Determining the Validity of ThinkSono Guidance for Ultrasound Image Acquisition and Remote Diagnosis (DVT GUARD)

A multi-center, prospective, double-blinded, pivotal study evaluating artificial intelligence driven automatic detection of proximal deep vein thrombosis.

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STUDY PROTOCOL

Note

This protocol is intended as an illustrative example of the protocols utilized at sites participating in the DVT GUARD study. Elements of this protocol are customized to each participating site as required. All critical elements of study protocols are conserved across sites. Protocols utilized in the study may differ from this example in content and verbiage.

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), any other applicable US government research regulations, and institutional research policies and procedures. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed the required trainings.

1. Introduction

1.1 Purpose of the Study

The purpose of this study is to confirm the safety and efficacy of the ThinkSono Guidance System as per the intended use defined as:

> *ThinkSono Guidance is a guidance, data acquisition, and communication tool that guides non-ultrasound-trained healthcare staff to collect point of care compression ultrasound data in the proximal deep venous system of the lower extremity for interpretation by qualified clinicians.*

1.2 Background

Deep vein thrombosis (DVT) is well recognized to cause 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 post-thrombotic syndrome which has a significant impact on patients' long-term quality of life.[1,2] Patients with DVT are also at risk of fatal pulmonary embolism (PE), with rates estimated to be 0.4% (95% Confidence Interval; 0.2-0.6%) during the initial anticoagulation period and 0.3/100 patient-years after treatment.[3]

With an estimated incidence of 1- 2 per 1,000 people, over to 300,000 people in the United States (USA) will be diagnosed with venous thromboembolism (VTE) per annum and two-thirds of these will be DVT.[4] However, positive cases only represent 12-25% of the total number of patients who present with suspected DVT.[5] In other words, between 75-88% of suspected DVT cases, when fully investigated, are negative. Estimates have placed the yearly cost of VTE to the USA healthcare system as up to $10 billion.[6]

It is notoriously difficult to diagnose a DVT by clinical evaluation alone. The standard approach to making a diagnosis of proximal DVT currently involves an algorithm combining pre-test probability assessment, such as using a Wells score, and compression ultrasonography. Handheld ultrasound (US) probes have recently become available and enabled 'app-based' compression ultrasonography to be performed without the need for bulky cart or laptop-based ultrasound machines. These new machines have a small form factor, meaning only the ultrasound probe is required for diagnostic purposes in conjunction with a smartphone or tablet.

Although the new handheld probes are smaller and are better suited for point of care diagnosis, they still require an experienced trained clinician or sonographer to perform the compression ultrasound exam. This means that these devices can only be used wherever sonographers/trained clinicians are located, which is most often hospital radiology departments. However, due to recent advances in "machine learning", software is now available for these 'app-based' probes to assist non-radiology healthcare professionals (e.g. nurses, non-radiologist physicians, general practitioners and other allied healthcare professionals), as well as caregivers and family members, to perform a compression ultrasound exam with minimal or no prior training.

The ThinkSono Guidance System is a guidance software expected to help non-specialist healthcare professionals produce compression ultrasound image data that meet or exceed the minimal image quality criteria for a remote diagnosis by an expert physician (e.g. radiologist).

This will be based on the American College of Emergency Physicians (ACEP) ultrasound image quality scores, where a score of 3 or more is considered adequate for diagnostic quality.

The ThinkSono Guidance System is not FDA approved; however, in the context of this research study, it meets the definition of a non-significant risk (NSR) device in accordance with 21 CFR 812.3(m) because:

