Imperial College London

Research Governance and Integrity Team

Imperial College Healthcare NHS Trust

Template Protocol for non-CTIMPs

ML in medical US

Benefit of Machine learning to diagnose Deep vein Thrombosis compared to gold standard Ultrasound

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MAIN SPONSOR: Imperial College London
FUNDERS: No funding required
STUDY COORDINATION CENTRE: Vascular Lab, D4 Hammersmith Hospital

IRAS Project ID: 313321
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Protocol authorised by:

Name & Role	Date	Signature

Study Management Group

Chief Investigator: Dr. M. Aslam

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Study Management: Miss Kerstin Saupe

Study Coordination Centre

For general queries, supply of study documentation, and collection of data, please contact:

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Clinical Queries

Clinical queries should be directed to the study coordinator, Kerstin Saupe who will direct the query to the appropriate person.

Sponsor

Imperial College London is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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Funder

No funding is required for this study.

This protocol describes the benefit of machine learning to diagnose Deep vein Thrombosis (DVT) compared to gold standard Ultrasound diagnostic and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to study coordinator, Miss Kerstin Saupe or to the chief investigator, Dr. M.Aslam.

This study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

AutoDVT	Automatic deep vein thrombosis software
DVT	Deep vein thrombosis
GP	General Practitioner
IRAS	Integrated research Application system
NHS	National Health System
PI	Principal Investigator
US	Ultrasound
USS	Ultrasound Scan
VTE	Venous Thromboembolism

KEYWORDS

AutoDVT software, non-specialist, DVT, USS, gold standard, benefit

STUDY SUMMARY

TITLE Benefit of Machine learning to diagnose Deep vein Thrombosis compared to gold standard Ultrasound

DESIGN This study aims to compare gold standard DVT diagnostic performed by a specialist sonographer to a scan by a non-specialist with a newly developed AutoDVT detection software device. Currently the process from the DVT symptom begin, to diagnosis and then treatment is all but not straight forward. It implements a laborious journey for the patient from their GP to A & E, then to a specialist sonographer. However, handheld Ultrasound devices have recently become available. The start-up company ThinkSono developed a software, which is hoped to divide between thrombosis and no thrombosis. In this single blinded pilot study, patients which present at St. Mary's DVT Clinic, The Bays will be scanned by the specialist with the gold standard Duplex Sonography and after this by a non-specialist with the machine learning supported device. The accuracy of the device will be compared to the gold standard. This would mean that in future DVT could be diagnosed at point of care by a non-specialist such as a community nurse or nursing home nurse, where patients are multi morbid and limited in their mobility. The technology could reduce emergency department presentations and free up specialist sonographer to focus on other clinical tasks. These improvements could reduce the financial burden of DVT diagnostic services for the NHS.

AIMS "AutoDVT" is a software system designed to assist non-specialist operators, such as nurses, general practitioners (GP) and other allied health professionals in the diagnosis of DVT. The software utilises a "machine learning" algorithm to assist non-specialists in the diagnosis of DVT as described below. Venous thrombosis commonly occurs in the deep leg veins as well as the deep veins of the pelvis, and they are divided clinically into above knee (iliac, femoral, popliteal) and below knee (calf veins) DVT. DVT is well recognised to cause globally significant morbidity and mortality both at the time of diagnosis and post diagnosis. Between 30 – 50% of patients diagnosed with DVT will go on to develop a post-thrombotic syndrome, which has a significant impact on patients' long-term quality of life. Patients with DVT are also at risk of a oft fatal pulmonary embolus (PE), with rates estimated to be 0.4% during the initial anticoagulation period and post-treatment.

According to the Charity Thrombosis UK dies every 37 seconds a person of a venous thromboembolism in developed countries (Thrombosis UK, 2019). However, positive cases only represent 12-25% of the total number of patients who present with suspected DVT. In other words, between 75-88% of suspected DVT cases, when fully investigated, are negative.
It is important to note that this does not consider time lost from work, hospitalisation, treatment costs and costs for repeat ultrasound scans. It is notoriously difficult to diagnose a DVT by clinical exam alone. The standard approach to make a diagnosis of proximal DVT currently involves an algorithm combining pre-test probability- Wells Score, D-dimer (blood) testing, and compression ultrasonography (typically a three-point compression examination). There are new handheld ultrasound (US) probes available, meaning only the US probe is required for diagnostic purposes in conjunction with a smartphone or tablet. At present, although the new handheld probes are smaller and are better suited for point of care diagnosis, they still require an experienced radiologist or sonographer to perform the three-point compression exam.

