ThrombUS+

Clinical Study A Protocol

28 May 2024

Horizon Innovation Action | Agreement No. 101137227
HORIZON-HLTH-2023-TOOL-05-05
Co-funded by the European Union

ThrombUS+ Consortium

ATHENA	Research and Innovation Center in Information, Communication and Knowledge Technologies, Greece	Eleni Kaldoudi kaldoudi@med.duth.gr
KTU	Kaunas University of Technology Lithuania	Vaidotas Marozas vaidotas.marozas@ktu.lt
VERMON	Vermon SA France	Mathieu Legros m.legros@vermon.com
FRAUNHOFER	Institute for Photonic Microsystems, Fraunhofer Germany	Marco Kircher Marco.kircher@ipms.fraunhofer.de
TELEMED	Telemed Ultrasound Medical Systems Lithuania	Dmitry Novikov d.novikov@pcultrasound.com
EchoNous	EchoNous Inc USA	Pavlos Moustakidis pavlos.moustakidis@echonous.com
MEDIS	medis Medizinische Messtechnik GmbH Germany	Susann Balling sb@medis.company
ComfTech	ComfTech SLR Italy	Lara Alessia Moltani alessia.moltani@comftech.com
TAU	Faculty of Medicine and Health Technology Tampere University, Finland	Antti Vehkaoja antti.vehkaoja@tuni.fi
LMSU	Lithuanian University of Health Science Lithuania	Andrius Macas andrius.macas@lsmu.lt
GNP	Papageorgiou General Hospital Greece	Maria Bigaki pmo@papageorgiou-hospital.gr
CSS-IRCCS	Home Relief of Suffering Hospital Italy	Elvira Grandone e.grandone@operapadrepio.it
HSV	Simon Veil Hospital France	Maxime Gautier maxime.gautier@ch-simoneveil.fr
VDE	Association for Electrical, Electronic & Information Technologies, Germany	Thorsten Prinz thorsten.prinz@vde.com
MEDEA	MEDEA SRL Italy	Pietro Dionisio p.dionisio@medeaproject.eu
PHAZE	Clinical Research and Pharma Consulting SA Greece	Spiros Anagnostopoulos spiros.anagnostopoulos@phazeclinical.com
PBY	PredictBy Research and Consulting SL Spain	Frans Folkvord ffolkvord@predictby.com
SciGen	SciGen Technologies SA Greece	Katerina Pavlidi katerina.Pavlidi@scigentech.com

Disclaimer

ThrombUS+ is an Innovation Action Project co-funded by the European Union, under HORIZON-HLTH-2023-TOOL-05-05 “Harnessing the potential of real-time data analysis and secure Point-of-Care computing for the benefit of person-centred health and care delivery”.

Contents

About ThrombUS+

Deep vein thrombosis (DVT) is the formation of a blood clot within the deep veins, most commonly those of the lower limbs, causing obstruction of blood flow. In 50% of people with DVT, the clot eventually breaks off and travels to the lung to cause pulmonary embolism. Clinical assessment of DVT is notoriously unreliable because up to 2/3 of DVT episodes are clinically silent and patients are symptom free even when pulmonary embolism has developed. Early diagnosis of DVT is crucial and despite the progress made in ultrasound imaging and plethysmography techniques, there is a need for new methods to enable continuous monitoring DVT diagnosis at the point of care.

ThrombUS+ brings together an interdisciplinary team of industrial, technology, regulatory, social science and clinical trial experts to develop a novel wearable diagnostic device for point-of-care, operator free, continuous monitoring in patients with high DVT risk. The device will combine autonomous, AI driven DVT detection based on a novel wearable ultrasound hardware, impedance plethysmography and light reflection rheography for immediate detection of blood clot formation in the lower limb. Activity and other physiological measurements will be used to provide a continuous assessment of DVT risk and support DVT prevention via serious gaming. The aggregated data will drive an intelligence decision support unit that will provide accurate monitoring and alerts. Extended reality will be used to guide experts to design exercises and patients to use the device optimally.

ThrombUS+ is intended for use by postoperative patients in the ward, during long surgical operations, cancer patients or otherwise bedridden patients at home or in care units, and women during pregnancy and postpartum. ThrombUS+ will use big data sets for AI model training collected in the project via 3 large scale clinical studies and will validate the outcome in the clinical setting via 1 early feasibility study and 1 multi-centre clinical trial.