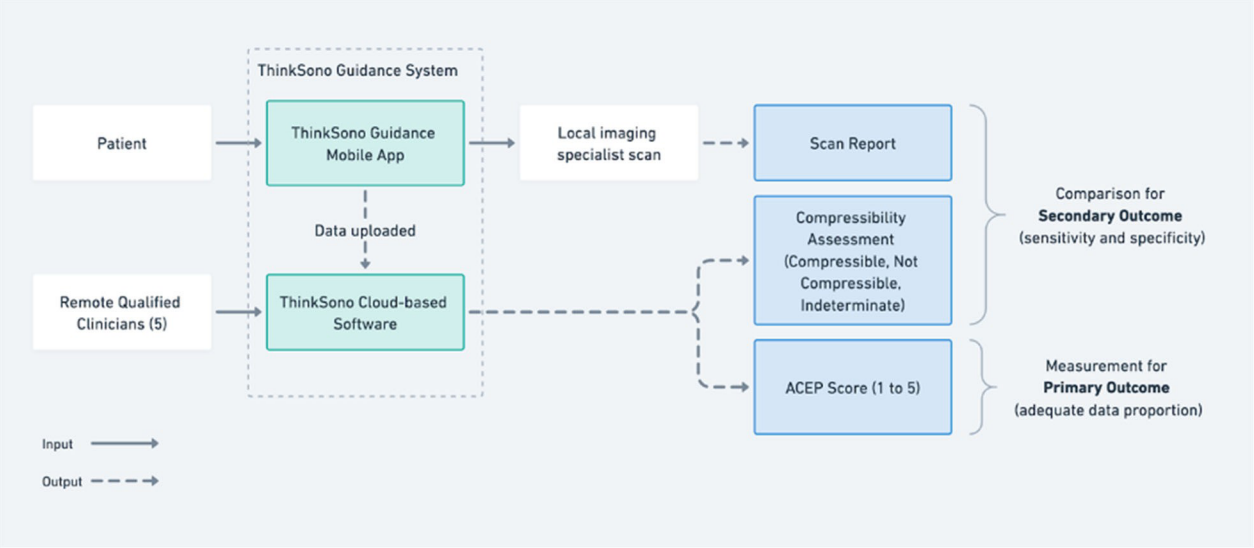
1. It is not an implant;
2. It is not purported or represented to be for a use in supporting or sustaining human life;
3. It is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health in a way that presents a potential for serious risk to the health, safety, or welfare of a subject; and
4. It does not present a potential for serious risk to the health, safety, or welfare of a subject.

2. Study Design

This is a multi-site non-randomized, double-blinded, prospective cohort pivotal study.

Double blinding will be done by the ThinkSono software itself because it will not be giving any indication of diagnosis or image quality to the operator. The comparison scan will be done by a qualified imaging specialist as per standard of care, but they will also not know the results of the ThinkSono scan. There will also be "remote qualified clinicians" reviewing the ThinkSono data who will not know the results of the local imaging studies at sites.

Below is a diagram of the blinding:



3. Subject Population

3.1 Number of Subjects, Specimens, and Records

The study population consists of patients in inpatient vascular labs, emergency departments, medical/surgical wards, outpatient offices, or intensive care units requiring a lower extremity venous duplex ultrasound scan. These patients will receive a full duplex scan by a trained technologist as per the standard of care at sites, and ThinkSono Guidance will be used as an adjunctive test.

3.2 Sample Size

The sample size will be calculated and adjusted for each site to ensure adequate power within local site constraints. This study is powered at 80% with a two-sided 95% confidence interval assuming a 75% point estimate of adequate image quality to ensure the lower bound of the CI is ≥ 60%.

3.3 Inclusion Criteria

Any patient for whom a compression ultrasound scan of the lower extremity is clinically indicated will be eligible for enrollment in this study. This means the following:

1. The participant is willing to provide written informed consent to participate in this research.
2. The participant is over the age of 18
3. The participant has signs/symptoms suggestive of a deep venous thrombosis (DVT)
4. The diagnostic DVT algorithm indicates that an ultrasound is needed

3.4 Exclusion Criteria

1. Patient consent not given or retracted during the study.
2. Patients who undergo a local imaging scan and initiation of new treatment for DVT (e.g.) lytic agents, therapeutic anticoagulation, or intervention after the local imaging scan) before a ThinkSono scan can be performed.

   To address this, the ThinkSono scan should be performed before the duplex ultrasound scan, or after the duplex ultrasound scan but before any treatment/intervention has occurred. If a patient was already on anticoagulation before the duplex ultrasound scan, then they can undergo a ThinkSono scan while on anticoagulation, as these conditions will be the same between the two scans.

3. Local imaging specialists fail to scan the patient or fail to produce a conclusive imaging diagnosis.

4. Incomplete ThinkSono Guidance scan due to logistical or other issues such as pain, lack of patient cooperation, barriers such as a cast or other physical limitations.

5. Pregnant subjects

3.5 Vulnerable Subjects

The study will not include vulnerable subjects as defined by federal regulations and institutional policies.