This means that these devices can only be used wherever radiographers/ radiologists are based most often in hospitals. However, due to recent advances in “machine learning”, software is now being developed for these ‘app-based’ probes that can assist non-specialist healthcare professionals to carry out the compression US exam with minimal training. The previous data-collecting study with 53 participants at Oxford University Hospital (OUH) were used to develop a highly sensitive and specific software (AutoDVT) that can be used by non-specialist healthcare professionals.
It is expected that this technology will have similar diagnostic test accuracy to standard compression US. The study outlined in this protocol will test this hypothesis.

OUTCOME MEASURES

1)To compare the accuracy of the AutoDVT software with the scan carried out by a qualified sonographer as part of standard care.

2) To compare the accuracy of the AutoDVT software in perspective of different patient groups.

POPULATION

Patients attending the DVT clinic, The Bay, at St.Mary’s NHS Trust with a suspected DVT will be initially screened by the clinical team for potential inclusion into the trial. If the patient is eligible for inclusion in this study, they will be approached to consider taking part in the study. Patients will be given sufficient time to read the participant information sheet, and to consider taking part and ask any questions they may have. If they agree, they will be asked to sign an informed consent form. Once consent has been obtained, the study coordinator, Miss Kerstin Saupe will perform the three-point compression ultrasound scan (USS) with the AutoDVT Software on the participant. At the end of the scan, the AutoDVT software will indicate "exam complete" or "repeat exam". The AutoDVT software will store the results of the scan for analysis and review. Following the AutoDVT scan, patients will continue with the standard DVT diagnostic pathway, including a standard compression ultrasound scan.

ELIGIBILITY

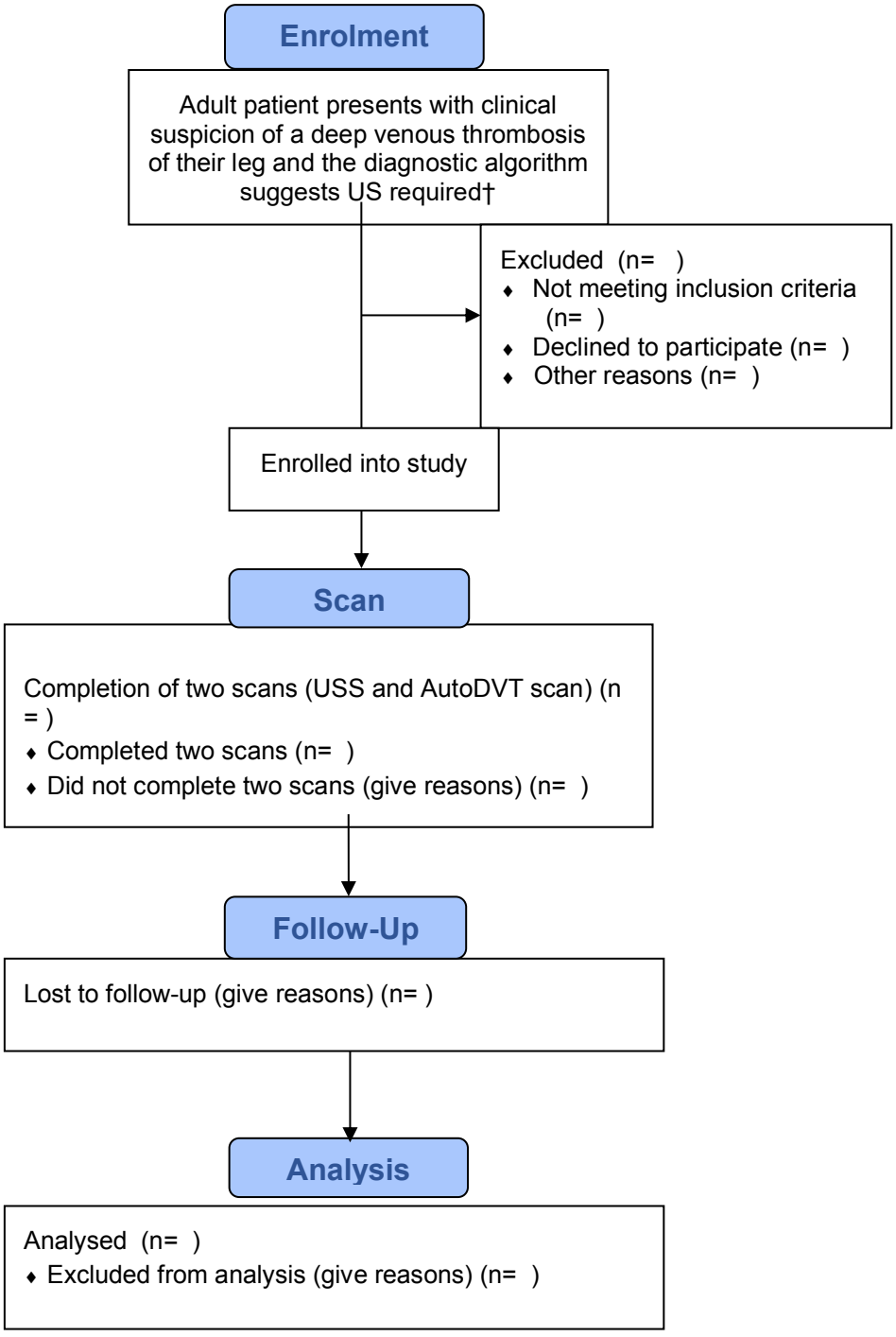
Patients are eligible for this trial if:
1. The participant has capacity to consent and consent is obtained
2. The participant is an adult (18 or older in the UK)
3. The participant has symptoms suggestive of a deep venous thrombosis
4. The diagnostic DVT algorithm indicates that an ultrasound is needed