Terms and Definitions

Term	Definition
AIA	Artificial Intelligence Act
ALCOA+	Attributable, Legible, Contemporaneous, Original, Accurate, and also Complete, Consistent, Enduring, and Available
CDC	Centres for Disease Control and Prevention
CO	Coordinator
CRO	Contract Research Organization
DALY	Disability-adjusted Life-years
DICOM	Digital Imaging and Communications in Medicine
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
EHDS	European Health Data Space
EOSC	European Open Science Cloud
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GPP	Good Pharmacoepidemiology Practice
ICD-11	International Classification of Diseases
IEC	Independent Ethics Committee
IRB	Institutional Review Board
N/A	Not Applicable
PE	Pulmonary Embolism
SOPs	Standard Operating Procedures
ISF	Investigator Site File
VTE	Venous Thromboembolism

ThrombUS_A Clinical Trial Protocol

Title:	A multi-center cohort study for conventional ultrasound image set collection to create a training data set for research purposes (image processing and analysis, AI model training).
Short title:	ThrombUS_A
Protocol version/ date:	1.0_28may2024
Sponsor:	ThrombUS + EU Horizon Project Consortium represented by Consortium Coordinator "ATHENA".
Supported by:	EU Horizon Innovation Action Grant Agreement. No: 101137227
Study design:	Non-Interventional diagnostic image data collection study.
Countries:	Finland, France, Greece, Italy, Lithuania.
Sponsor's/ consortium's coordinator:	ThromUS+ Project Coordinator Professor Eleni Kaldoudi. Professor of Medical Physics and Medical Informatics, School of Medicine, Democritus University of Thrace, Greece Adjunct Researcher, ATHENA Research and Innovation Centre in Information, Communication and Knowledge Technologies, Greece.

ThrombUS+ is an Innovation Action Project co-funded by the European Union, under HORIZON-HLTH-2023-TOOL-05-05 "Harnessing the potential of real-time data analysis and secure Point-of-Care computing for the benefit of person-centred health and care delivery".

1. Sponsors' Protocol Signature Page

Protocol Version 1.0 28 May 2024

I herewith certify study's design.

Sponsor's responsibility for the study name: **Professor Eleni Kaldoudi, ThrombUS+ Project Coordinator**

Signature:

Date: 28 May 2024

2. Principal Investigator's Protocol Signature Page

Signature of the principal investigator at the study site

Protocol Version 1.0, 28 May 2024

The signatory agrees to the content of the final clinical study protocol as presented.

Principal Investigator Name:

Site number:

Signature:

Date:

3. Abstract

Title:	A multi-center cohort study for conventional ultrasound image set collection to create a training data set for research purposes (image processing and analysis, AI model training).
Short title:	ThrombUS_A
Protocol version/ date:	1.0 31 May 2024
Sponsor:	ThrombUS+ EU Horizon Project Consortium represented by Consortium Coordinating Partner "ATHENA".
Grant Agreement Nr. (Funded by EU)	EU Horizon Innovation Action Grant Agreement. No: 101137227
Rationale and background:	Deep vein thrombosis (DVT) and its fatal complication pulmonary embolism (PE) afflict millions of people worldwide and are responsible for a large percentage of acute hospitalizations. Early diagnosis of DVT is crucial and has been proven to prevent life-threatening complications (pulmonary embolism), minimize the risk of long-term disability (post-thrombotic syndrome, recurrent DVT), improve treatment outcomes, and reduce healthcare costs. Despite the progress made in ultrasound imaging, impedance plethysmography and light reflection rheography techniques, there is a need for new methods to enable continuous monitoring DVT diagnosis in hospitalized and other high-risk patients at the point of care. ThrombUS+ EU Horizon project brings together an interdisciplinary team of industrial, technology, regulatory, social science and clinical trial experts to develop a novel wearable device for operator free, continuous monitoring in patients with high DVT risk. The device and software to be developed during this project are expected to achieve automated early DVT detection, provide a continuous assessment of DVT risk and support DVT prevention via extended reality and serious gaming. ThrombUS+ wearable is intended for use by postoperative patients in the ward, during long surgical operations, cancer patients or otherwise bedridden patients at home or in care units, and women during pregnancy and postpartum. ThrombUS+ will use big data sets for artificial intelligence (AI) model training collected in the project via 3 large scale clinical studies and will validate the outcome in the clinical setting via 1 early feasibility study and 1 multi-centre clinical trial.
Aim:	This study aims to collect and create a labelled ultrasound image data set containing ultrasound image series and video clips of patients that undergo routine ultrasound scans on lower limbs, because of suspected deep vein thrombosis. The data will be used to train an AI model within ThrombUS+ project to achieve automated detection of deep vein thrombosis on conventional ultrasound scans.
Objectives:	Primary objectives: 1. Collect and curate imaging data from ultrasound scans of patients suspected for DVT. 2. Collect accompanying metadata on patient demographics, referral note, existing known medical conditions at the time of scan, diagnosis based on the scan, operator anonymized ID, metadata on the ultrasound equipment used. 3. Anonymize the data set according to established regulations to be used for research purposes and in specific for training an artificial intelligence model to achieve automated DVT detection. Secondary objectives: 1. Describe the data set in the Argos/OpenAIRE tool and make it publicly available through the European Open Science Cloud (EOSC) portal via OpenAIRE, to be used by other researchers for image processing, analysis, and AI model training.

