SC view between ES vs BS.

- (d) ICC of IVC max and IVC CI assessed in the SC view performed by the same sonographer (ES or BS) vs AI-guided assessment before and after PLR.
- (e) Endpoints (a) to (d) assessed in the RI view.
- (f) Endpoints (a) to (e) assessed in pre-defined subgroups: age, sex, body mass index, fluid intake in liters on the day of assessment, IVC visualization depth.
- (g) ICC of IVC max and IVC CI assessed in the SC view vs the RI view when performed by the same sonographer (BS or ES) with and without AI-guided measurement.
- (h) Correlation between IVC max and IVC CI before and after PLR and participants' endurance sport activity level, expressed as number of hours per week.
- (i) Feasibility (composed of two binary variables: possibility of visualization of IVC (yes/no), possibility of AI-guided recognition of IVC (yes/no); and a continuous variable: time in seconds until proper visualization of IVC) of IVC US visualization in the SC view vs the RI view for ES and BS.
- (j) Tolerability of the assessments by the participant, evaluated by the continuous VAS (1=worse, 10=best).
- (k) Number and percentage of AI-guided IVC measurements requiring manual correction of the measuring-point by ES.

## 2.3 Project design

This is an exploratory, observational, single-center, cross-sectional pilot project. US assessment will be performed by two sonographers, one beginner (BS) and one experienced (ES), blinded to each other's measurements. The BS is defined as a doctor who has not performed more than 20 US assessments of the IVC and has not performed clinical US of the abdominal region (at least 1x/week) in the past 6 months. The ES is defined as a doctor who has performed at least 20 US assessments of the IVC and uses US at least 1x/week in the past 6 months. Both BS and ES will perform a 2-hour training session in IVC sonography in two views (SC, RI) with a US-experienced doctor and will have full access to the protocol and measurement techniques during the assessments.



### 3 PROJECT POPULATION AND STUDY PROCEDURES

#### 3.1 Project population, inclusion and exclusion criteria

Fifty healthy individuals who provide written informed consent will be included.

##### Inclusion criteria:

Healthy adults aged 18 years or older, 50% biological women

##### Exclusion criteria:

1. Pregnant or lactating women
2. History of thrombosis of the inferior vena cava
3. Major cardiovascular event in the last 3 months
4. History of peripheral arterial disease of the legs
5. History of heart failure of any grade
6. History of atrial fibrillation or atrial flutter
7. History of severe valvular disease
8. History of renal failure
9. History of liver cirrhosis
10. History of chronic obstructive lung disease (COPD), chronic bronchitis, pulmonary emphysema
11. History of diabetes mellitus
12. History of arginine-vasopressin (AVP) disturbance
13. Abdominal surgery within the last 3 months
14. Volume loss (diarrhoea, vomiting, or bleeding) within the past 3 days
15. Respiratory distress of any grade
16. Any diuretic therapy, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs)
17. Inability to follow procedures or insufficient proficiency in the study language
18. Inability to provide informed consent
19. Vital signs outside normal limits: tachycardia >100 bpm, systolic blood pressure <85 mmHg, or SpO<sub>2</sub> < 92%
20. Employees or colleagues in a direct supervisory, subordinate, or collaborative relationship with the study team

Exclusion criteria 1-16 will be checked by asking participants about their medical history

Exclusion criteria 17-18 will be assessed at the discretion of a staff member

Exclusion criteria 19-20 will be checked by a staff member

### **3.2 Recruitment, screening and informed consent procedure**

Recruitment will take place at the University Hospital of Basel through flyers, e-mails, and word of mouth addressed to healthy visitors and employees. Interested individuals will receive further information about the study and are invited to direct questions to one of the staff members. In case of interest, exclusion criteria will be reviewed. If eligible, an appointment for US assessment will be scheduled, at least two hours after the screening visit, to give the participants time for consideration.

The recruitment is planned to start in March 2026 and be concluded by the end of December 2026.