4. Study Methods and Procedures

4.1 Sources of Data / Materials

The primary sources of data/materials will be venous ultrasound scans of the lower extremities of patients conducted utilizing ThinkSono Guidance. Additional information may be retrieved from patients' medical records as required.

4.2 Variables of interest

The primary sources of information will be the standard of care and ThinkSono Guidance scans.

Primary Endpoints:

At least 75% of the data collected by non-specialist operators of the study team via the ThinkSono Guidance App is adequate for interpretation (i.e., with an ACEP score equal to or greater than 3) as rated by a remote qualified clinician.

For clarification, this means a lower 95% confidence interval (CI) limit of at least 60% needs to be achieved in this study to pass the primary endpoint.

The lower 95% CI for sensitivity for overall triage performance (triage sensitivity) is at least 85% relative to standard of care comparison.[8]

The lower 95% CI for specificity for overall triage performance (triage specificity) is at least 30% relative to d-dimer comparison.[8]

The lower 95% CI for specificity for prioritizing patients (prioritization specificity) is at least 93% relative to standard of care comparison.[8]

Secondary Endpoint:

Measure the negative predictive value and positive predictive value of ThinkSono Guidance for proximal lower extremity DVT.

Additional Analyses:

Estimate serial ultrasound sensitivity according to a guideline-recommended 1 week repeat scan.

Further details and endpoint definitions are discussed in the Statistical Analysis Plan.

4.4 Device

The investigational device is the ThinkSono Guidance System, consisting of the ThinkSono Guidance Mobile App ("Mobile App") which guides non-specialist operators (e.g., registered nurses) to collect compression ultrasound data, and the ThinkSono Guidance Cloud-based Software (Cloud-based Software", also referred as "Cloud-based Dashboard") used by remote or local qualified clinicians to review collected ultrasound cine loop clips and to document image quality and vein compressibility assessments.

4.5 Indications for Use

The Indications for Use are defined as:

The ThinkSono Guidance software is intended to triage suspected DVT patients.

ThinkSono Guidance is a guidance, data acquisition and communication tool. It guides non-ultrasound-trained healthcare professionals to collect point of care compression ultrasound data related to deep vein thrombosis (DVT), in the deep venous system of the lower extremity, for interpretation by qualified clinicians. To be used for patients aged 18 or older, for whom a lower extremity compression ultrasound is indicated.

ThinkSono Guidance consists of the ThinkSono Guidance Mobile App and the ThinkSono Guidance Cloud-based Dashboard.

The ThinkSono Guidance Mobile App is indicated to guide non-ultrasound-trained healthcare professionals ("operators") in the acquisition of point of care compression ultrasound cine loops of the deep venous system of the leg. The ThinkSono Guidance Mobile App interfaces with a compatible ultrasound device, analyzing its output and providing guidance to the operator for recording venous compressions.

The ThinkSono Guidance Cloud-based Dashboard is indicated to present acquired ultrasound data to qualified clinicians, for review and interpretation of compression ultrasound cine loops and communicating with the operators.

In this study, the ThinkSono Guidance System software will be used in addition to a standard ultrasound scan for a population of adult patients who present with symptoms suggestive of a DVT.

The standard clinical pre-test probability algorithm will be used for all presenting patients and the software will be used in a double-blinded manner as described above whenever a compression ultrasound is indicated. Patients will receive a full duplex scan by a trained technologist as per the standard of care, and the ThinkSono Guidance System will be used as an adjunctive data collection tool.

This ThinkSono Guidance System software will guide the user to conduct a multi-point compression ultrasound. This involves finding specific areas of the leg and compressing the veins to collect compression ultrasound data that follows the American College of Emergency Physicians (ACEP) Guidelines.

The multi-point exam involves the groin to assess the common femoral vein, points along the thigh to assess the femoral vein, and the popliteal fossa to test the popliteal vein.

Once a scan is carried out using ThinkSono Guidance System, the data will be sent to remote qualified clinicians (RQC) for assessment.

Each RQC will rate each ThinkSono Guidance System scan using the ACEP image quality 1 to 5 scale. An average rating of 3 or more will mean the image data presented meet or exceed the minimal criteria for a diagnosis (‘diagnostic quality scan’).

Subsequently each remote clinician will make their own assessment if the data shows fully compressible, not compressible, or indeterminate results.

These results will then be compared to a local imaging specialist (in a blinded manner) to measure the agreement made by the RQC agree with the local imaging specialist.