Study design:	This is a one visit, non-interventional, multicentre, diagnostic image data collection study. The study refers to data collection from conventional, routinely performed diagnostic ultrasound imaging.
Population:	Patients with suspected DVT referred for a DVT ultrasound scan will be consecutively selected to account for demographics, medical condition and ultrasound operator diversity in the sample; data selected will be anonymized and included in the data set. In and out-patients referred for an ultrasound scan for suspected DVT will be asked to participate (informed consent process).
Inclusion/Exclusion Criteria:	This study will include patients aged ≥18 years who are referred for a standard ultrasound scan to see if they have a DVT. For a patient to be considered eligible for participation in this study all the following inclusion criteria must be met: 1. Age ≥18 years. 2. The participant has the capacity to consent, and consent is obtained prior to any study-specific procedures. 3. The conventional diagnostic DVT algorithm indicates that an ultrasound is needed, or the patient has been referred for a scan on suspicion of DVT. A patient who meets any of the following exclusion criteria will not be permitted to participate in this study: 1. With a known condition or reason that may potentially result in interrupting or stopping the ultrasound examination before its completion. 2. Patients considered by their treating physician or the ultrasound operator as non-suitable for a standard ultrasound scan. 3. Patients who have not signed the informed consent.
Study size:	A minimum of 3000 patients.

4. Amendments and Updates

None

5. Milestones

Table 1. A summary of milestones regarding the ThrombUS+ Clinical Study A

Milestone	Planned date
IRB/IEC approval	June 2024
Start of data collection	July 2024
Midterm recruitment report	December 2024
End of data collection	June 2025
Final report of study results	July 2025

6. Rationale and Background

Deep vein thrombosis (DVT) and its fatal complication pulmonary embolism (PE) afflict millions of people worldwide and are responsible for a large percentage of acute hospitalizations. Clinical assessment of DVT is notoriously unreliable because up to 2/3 of DVT episodes are clinically silent and patients are symptom free even when PE has developed. Symptomatic DVT events, that are eventually referred for ultrasound imaging are only the tip of the DVT iceberg[1]. The subgroup of events that evolve to develop clinical indications cannot be accurately predicted and often lead to sudden death from PE regarded as "the leading cause of preventable death in hospitalized patients" and "the number one priority for improving patient safety in hospitals"[2].

Deep vein thrombosis (DVT) is the formation of a blood clot within the deep veins, most commonly those of the lower limbs, causing obstruction of blood flow. In 50% of people with DVT, the clot is at some point detached from the vein wall and travels to the lung to cause pulmonary embolism. About 25% of people experiencing pulmonary embolism (PE) will die from it, making it the 3rd leading cause of cardiovascular death worldwide after stroke and heart attack[3]. Even in patients who do not get PE, recurrent thrombosis and "post-thrombotic syndrome" are major causes of mortality and reduced quality of life[4].