A patient will not be eligible for this study if they fulfil one or more of the following criteria:
1. Patient is under the age of 18.
2. No data of D-dimer result
3. The participant is found to have a distal DVT during the US scan (retrospective exclusion)
4. The participant did not sign the consent form

DURATION

5 months

REFERENCE DIAGRAM



1. INTRODUCTION

1.1. BACKGROUND

Previous Study:
The AutoDVT software has been piloted at OUH in the UK for image and data collecting to feed the software. Since then, its sensitivity and specificity for DVT detection has been optimised.
(Ethics: 18/SC/0220, IRAS 234007). Hence, this study will compare three-point compression AutoDVT to estimate the sensitivity of the software to detect proximal DVT of the leg compared to the gold standard. Patient groups, which could profit from this new diagnostic tool will be evaluated.

Current Procedure:
Currently the process from the DVT symptom begin, to diagnosis and then treatment is all but not straight forward. It implements a laborious journey for the patient from their GP to A & E, then to a specialist sonographer. However handheld Ultrasound device how recently become available. The start-up company ThinkSono developed a software which is hoped to divide between thrombosis and no thrombosis. In this single blinded pilot study, patients which will present at St Mary's DVT Clinic will be scanned by the specialist with gold standard and after this by a non-specialist with the machine learning supported device. The accuracy of the device will be compared to the gold standard. This would mean that DVT could be diagnosed at point of care by a non-specialist such as a community nurse or nursing home nurse, where patients are multi morbid and limited in their mobility. The technology could reduce emergency department presentations and free up specialist sonographer to focus on other clinical tasks. These improvements could reduce the financial burden of DVT diagnostic services for the NHS.

Risks and benefits for participants of study
Risks:
The risks to participants are minimal with no proven risks from DVT ultrasound. Careful monitoring of adverse events will ensure that any clinical issues are identified promptly. Patients will receive an additional scan of their leg to that of routine clinical care, which may increase the length of time at the clinic. All patients will be fully informed of what the study involves prior to entry.

Benefits:
There is no direct benefit to the participants but there will be a future potential benefit as patients might have access to:

- Rapid access to a diagnostic test
- Local point of care testing, reducing the need for patients to be seen by specialists at hospitals
- Reduced need for prophylactic anticoagulation whilst waiting for a scan, thereby reducing the potential risk to patients of bleeding whilst taking an anticoagulant medication
- Reduced cost for diagnosis to NHS due to no longer requiring radiographer led services and high technology US devices and reduces the use of anticoagulation
- Higher patient satisfaction with their diagnostic clinical pathway

1.2. RATIONALE FOR CURRENT STUDY

This study will compare three-point AutoDVT to estimate the sensitivity of the software to detect proximal DVT compared to the gold standard. Patient groups, which could profit from this new diagnostic tool will be evaluated. The aim of the study is to estimate the sensitivity and specificity of the AutoDVT software and AutoDVT with an additional review by a suitably qualified clinician with more than one year of experience diagnosing DVTs (e.g., sonographer or radiologist) compared to two or three-point compression ultrasound exam.