4.6 Concomitant therapy

The ThinkSono Guidance System software is being investigated as a data collection device in parallel with the current standard of care. All patients will receive the standard of care diagnostic evaluation--a full duplex compression ultrasound by a trained technologist in addition to ThinkSono Guidance System evaluation. The usage of the ThinkSono Guidance System software **will not interfere** with or preclude any standard care.

4.7 Adverse Events Definition and Reporting

The definitions to be applied to adverse events recorded in this study are given in table below. As this is a study involving ultrasound scans collecting US data from patients who may have a DVT, events of interest are those related to symptomatic venous thrombotic events, which are also study outcomes.

Term	Definition

Serious Adverse Event (SAE)	Respectively any adverse event that: · results in death · is life-threatening* · requires inpatient hospitalization or prolongation of existing hospitalization · results in persistent or significant disability or incapacity · consists of a congenital abnormality or birth defect · is otherwise considered medically significant by the investigator.
Unexpected Related Serious Adverse Event	A serious adverse event, the nature or severity of which is not consistent with the known risks of ultrasound scans
Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. Note 1 to entry: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. Note 2 to entry: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. Note 3 to entry: This includes 'comparator' if the comparator is a medical device.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Any other adverse or serious adverse event not listed above will not require recording. All SAE will be reported within 24 hours to the ThinkSono sponsor contact and to the IRB according to local reporting policies.

4.8 Recruitment, enrollment, and retention

Adult DVT patients will be identified in one of two ways:

1. A member of the site team, trained as part of the study, will review clinical lists and medical records to identify potentially eligible patients, prior to their appointments or scans. Providers will refer potential candidates to the approved research team staff to provide more study information to a patient.
2. If the participant's appointment is imminent, on arrival at the facility, potential participants will be asked if they are willing to hear more about the research study, while they wait for their diagnostic scan in the routine care clinical pathway.

Patients will be assessed for eligibility to enter the study according to the criteria set out above. If patients are eligible for entry into the study following initial screening, consent for entry into the study will be sought.

Participants will be considered eligible for enrollment in this study if they fulfil all the inclusion criteria and none of the exclusion criteria previously detailed.

Enrollment will occur as soon as possible after consent and screening for entry into the study has been obtained. Background data (patient characteristics) will be collected.

It should be noted that all the above are part of the normal care for a patient with a suspected DVT.

Participants will also be asked if they are participating in any other research studies relevant to deep vein thrombosis and if yes, the name(s) of the study/studies which will be recorded. This is significant because if the other study they are in can potentially impact the screening, diagnosis, or treatment of deep vein thrombosis then there could be bias on the results.

4.9 End of Study and follow-up

The study will be considered closed when an adequate number of patients have been recruited, the study data have been cleaned and analyzed, the database locked, and archiving arrangements are in place.

5. Data Analysis and Data Monitoring

All analysis will be conducted according to the Statistical Analysis Plan.

Annual progress reports will be submitted to the IRB with the continuing review submissions.

6. Data Storage and Confidentiality

Confidentiality will be fully preserved by the research team in accordance with regulatory and local IRB requirements. Subjects will not be identified by any of the positive identifiers in any publication.

7. Risk/Benefit Assessment

7.1 Risk and Protection Against Risks

The potential risks of the intervention are minimal. As the ultrasound probe will be applied by a relatively inexperienced operator, there is a risk that too much or too little compression will be applied. Too little compression might lead to a failed scan — however, the instructions that are provided by the ThinkSono Guidance System software will mitigate this likelihood, because if the probe does not pick up the requisite information, it will direct the operator to repeat the scan.

Too much compression or just having a second scan could lead to increased discomfort for the patient. It will be made clear to the participant that they can stop or withdraw at any time. As the study scan is not used to direct clinical care there is no risk from a failed scan.

Other data that may be reviewed are part of the standard electronic medical record system. Data will be recorded anonymously in a database using a unique identifier that does not link the subjects to their patient information. In publications of this research, subject data will remain de-identified. The principal investigator of the study will ensure patient privacy is protected. The risk of breach of confidentiality is nonzero given the use of patient-specific information; although, given the use of unique identifiers and minimal handling of PHI, we anticipate this risk to be low.