Recent European population studies report DVT incidence of 70-140 cases/100,000 person-year[5], which translates to roughly 522,000 to 1.04 million cases per year in Europe. Respectively, Center for Disease

---

1 Sharif-Kashani B, Behzadnia N, Shahabi P, Sadr M. Screening for deep vein thrombosis in asymptomatic high-risk patients: a comparison between digital photoplethysmography and venous ultrasonography. Angiology. 2009 Jun-Jul;60(3):301-7. https://doi.org/10.1177/0003319708323494

2 Agency for Healthcare Research and Quality. Preventing Hospital Associate Venous Thromboembolism. A Guide for Effective Quality Improvement, Last Review Feb 2924. https://www.ahrq.gov/patient-safety/settings/hospital/vtguide/index.html

3 Waheed SM, Kudaravalli P, Hotwagner DT. Deep Vein Thrombosis. [Updated 2023 Jan 19]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507708/

4 Nicholson M, Chan N, Bhagirath V, Ginsberg J. Prevention of Venous Thromboembolism in 2020 and Beyond. J Clin Med. 2020 Aug 1;9(8):2467. https://doi.org/10.3390/jcm9082467

5 ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to the global disease burden. J Thromb Haemost. 2014 Oct;12(10):1580-90. https://doi.org/10.1111/jth.12698

Control and Prevention (CDC) reports around 900,000 DVT incidents per year in USA[6], with an estimate of 60,000-100,000 related deaths per year. Venous thromboembolism (that collectively defines DVT and/or PE) during hospitalization is the leading cause of disability-adjusted life-years (DALYs) lost in low- and middle-income countries, and the second most common cause in high-income countries, causing loss of more DALYs than nosocomial pneumonia, catheter-related bloodstream infections, and adverse drug events[7]. No identifiable provoking risk factor is reported in about 25%-40% of DVT and pulmonary embolism incidents[8]. Surgery is reported to account for 15% of the cases and especially orthopaedic surgery with postoperative rates of around 1% reported despite pharmacological thromboprophylaxis[9]; immobilization is reported to account for 15% and cancer for about 20% of cases.

Early diagnosis of DVT is crucial and has been proven to prevent life-threatening complications (pulmonary embolism), minimize the risk of long-term disability (post-thrombotic syndrome, recurrent DVT), improve treatment outcomes, and reduce healthcare costs. Despite the progress made in ultrasound imaging and plethysmography techniques, there is a need for new methods to enable continuous monitoring DVT diagnosis in hospitalized and other high-risk patients at the point of care.

ThrombUS+ EU Horizon project brings together an interdisciplinary team of industrial, technology, regulatory, social science and clinical trial experts to develop a novel wearable device for operator free, continuous monitoring in patients with high DVT risk. The devices and software to be developed during this project are expected to achieve automated early DVT detection, provide a continuous assessment of DVT risk and support DVT prevention via extended reality and serious gaming. ThrombUS+ is intended for use by postoperative patients in the ward, during long surgical operations, cancer patients or otherwise bedridden patients at home or in care units, and women during pregnancy and postpartum. ThrombUS+ will use big data sets for artificial intelligence (AI) training collected in the project via 3 large scale clinical studies and will validate the outcome in the clinical setting via 1 early feasibility study and 1 multi-centre clinical trial.

This study aims to collect and create a labelled ultrasound image data set containing ultrasound images series of patients that undergo routine ultrasound scans on lower limbs, because of suspected deep vein thrombosis.

The data will be used to train AI models within ThrombUS+ project to achieve automated detection of deep vein thrombosis on conventional ultrasound scans.

The data set will include negative scans, positive for deep vein thrombosis scans, positive for other diagnosis scans and scans of insufficient quality to aid towards diagnosis, together with imaging metadata and a set of labels for each scan. In addition, the dataset will include pseudonymized patient demographics, referral note, existing known medical conditions at the time of scan, diagnosis based on the scan, operator anonymized ID, and metadata on the ultrasound equipment and scanning protocol parameters.

The data set will be completely anonymized to be used for research purposes, in compliance with the General Data Protection Regulation (GDPR) and the European Health Data Space (EHDS) and the upcoming Artificial Intelligence Act (AIA). Furthermore, the anonymized data set will be described in the Argos/OpenAIRE tool and will be made available through the European Open Science Cloud (EOSC) portal via OpenAIRE, to be used by other researchers for image processing, analysis, and AI model training. This is a non-interventional diagnostic image data collection study.