We will ensure sex neutrality by enrolling 50% biological men and 50% biological women. Gender will not be asked. Participation will be voluntary. Up to a maximum of 10 CHF (Swiss francs) will be reimbursed to the participant to cover travel expenses.

### **3.3 Study procedures**

The study consists of a screening visit and a study visit, which can be performed on the same day, with at least 2 hours interval between the two. Both are performed at the University Hospital of Basel. The screening visit will take approximately 15 minutes, and the study visit will last about 60 minutes. Participants will be discharged from the study after the study visit.

#### Screening visit:

Potential participants will be instructed in advance to eat and drink as usual and to take their regular medication as prescribed. During the screening visit, inclusion and exclusion criteria will be checked by a dedicated questionnaire (Questionnaire 1). Potential participants will have the opportunity to ask questions.

#### Study visit:

After signing informed consent, another questionnaire (Questionnaire 2) will be completed. Blood pressure, heart rate, oxygen saturation as well as height and weight will be assessed and recorded. Exclusion criteria will be checked again before starting the assessment.

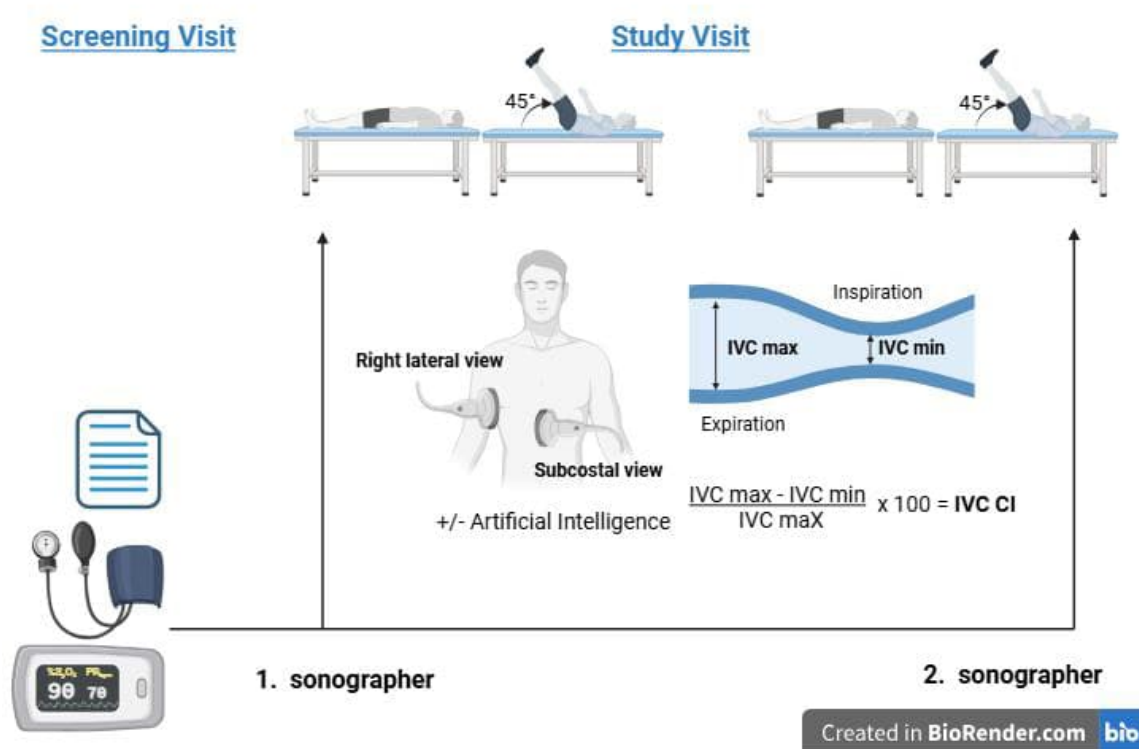
Each participant will be independently assessed by two sonographers (one ES, one BS) blinded to the results of each other. These assessments will take place on the same day, with the participant examined on the same examination table while the investigators rotate, to minimize bias related to differences between tables.