2. STUDY OBJECTIVES

The primary objectives of this pilot study are:

1) To compare the accuracy of the AutoDVT software with the scan carried out by a qualified sonographer as part of standard care.

2) To compare the accuracy of the AutoDVT software in perspective of different patient groups.

3. STUDY DESIGN

This is a non-randomised, single-blinded, prospective cohort pilot study.
Participants attending the DVT clinic at St. Mary's NHS Trust with a suspected DVT will be initially screened by the clinical team for potential inclusion into the trial. If the patient is eligible for inclusion, they will be
approached to consider taking part in the study. Patients will be given sufficient time to read the participant information sheet, and to consider taking part and ask any questions they may have. If they agree, they will be asked to sign an informed consent form. Once consent has been obtained, Miss Kerstin Saupe will perform the three-point compression ultrasound scan (USS) with the AutoDVT software on the participants. At the end of the scan, the AutoDVT software will indicate "exam complete" or "repeat exam". The AutoDVT software will store the results of the scan for analysis and review. Following the AutoDVT scan, patients will continue with the standard DVT diagnostic pathway, including a standard compression ultrasound scan.

Duration: 5 months
Number and type of subjects: estimation of recruitment of approx. 50 participants

3.1. STUDY OUTCOME MEASURES

Primary Outcome:
Estimate the sensitivity of the AutoDVT software to detect proximal DVT compared to the gold standard.

Secondary Outcome:
The study will evaluate the accuracy and quality, practicality and user acceptance of the AutoDVT software. (Specificity of AutoDVT, positive and negative predictive values of AutoDVT, imaging failure rates (with reasons), numbers of eligible patients not enrolled (with reasons), duration of AutoDVT scans, number of repeat scans).

4. PARTICIPANT ENTRY

4.1. PRE-REGISTRATION EVALUATIONS

GP/ nurse practitioner obtains certain data before refereeing patient for DVT Scan: age, gender,
underlying malignancy, pregnancy, previous DVT (if yes: when, where). This information gets obtained when estimating the Wells Score as one of the main indicators for DVT. Furthermore, the referring GP would take a blood test to test for elevated D-Dimer, as second indicator for DVT. If the blood test was not obtained from the GP or the result is unknown, it will get retested at the DVT clinic.

4.2. INCLUSION CRITERIA

Patients are eligible for this trial if:
1. The participant has capacity to consent, and consent is obtained
2. The participant is an adult (18 or older in the UK)
3. The participant has symptoms suggestive of a deep venous thrombosis
4. The diagnostic DVT algorithm indicates that an ultrasound is needed

4.3. EXCLUSION CRITERIA

A patient will not be eligible for this study if they fulfil one or more of the following criteria:
1. Patient is under the age of 18 years.
2. No data of D-dimer result
3. The participant is found to have a distal DVT during the US scan (retrospective exclusion)
4. Participant did not sign consent form

4.4. WITHDRAWAL CRITERIA

All patients will be fully informed of the risks/ benefits of the study. They have the right to withdraw.

5. ADVERSE EVENTS

5.1. DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward medical occurrence or effect that:

- Results in death
- Is life-threatening – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

The potential risks of the intervention are minimal. The participants will require an extra scan of their leg which will increase the diagnostic process time. The participants will be fully informed prior to entry about risks and expected study scan time. Staff doing the extra scan will be thoroughly trained to help minimise participants delay.

5.2. REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the chief investigator or the study coordinator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded. It should be specified if only some non-serious AEs will be recorded, any reporting should be consistent with the purpose of the trial end points.

5.3.2 Serious AEs

An SAE form should be completed and emailed to the study coordinator or chief investigator within 24 hours. However, hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the Imperial College Research Ethics Committee (ICREC) where in the opinion of the Chief Investigator, the event was:

- 'related', i.e., resulted from the administration of any of the research procedures; and
- 'unexpected', i.e., an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
RGIT@imperial.ac.uk

Chief investigator: Dr.M. Aslam (m.aslam@imperial.ac.uk, Vascular Lab/ D4, Hammersmith Hospital, 72 Du Cane Rd., W12 0HS
Study Coordinator: Miss Kerstin Saupe (ks1221@ioc.ac.uk, Vascular Lab./D4, Hammersmith Hospital, 72 Du Cane Rd., W12 0HS)

6. ASSESSMENT AND FOLLOW-UP

There won't be a follow up. This study does not require any continued involvement of the participants after their scan. No information of the AutoDVT scan will be given to 2nd parties such as the GP or the clinical care team.