---

6 CDC, Data and Statistics on Venous Thromboembolism, 2023, https://www.cdc.gov/ncbddd/dvt/data.html

7 ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to the global disease burden. J Thromb Haemost. 2014 Oct;12(10):1580-90. https://doi.org/10.1111/jth.12698

8 Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. J Thromb Thrombolysis. 2016 Jan;41(1):3-14. https://doi.org/10.1007/s11239-015-1311-6

9 Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. Lancet. 2016 Dec 17;388(10063):3060-3073. https://doi.org/10.1016/S0140-6736(16)30514-1

To our knowledge there is no such data sets (images and labels) publicly and readily available for research purposes, and especially for the purpose of training an AI model to achieve automated DVT detection. There are clinical studies that include ultrasound scanning of patients suspected for DVT, but none with primary or secondary objective to create the dataset planned in this study.

7. Objectives of the Study

Primary objectives:

1. Collect and curate imaging data from ultrasound scans of patients suspected for DVT.
2. Collect accompanying metadata on patient demographics, referral note, existing known medical conditions at the time of scan, diagnosis based on the scan, operator anonymized ID, metadata on the ultrasound equipment used.
3. Anonymize the data set according to established regulations to be used for research purposes and specifically for training an artificial intelligence model to achieve automated DVT detection.

Secondary objectives:

1. Describe the data set in the Argos/OpenAIRE tool and make it publicly available through the European Open Science Cloud (EOSC) portal via OpenAIRE, to be used by other researchers for image processing, analysis, and AI model training.

8. Study Design

This is a one visit, non-interventional, multi-centre, diagnostic image data collection study. The study refers to data collection from conventional, routinely performed diagnostic ultrasound imaging. Patients with suspected DVT referred for a DVT ultrasound scan will be consecutively selected to account for demographics, medical condition and ultrasound operator diversity in the sample; data selected will be anonymized and included in the data set.

In and out-patients referred for an ultrasound scan for suspected DVT will be asked to participate (informed consent process).

8.1. Study Sites

Participating sites are partners in the ThrombUS+ consortium, to be funded by the project to undertake the study (Table 2).

Table 2. Hospitals participating in the ThrombUS+ Clinical Study A.

Hospital	TAU	LSMU	GNP	CSS-IRCCS	HSV	Total
Country	Finland	Lithuania	Greece	Italy	France	5 countries
Number of beds	1,000	2,232	745	750	976	5,703
Hospitalizations per year	82,897	83,192	94,205	45,000	30,078	335,372
Out-patients per year	1,162,227	1,228,783	244,227	300,000	236,164	3,171,401
Patients scanned for suspected DVT per year	3,500	4,000	939	2,400	350	11,189

These partners were selected on the merits of research interest in the proposed smart wearable technology, their research background on respective fields and their strong collaboration links with technical partners of the consortium which ensures their willingness to participate and carry out the proposed clinical study.

During the study, additional sites may be included to enhance recruitment progress without necessitating protocol amendments. The definitive list of participating sites will be documented in the Study Report.

9. Study Population

This study will include patients aged ⩾18 years who are referred for a standard ultrasound scan to see if they have a DVT.

For a patient to be considered eligible for participation in this study all the following **inclusion criteria** must be met:

1. age ≥18 years,
2. the participant has the capacity to consent and consent is obtained prior to any study-specific procedures,
3. the conventional diagnostic DVT algorithm indicates that an ultrasound is needed, or the patient has been referred for a scan on suspicion of DVT.

A patient who meets any of the following **exclusion criteria** will not be permitted to participate in this study:

1. patients with a known condition or reason that may potentially result in interrupting or stopping the ultrasound examination before its completion,
2. patients considered by their treating physician or the ultrasound operator as non-suitable for a standard ultrasound scan,
3. patients who have not signed the informed consent.

10. Study Visits

The enrolment period for this study will commence once the approval of the appropriate Ethics Board has been granted and will continue till the required number of patients is reached, approximately for one year. After obtaining the written informed consent of participants, the investigators will collect data about:

- demographics (age, sex, race),
- body composition (height, weight, BMI, thigh/waist circumference, lower limb dimensions),
- medical history that may be risk factors for DVT,
- result of DVT ultrasound scan.