Participants will be positioned in a supine position (0°), with the arms placed comfortably above the head instructed to breathe normally. The assessment will take place using a Mindray TE 7

ACE device with the abdominal preset with a 1.3 - 5.7 MHz convex array transducer (C5-2s). The device is equipped with an integrated AI-guided software ("Smart IVC") for the assessment of IVC indices and is in routine clinical use at the University Hospital of Basel.

Each participant will undergo a SC and a RI IVC US assessment before and after PLR by both sonographers, resulting in a total of 8 IVC US examinations with 8 additional AI-guided IVC indices assessments (Figure 1).

**Figure 1:** Overview of study procedures. After screening visit, participants undergo an ultrasound assessment of the inferior vena cava at rest and after passive leg raise in both subcostal and right intercostal view by two independent investigators blinded for the results of each other. IVC = inferior vena cava, CI = collapsibility index



For the SC view, the transducer is placed 1-2 cm below the xiphoid process, slightly to the right of the midline. The marker (indicator dot) initially points toward the participant's left to capture a four-chamber cardiac view. A gentle counterclockwise rotation (approximately 60-90°) reorients the probe to align with the long axis of the IVC as it enters the right atrium.

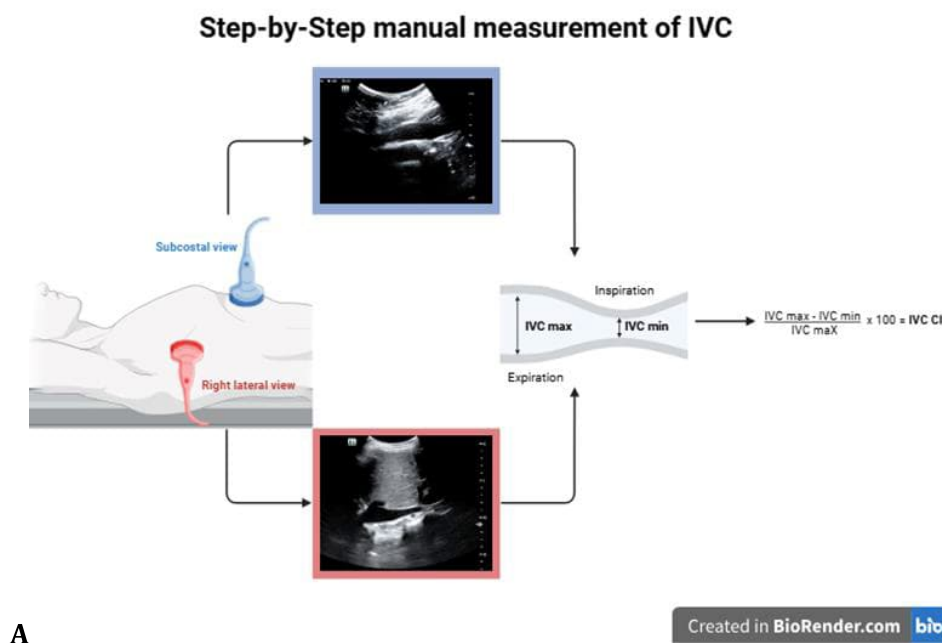
For the RI view, the transducer is placed along the right mid-axillary to anterior axillary line between the 8th and 11th intercostal spaces. The marker (indicator dot) is orientated toward the participant's head. The US beam is aimed posteriorly through the liver to visualize the IVC in a coronal plane as it enters the right atrium.