7.2 Potential Benefits to the Subjects

There are no anticipated benefits to the participants directly, but the potential benefits of successfully developing the ThinkSono Guidance System software include:

- Rapid access to an assessment by a qualified clinician
- Point of care scanning, reducing the need for patients to attend hospital radiology departments and hospital emergency departments
- Reduced need for prophylactic anticoagulation whilst waiting for a scan, thereby reducing the potential risk to patient of bleeding whilst taking an anticoagulant medication
- Reduced cost for diagnosis due to no longer requiring radiology-specific compression ultrasound services and reduced use of anticoagulation
- Higher patient satisfaction with their clinical pathway

8. Ethics / Protection of Human Subjects

IRB approval must be obtained before initiation of human subjects research activities.

8.1 Informed Consent

Patients with a suspected DVT will be discovered upon medical record review and referred to the study team. After provider receives patient's verbal permission to be contacted, the study team member will see the patient to explain the study, provide the information sheet, and give the patient ample time (up to a few hours) to consider participating in the study. Written and verbal versions of the participant information sheet and informed consent will be presented to the participants detailing: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any benefits or risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time.

The participant will consider the information and have the opportunity to question the research team to decide whether they will participate in the study.

Written informed consent will then be obtained by means of participant dated signature and dated signature of the person on the study team who presented and obtained the informed consent. The person who conducts the informed consent process and obtains informed consent must be suitably qualified and experienced and have been authorized to do so by the Principal Investigator. A copy of the signed informed consent will be given to the participant. The original signed form will be retained at the study site and a copy filed in the medical notes.

The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed. Informed consent will be obtained in line with guidance provided by the relevant institutional regulations and statutory laws.

Participants are free to withdraw their consent to participate in the study at any time, without their care being affected and with no obligation to give the reason for withdrawal. If the participant voluntarily gives a reason for withdrawal, this should be recorded. If participants withdraw, they may withdraw completely or may allow data collection to continue. Any data collected up to the point of withdrawal will be kept and used for the study.

9. References

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Statistical Analysis Plan

Methods

Categorical variables will be presented as proportions, normally distributed continuous variables will be presented as mean + standard deviation and skewed continuous variables will be presented as median [interquartile range]. Assumptions will be checked, non-parametric alternatives (such as Mann-Whitney U test), and mathematical transformations (such as Box-Cox) will be considered as needed for skewed distributions. Univariate and multivariable analysis will be performed with candidate variables and outcome measures. Statistical significance will be tested using a two-sided alpha level of 0.05 and with appropriate multiple testing correction (Bonferroni or Benjamini-Hochberg) approach when needed.

For the primary endpoint, the proportion of image adequacy for interpretation as rated by RQCs will be computed via majority voting across reviewers per patient. Additionally, the lower confidence interval according to the Clopper-Pearson method will be computed. For each individual RQC the proportion exams rates as adequate quality images (ACEP score equal to or above 3) will be reported. For the secondary endpoint, sensitivity and specificity of RQCs' compressibility assessments will be computed against the ground truth established by the local imaging technologist performing standard of care ultrasound on the same patients, as a part of the standard of care diagnostic evaluation.

The number of confirmed DVTs is defined as the number of patients for which the local imaging specialist ground truth scan reports incompressible. The number of false negatives is defined as all outcomes rated as compressible by the reviewer (which implies an adequate image quality of ACEP score above 3) which are confirmed as incompressible by the local imaging specialist scan. The number of true negatives is defined as all outcomes rated as compressible by the reviewer which are confirmed as compressible by the local imaging specialist scan. And the number of false positives is defined as all outcomes rated as incompressible by the reviewer which are not confirmed as incompressible by the local imaging specialist scan.

If a reviewer assesses a scan as indeterminate which the local imaging specialist deems incompressible, that DVT should still be considered towards the overall number of DVTs in the dataset, as the patient will be triaged correctly. Sensitivity and specificity will be reported per individual reviewer, as majority voting and via a bootstrapping analysis. The total number of images with "Indeterminate" overall compressibility assessments will be reported. Furthermore, sensitivity and specificity will be reported per individual RQC following the same inclusion and exclusion criteria. As ThinkSono Guidance is intended for a proximal point of care compression ultrasound exam, only confirmed thrombosis according to the reference ultrasound scan report that have been found in anatomical regions covered by the ACEP guidelines for proximal compression ultrasound will be included as "Incompressible" ground truth. Otherwise, the ground truth is considered "Compressible".