During the study, each participant referred for a conventional DVT ultrasound scan will undergo the scan as planned and following the routine clinical procedure. Specific guidelines outlining the required images will be provided to the radiologist in the "ThrombUS+ Clinical Study A Manual for DVT ultrasound scan". Both the radiologist and any other personnel conducting the ultrasound will be trained on the manual and the study's protocol prior to patient recruitment and scanning.

The data and metadata will be collected for the study data set (Table 3). It is expected that the patient will be involved in the informed consent recruitment phase for about 30 minutes in addition to the allocated typical time for the conventional DVT scan as initially planned.

Table 3. Flowchart

Activity	Visit
Informed consent	×
Inclusion/Exclusion criteria	×
Patient demographics (age, sex, race)	×
Body Composition (Height, Weight, BMI, Thigh/Waist circumference, lower limb dimensions).	×
Medical history (related to DVT risk factors)	×
DVT ultrasound scan	×
Result of DVT ultrasound scan	×

11. Study Continuation

Sponsor reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

- Discontinuation or alteration of the ThrombUS+ project workplan that results in the corresponding discontinuation or alteration of this study.
- Failure to meet expected enrolment goals overall or at a particular study site.
- The emergence of any effectiveness/safety information that could significantly affect the continuation of the study.
- Violation of the study protocol, disturbing the appropriate conduct of the study.

The sponsor will be responsible for informing IRBs/IECs of the early termination of the study.

12. Study Size

A minimum of 3000 scanned patients. Interim data sets can be used progressively to start training of the AI model. Data will be de-identified and processed for experts' annotation. Data will be partitioned based on stratified random sampling to ensure a similar distribution of measurements of vascular biomarkers in training and test sets.

Sampe size calculation for artificial intelligence training is rather complex and not straightforward. A recent review on AI in medical imaging presents methods to assess the effect of sample size on model performance (e.g. NxSubsampling, NxRepeated Cross-Validation, No Repetition), and there are also model based and learning curve fitting approaches to determine the sample size for AI training regarding applications in medical imaging[10]. However, many researchers simply follow the Widrow-Hoff learning rule that suggests ten data (patients) for every imaging feature that will be used in the model[11]. For ultrasound-based diagnosis and DVT and vessel recognition and diagnosis, studies have used proprietary datasets ranging from a few hundred

[10] Balki I, Amirabadi A, Levman J, et al. Sample-Size Determination Methodologies for Machine Learning in Medical Imaging Research: A Systematic Review. *Canadian Association of Radiologists Journal*. 2019;70(4):344-353. https://doi.org/10.1016/j.carj.2019.06.002

[11] Castiglioni I, Rundo L, Codari M, Di Leo G, Salvatore C, Interlenghi M, Gallivanone F, Cozzi A, D'Amico NC, Sardanelli F. AI applications to medical images: From machine learning to deep learning. Phys Med. 2021 Mar;83:9-24. https://doi.org/10.1016/j.ejmp.2021.02.006

to several thousand images[12,13,14,15]. ThrombUS+ AI models will progressively be trained during the course of the study to determine the optimal size of the training dataset.

All clinical partners are large hospitals routinely involved in various types of clinical trials. Evidence that supports their ability to recruit the required number of study participants is the current average number of screened patients for suspected DVT which is shown in the table above.

Based on recent numerical data (Table 4), the participating sites have collectively the following:

Table 4. Collective numerical data for the ThrombUS_A study.

Total number of patients referred for an ultrasound scan for suspected DVT per year	11,189
Positive DVT scans per year	2,547
Positive DVT scans as a percentage of referred and scanned patients per year	22%
Duration of the study (in months)	12
Estimated patients available for recruitment	11,000
Expected patients to recruit	3,000
Expected patients to recruit as a percentage for available for recruitment	27%
Expected positive scans in the recruited population (20%)	660

13. Data Management

Data management will be coordinated by the data managers of the Sponsor.

Image data will be collected in the DICOM format and collected via DICOM protocol. Additional metadata will comply with appropriate medical standards, e.g., medical conditions and diagnosis will be based on ICD-10/11 codes. Anonymization and security will be performed by technology and practices of the security expert ATHENA and follow all appropriate regulations: in particular, GDPR, and the ones currently under consultation: European Health Data Space and AIA.