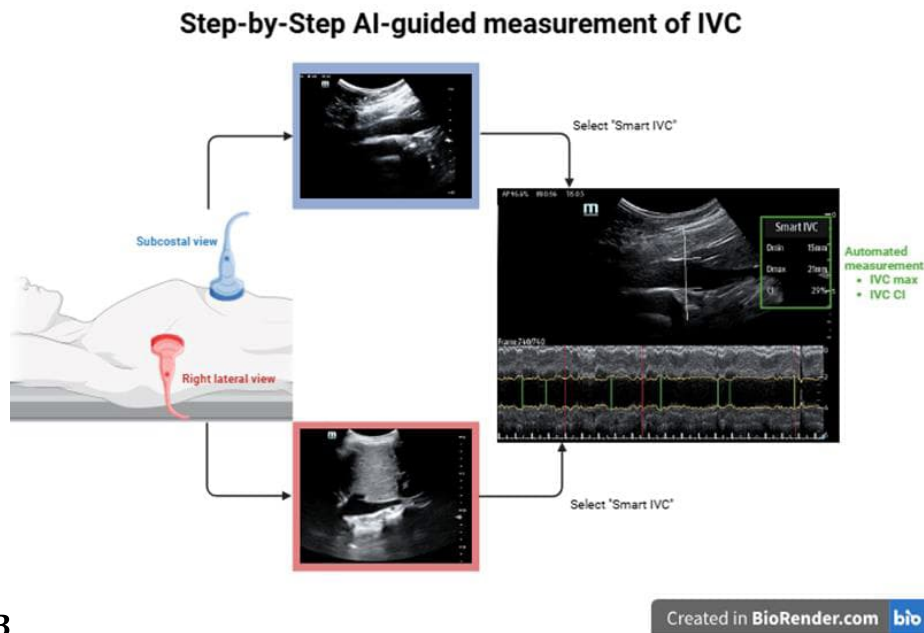
IVC US assessment consists of two parts, repeated for both SC and RI views, which are alternated to minimize bias.

Part 1 (US assessment in the supine position): The participant is positioned as described above. The IVC is visualized according to either SC or RI view. A video capturing two complete respiratory cycles is recorded in B-mode and stored (Figure 2A). Subsequently, the “Smart IVC” preset is selected, and an AI-guided measurement is obtained at the same anatomical point under identical conditions (Figure 2B).

Part 2 (US assessment after PLR): The participant’s legs are elevated to 45° while the upper body remains horizontal (0°). After 2 minutes, the sonographer performs the US assessment following the same protocol as in Part 1.

**Figure 2:** Step-by-step manual (A) and artificial intelligence-guided (B) assessment of the inferior vena cava. IVC = inferior vena cava, CI = collapsibility index, AI = artificial intelligence





**B**

After PLR, participants remain in the initial supine position for at least 2 minutes.

For each examination, the sonographer places the probe to obtain an optimal assessment point for both human- and AI-guided measurements. The time from examination start to achieving a satisfactory imaging window for both SC view and RI view in the supine position is recorded using a stopwatch. If no satisfactory imaging window can be achieved within 90 seconds, the sonographer will state “no proper visualization possible” and continue with the next view.

Participants will rate how pleasant or unpleasant they found the examination after PLR using a continuous VAS, distinguishing between SC view and RI view.

The sonographers will rate the examination conditions after each assessment (“poor”, “acceptable”, or “good”) and will state if “Smart IVC” measurement was applicable. If the sonographer requires more than 60 sec, he/she will state “Smart IVC not applicable”.

The ES will further state whether he/she had to adjust the measuring-point in “Smart IVC” to measure at approximately 2 cm from the IVC entrance into the right atrium, and if so, in which view and with or without PLR.

The BS will indicate which number examination it was for him/her.

#### Measurements:

AI-guided measurements of IVC max and IVC CI are recorded during the AI-guided assessment, and a corresponding image is stored to document the results. Human operator IVC max and IVC CI are determined from the acquired videos in a diagnostic image viewer program (IDS7 Viewer) and reviewed by an independent investigator who is not involved in the study visit and is blinded

to the AI-guided measurements. Corresponding images are stored to document the results. IVC max is defined as the largest diameter of the inferior vena cava, measured at end-expiration in spontaneously breathing participants, approximately 2 cm from the inflow of the IVC into the right atrium.