This study will only focus on acquired images of AutoDVT software. No incidental findings will be reviewed and reported. Participants will receive a DVT diagnostic scan by specialist, who can review and report potential findings.

The AutoDVT scan will not be available after the research has finished.
The collection of data will be finished by the 04.08.2022. The submission of the dissertation will be on the 26.08.2022.

7. STATISTICS AND DATA ANALYSIS

Personal data will be kept on the hospital computer systems. Anonymised data will be entered on a secure database by study Coordinator. The database itself will be a secure, validated system with restricted access, stored on a secure NHS server.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1. ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the Research Ethics Committee (REC) of Imperial College and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2. CONSENT

(If study does not involve consent, this section is not relevant)
Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet will be offered, and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3. CONFIDENTIALITY

Pseudonymised data is data that can be linked back to a person (e.g., coded data). It is considered both personal and identifiable data. Anonymised data is data that has no code and cannot be linked back to a person (e.g., aggregated data for publication, data without a code that cannot be linked back to a person).

The chief investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Data will be pseudonymised.

No identifiable data will be transferred. Anonymised images will be shared with ThinkSono to further optimise AutoDVT software.

8.4. INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study

8.5. SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6. FUNDING There are no funding this study.

No payments are involved in this study, neither to participants, nor to principal investigator.

8.7. AUDITS

The study may be subject to audit by Imperial College London and their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the study coordinator, Miss Kerstin Saupe.

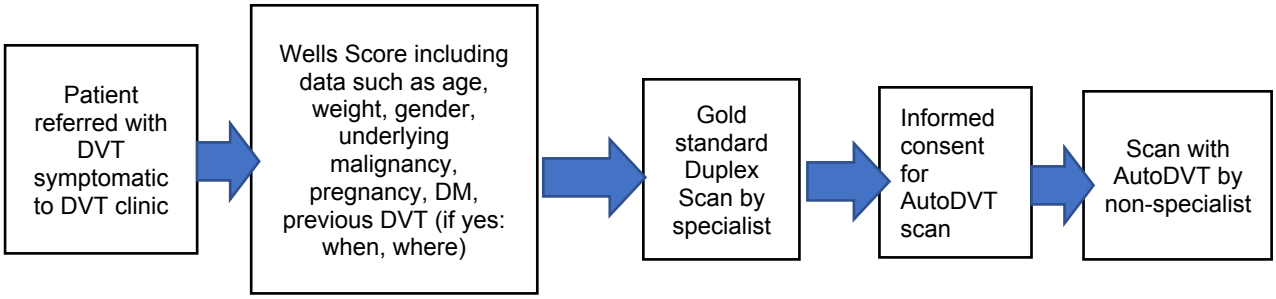
10. PUBLICATION POLICY

The research will be available to audit by regulatory authorities such as statistics at Imperial College, IRAS and supervisor at vascular Lab and the chief investigator Dr. M. Aslam at Hammersmith Hospital. Publication may take place in medical peer reviewed journals.

APPENDICES

- CE Certificate AutoDVT software
- Patient information sheet 1
- Patient information sheet 2
- Consent form
- Reference list
- Summary of investigations, treatment and assesment

Appendix 1. Summary of investigations, treatment and assessments



ThinkSono

EU Declaration of Conformity

CE

ThinkSono Limited
Flat 35
Healthcroft
LONDON
W5 3BF
United Kingdom

declares that under our sole responsibility, the product:

AutoDVT R1

is in conformity with the Essential Requirements and provisions of the following EC Directives, including all amendments and national legislation implementing these Directives:

Directive 93/42/EEC (Medical Devices)

Classification:

Class 1 - Active Medical Device – Ultrasound Imaging System Application Software (40873)

The following standards and technical specifications have been applied:

BS EN ISO 13485:2016
BS EN ISO 14971:2012
DCB0129:2018
ISO 15233-1:2016

This product carries the CE Mark, which was first affixed in June 2020.

Place	Signature	Date
London, England		**24th June 2020**

Beverley Scott
Regulatory Affairs Officer
(BCS Clinical Consulting Limited)
On behalf of ThinkSono

Reference list

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