The Technical Coordinator of the study (ATHENA) will provide on-site software for image data anonymization and a secure, on-line platform for image and accompanying data collection.

Patient-related data from medical records will be collected through the eCRF system. The use of eCRF system offers improved data quality, online discrepancy management, multicentre management, faster database lock etc. Main objectives behind eCRF development are preserving and maintaining quality and integrity of

[12] Nakayama Y, Sato M, Okamoto M, Kondo Y, Tamura M, Minagawa Y, Uchiyama M, Horii Y. Deep learning-based classification of adequate sonographic images for self-diagnosing deep vein thrombosis. PLoS One. 2023 Mar 6;18(3):e0282747. https://doi.org/10.1371/journal.pone.0282747

[13] Kainz B, Heinrich MP, Makropoulos A, Oppenheimer J, Mandegaran R, Sankar S, Deane C, Mischkewitz S, Al-Noor F, Rawdin AC, Ruttloff A, Stevenson MD, Klein-Weigel P, Curry N. Non-invasive diagnosis of deep vein thrombosis from ultrasound imaging with machine learning. NPJ Digit Med. 2021 Sep 15;4(1):137. https://doi.org/10.1038/s41746-021-00503-7

[14] Mittmann BJ, Braun M, Runck F, Schmitz B, Tran TN, Yamlahi A, Maier-Hein L, Franz AM. Deep learning-based classification of DSA image sequences of patients with acute ischemic stroke. Int J Comput Assist Radiol Surg. 2022 Sep;17(9):1633-1641. https://doi.org/10.1007/s11548-022-02654-8

[15] Du T, Xie L, Zhang H, Liu X, Wang X, Chen D, Xu Y, Sun Z, Zhou W, Song L, Guan C, Lansky AJ, Xu B. Training and validation of a deep learning architecture for the automatic analysis of coronary angiography. EuroIntervention. 2021 May 17;17(1):32-40. https://doi.org/10.4244/EIJ-D-20-00570

data. The collected data will be pseudonymized with the key file to be kept secured to each clinical site according to each site's Standard Operational Procedures (SOPs).

14. Data Analysis

The study involves data collection from routine diagnostic imaging to be used for research purposes.

The data will be de-identified and processed for experts' annotation. Anonymized imaging data will be labelled via professional labelling tools.

Data will be partitioned based on stratified random sampling to ensure a similar distribution of measurements of vascular biomarkers in training and test sets for the AI model training procedure.

FAIR principles will be applied for the preparation of the dataset to be published in EOSC as open science data set.

Statistical analysis is not applicable.

15. Limitations of the Research Methods

Limitations to the design of this study mainly involve patient selection bias, information bias, potentially missing data (including loss of data during transfer from paper to electronic sources), and selection bias related to including only patients referred to the hospital department participating in the study (and not other hospital departments potentially deploying DVT ultrasound scanning). To control and mitigate patient selection bias, the participating physicians will be requested to consecutively and non-selectively enrol all patients attending their clinic if they meet the eligibility criteria of the study. Moreover, the decision-making of each investigator to perform an ultrasound scan for suspected DVT will be based on the current medical practice and precede the consideration of the patient's eligibility for study enrolment, while a screening log of all potentially eligible patients will be kept at each site.

16. Source Documents

Source documents provide evidence of patient participation and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

Source data as well as reported data should follow the "ALCOA+ principles" to be Attributable, Legible, Contemporaneous, Original, Accurate, and be Complete, Consistent, Enduring, and Available. Changes to the data should be traceable (by audit trail).

Data reported on the eCRF must be consistent with the source data or the discrepancies must be clearly documented and justifiable.

Due to the characteristics of this study and the nature of the data collected it is possible for the eCRF to be considered source for certain types of data in some of the participating sites. In this case care must be taken by the Investigator to ensure that information important for patient management is transferred from the eCRF to the patient's medical records/case notes. Such information is vital for patient management when patients are managed outside the trail team by different medical specialties.

When the information is transferred from the eCRF to the medical records, Investigator also needs to clearly state which is the original source of the information (i.e) the CRF.