IVC CI is defined as the variation of IVC diameter during respiration and is calculated using the following formula:

$$\text{IVC CI (\%)} = \frac{\text{IVC max} - \text{IVC min}}{\text{IVC max}} \times 100$$

with IVC min being the narrowest diameter of the IVC at end-inspiration, measured in centimeters. For both views, SC and RI, in the supine position (0°), the depth of the IVC will be assessed, defined as the distance between the skin and the anterior wall of the IVC at end-expiration.

### **3.4 Withdrawal and discontinuation**

Participants have the right to withdraw or discontinue the study at any time. In case this happens after the beginning of the US assessments, we will ask for permission to keep the data related to the primary endpoint in anonymized form so that they can be included in the analysis for the primary endpoint.

## 4 STATISTICS AND METHODOLOGY

### 4.1 Statistical analysis plan

Statistical analysis will be carried out in collaboration with the Clinical Trial Unit (CTU) of the University of Basel. Data will be analyzed using the R Language and Environment for Statistical Computing [v]. The full analysis set (FAS) will contain all participants in whom either a SC or a RI view assessment was performed. The per-protocol set (PPS) will contain all participants for whom the primary outcome is available. Baseline characteristics of participants in the FAS will be summarized in a table stratified by sex. For continuous numerical variables, the mean and standard deviation (SD) or interquartile range (IQR) will be calculated according to the underlying distribution. For categorical variables, percentages and absolute numbers will be reported.

Hypothesis: The null hypothesis is that AI-guided IVC measurements and human operator measurements will classify the same participants as hypervolemic, with no differences related to the experience level of the sonographer.

Determination of sample size: Since this is an exploratory analysis without directly comparable prior studies, a sample size of 50 participants, 50% female, was chosen for pragmatic reasons.

Primary analysis: Analysis of the primary objective will be descriptive, reporting the percentage of healthy, euvoletic participants having IVC max >2.1 cm and IVC CI <50% when assessed by an ES, by a BS, and by an AI-guided system applied by ES and BS, before and after PLR.

Secondary analysis:

- Intra-rater and interrater agreement will be analyzed as described for the primary outcome; in addition, ICC will be calculated for comparison of the assessments performed by ES and BS with and without AI-guidance.
- These same analyses will also be conducted for pre-specified subgroups based on age, sex, body mass index, daily water intake, IVC depth, and weekly hours of physical activity
- Feasibility: We will perform a descriptive analysis including the proportion of successful visualization (percentage), successful application of AI-guided measurement (percentage), and the time in seconds to achieve proper visualization (IQR). Moreover, we will perform paired comparisons between ES and BS using the chi-square test for categorical outcomes and the Wilcoxon signed-rank test for continuous outcomes.
- Tolerability: We will perform a descriptive analysis of the VAS results (IQR) and paired comparisons for ES and BS with and without AI-guidance using Wilcoxon signed-rank test.
- Manual correction: We will perform a descriptive analysis (percentage of corrections needed) for the whole sample and according to the same pre-specified subgroups described above.

## **4.2 Handling of missing data**

In case of dropout with missing data regarding the primary endpoint, the participant will not be replaced.



## **5 REGULATORY ASPECTS AND SAFETY**

### **5.1 Local regulations / Declaration of Helsinki**

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [iii], the principles of Good Clinical Practice, the Human Research Act (HRA) [ii] and the Human Research Ordinance (HRO) [i] as well as other locally relevant regulations. The project leader acknowledges responsibility both as project leader and sponsor.

### **5.2 Notification of safety and protective measures (HRA Art. 15, HRO Art. 20)**

If, during the research project, circumstances arise which could put at risk the safety or health of the participants or lead to a disproportionate relationship between the risks and burdens and the benefits, all the measures required to ensure protection are to be taken without delay.

The project leader is promptly notified (within 24 hours) if immediate safety and protective measures must be taken during the conduct of the research project. The Ethics Committee will be notified via Business Administration System for Ethical Committees (BASEC) of these measures and of the circumstances necessitating them within 7 days.

### **5.3 Serious events (HRO Art. 21)**

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21<sup>1</sup>.