17. Monitoring

Monitoring is defined as the act of overseeing the progress of a clinical study, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, applicable Standard Operating Procedures (SOPs), and the principles of GCP.

The sponsor in collaboration with the CRO will develop a systematic, prioritized, risk-based approach to monitor this clinical study.

Each site will appoint their own Principal Investigator to oversee and coordinate the local study and confer respectively with CRO and Sponsor CO.

The risks to clinical study processes & clinical study data will be evaluated at both the system level (e.g., Standard Operating Procedures (SOPs), computerized systems, personnel) and clinical study level (e.g., study design, data collection, informed consent process) against existing risk controls by considering:

1. The likelihood of errors occurring.
2. The extent to which such errors would be detectable.
3. The impact of such errors on human subject protection and reliability of study results.

The sponsor will document the rationale for the resulting monitoring strategy in applicable manuals (e.g., in the Monitoring Manual)".

18. Audit and Inspection

The investigator/institution will allow site study-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access must be provided to the eCRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must always be available for review by the monitor, auditor, and regulatory inspector. The accuracy of the data will be verified by direct comparison with the source documents described above. The sponsor/CRO will also monitor compliance with the protocol and GCP. The investigator should notify the sponsor/CRO immediately of any such inspection. Audits and inspections may occur at any time during or after completion of the study.

19. Storage Period of Records

The Investigator Site File (ISF), which includes records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion in accordance with Article 58 of the Clinical Trial Regulation, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor/CRO. No records may be transferred to another location or party without written notification to the sponsor/CRO. However, the participants' medical records at the study site shall be archived in accordance with national law with which the sponsor is responsible to familiarize itself with.

20. Data Protection

Data protection and data security measures are implemented for the collection, storage, and processing of participant data in accordance with EU regulation 2016/679 GDPR.

To ensure confidentiality of records and personal data, only pseudonymized data will be transferred to the sponsor, following state-of-the-art pseudonymization techniques to make them globally anonymous and using an artificial identifier (pseudonym) for each participant instead of the participant's name (or any other personally identifiable information). The real identity of participant is only available at the site and must not be forwarded to the sponsor/CRO. Access to the participant files and clinical data is strictly limited; personalized treatment data may be given to the participant's personal physician or to other appropriate

medical personnel responsible for the participant's welfare irrespective of this study and according to conventional practise of each site. Data generated at the site because of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC, and the regulatory authorities.

A potential data security breach will be assessed regarding the implications for the rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs/IECs, and participants will be notified as appropriate under Articles 33 and 34 of the GDPR.

Moreover, all information required to be given to data subjects in accordance with Article 13 of the GDPR shall be provided through the Informed Consent Form (ICF).

21. Completion of the Study

The Institutional Review Board (Scientific/Administrative Board, IRB) of each participating hospital centre needs to be notified about the end of the study (last patient out) or early termination of the study unless it is differently required by the national regulations that govern the conduct of such studies in case these regulations have been amended until the completion of the study.

22. Protocol Deviations

No waivers to inclusion/exclusion criteria will be granted; participants need to meet all criteria, exactly as specified, to be enrolled. Deviations that occur unintentionally or are the result of action by the participant must be documented and reported to the competent authorities, if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

23. Protection of Human Subjects

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, Guidelines for Good Pharmacoepidemiology Practice (GPP), and the relevant Standard Operating Procedures (SOPs). Standard medical care remains the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and of any serious breaches of the protocol.

24. Study Approval, Patient Information, and Informed Consent

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB/IEC according to national and international regulations. The same applies to the implementation of changes introduced by amendments.

Prior to patient participation in the study, written informed consent must be obtained from each patient per GPP and according to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent, and any additional patient information form retained by the Investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient. Re-consenting may become necessary when new relevant information becomes available that could influence the decision for participating in the study and should be conducted according to the sponsor's/CRO's instructions and timelines. The consent and re-consenting process should be properly documented in the source documentation.

25. Safety

Not applicable for this study.

26. Publication Policy

To maintain the scientific integrity of the study, data will not be released outside the consortium prior to the first publication of the analysis of the primary endpoints, without the permission of the ThrombUS+ Consortium. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the objectives of this study until the first publication of the analysis of the primary endpoints.