### **5.4 Procedure for investigations involving radiation sources**

Not applicable

### **5.5 Amendments**

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that must be taken immediately to protect the participants.

### **5.6 End of project**

Upon project completion or discontinuation, the Ethics Committee is notified within 90 days. All health-related data are anonymized upon termination of data analysis.

### **5.7 Insurance**

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<sup>1</sup> A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:

- a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
- b. results in permanent or significant incapacity or disability; or
- c. is life-threatening or results in death.

In the event of project-related damage or injuries, the sponsor will be liable, except for damages that are only slight and temporary; and for which the extent of the damage is no greater than would be expected in the current state of scientific knowledge (Art. 12 HRO).

## **6 FURTHER ASPECTS**

### **6.1 Overall ethical considerations**

#### Aim and burden for participants:

This study aims to assess the number of healthy, euvoletic participants falsely identified as hypervolemic when using currently valid sonographic cut-offs of IVC parameters. Furthermore, the accuracy of AI-guided sonographic IVC measurements compared to measurements by human operators will be assessed. The lack of studies on a) assessing normal values for sonographic IVC parameters in healthy participants and b) the performance of AI-guided sonographic IVC measurements in the literature guided our choice to perform this analysis in healthy participants. The burden for the participants is low as they will only undergo one screening visit of a maximum of 15 minutes and one study visit of up to 60 minutes, with non-invasive, radiation-free assessments.

#### Overall value of the project:

Results from this project will help improve sonographic IVC measurements in clinical practice, therefore improving hydration status assessment.

#### Incidental findings:

The US assessment will be restricted to the SC and RI view of IVC. Participants will be asked in advance how they would like to handle accidental findings (i.e. presence of hepatic lesions, suspicious lymph nodes, signs suggestive for a vein thrombosis). In case of health-relevant incidental findings, participants will be referred to a specialist, and the investigator will inform the participants general practitioner about this finding, if the participant agrees.

### **6.2 Risk-Benefit Assessment**

US assessment is a non-invasive, radiation free assessment. Therefore, there will be no risks associated with participation in this project. Project participants will not directly benefit from the project; however, the findings may contribute to improving sonographic IVC measurements in clinical practice.

### **6.3 Rationale for the inclusion of vulnerable participants**

We will include healthy volunteers to test the methods in physiological states. Testing the methods on physiological status will put the basis for their applicability on patients in clinical setting.

## **7 QUALITY CONTROL AND DATA PROTECTION**

### **7.1 Quality measures**

Project personnel will be trained in all important project-related aspects. Internal monitoring will be organized to ensure the quality of data. For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

## **7.2 Data recording and source data**

Data will be recorded by RedCAP®, an electronic Case Report Form (eCRF). Source data will be the pictures of the US assessment safely stored in the password-protected, one-drive cloud of University Hospital of Basel with restricted access to study staff members. Every access will be trackable.

## **7.3 Confidentiality and coding**

**Project data** will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the eCRFs and other project specific documents, participants are only identified by a unique participant number.

The participant identification list will be safely stored in the password-protected, one-drive cloud of University Hospital of Basel with restricted access to study members.

## **7.4 Retention and destruction of project data and biological material**

Health-related data are stored for 10 years after publication of the research project.

## **8 FUNDING / PUBLICATION / DECLARATION OF INTEREST**

The project will be financed by a grant to Dr. med. sc. Laura Potasso. Employment of further investigators is possible through a collaboration with the Division of Internal Medicine at the University Hospital of Basel. The results will be applied for publication in a peer reviewed journal. Raw data will not be published, but it will be made available in anonymized form in case of request by the reviewer or a reasonable request.

We will collect data only about biological sex, not about gender feeling, so there will be no assessment of “sex and gender” effect. However, data will be published about the sex effect, either if present or not.

The principal investigator and the co-investigators declare no conflict of interest.

## 9 REFERENCES

- i. Ordinance on Human Research with the Exception of Clinical trials (HRO)  
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  - iii. Declaration of Helsinki  
<https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects>
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## **Appendix: Study administrative structure**

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