Endpoints

Adequate Image Quality

Definition

The proportion of adequate image quality measures the amount of ThinkSono Guidance ultrasound scans acquired by non-ultrasound-trained operators which have been rated as adequate image quality by qualified clinician reviewers.

Image quality represents the critical safety gate for all triage decisions in the ThinkSono Guidance workflow. Each ThinkSono Guidance scan is first reviewed by a qualified clinician before a triage decision is made. The clinician assigns an image-quality score using the ACEP Emergency Ultrasound Reporting and Quality Assurance Guidelines scale. [1]

A score of ≥ 3 is defined by ACEP as “structures recognizable and diagnosis supportable,” indicating that the study meets minimal criteria for diagnostic interpretation. Scans scoring < 3 are automatically labeled indeterminate and immediately referred to an ultrasound scan by an imaging specialist for confirmation in the same care episode. This structure ensures that when an image of adequate quality is presented, the subsequent decision on vein compressibility is made by a qualified clinician using interpretable data, thereby preserving patient safety by design.

Sensitivity and Specificity

Triage Sensitivity

Definition

Triage sensitivity measures the proportion of patients with DVT confirmed by duplex ultrasound who are correctly identified by the ThinkSono Guidance workflow as *incompressible* or *indeterminate* (i.e., not ruled out). It reflects the system’s ability to safely detect DVT cases during initial triage.

Triage Specificity

Definition

Triage specificity measures the proportion of patients without DVT on duplex ultrasound who are correctly ruled out by the ThinkSono Guidance workflow, i.e., classified as *compressible* by a qualified clinician reviewer. It quantifies the efficiency of the device in safely reducing unnecessary confirmatory imaging.

Prioritization Specificity

Definition

A high prioritization specificity means that there are very few false-positives that end up being prioritized unnecessarily. The measure quantifies how reliably the device's *incompressible* outcome, i.e. when the qualified clinician reviewer is convinced of the presence of a DVT, identifies patients who merit high-urgency imaging specialist assessment.

Every *incompressible* or *indeterminate* triage outcome in the ThinkSono Guidance workflow proceeds to a scan by an imaging specialist. However, distinguishing between indeterminate and incompressible referrals provides institutions with an additional prioritization tool. High prioritization specificity ensures that when a patient is referred with an *incompressible* finding, i.e. when the qualified clinician reviewer is convinced of the presences of a DVT, the local institution implementing the standard of care ultrasound pathway can trust that an *incompressible* outcome very likely represents a true-positive case.

Safety is ensured because all indeterminate and incompressible cases are confirmed by duplex scan.

This metric complements the **triage sensitivity** (safety of rule-out) and the **triage specificity** (efficiency of rule-out). Together, they show that the ThinkSono Guidance Workflow:

- captures the vast majority of true DVTs
- safely reduces unnecessary imaging for ruled-out patients
- provides a tool for scan prioritization that minimizes unnecessary priority escalation, aligned with imaging specialist compression ultrasound performance.

Statistical Assumptions

The endpoints are defined as follows:

$$sensitivity_{triage} = \frac{\#\ true\ positive\ triage}{\#\ total\ positives} = \frac{\#\ total\ positives - \#\ false\ negatives}{\#\ total\ positives}$$

$$specificity_{triage} = \frac{\#\ true\ negative\ triage}{\#\ total\ negatives}$$

$$specificity_{priority} = \frac{\#\ total\ negatives - \#\ false\ positives}{\#\ total\ negatives}$$

- # *true positive triage* is defined as the number of all confirmed DVTs as per references standard that have been correctly referred to an imaging specialist scan by the assessment of the qualified clinician.
- # *total positives* is defined as the number of all confirmed DVTs as per reference standard in the studies.
- # *false negatives* are defined as the number of scans rated as adequate image quality and all individual cine-loops of the exam have been rated as compressible by the reviewer though the reference standard scan in the studies has confirmed the presence of DVT.
- # *true negative triage* is defined as the number of scans in which DVT has been correctly ruled out by the review of the qualified clinician, i.e the all scans rated as adequate image quality and all individual cine-loops of the exam have been rated as compressible by the reviewer and the reference standard scan in the studies has confirmed no evidence of DVT.
- # *total negatives* is the number of all scans where the reference standard confirmed no evidence of DVT.
- # *false positives* is defined as the number of scans rated as adequate image quality and at least one cine-loop has been rated as incompressible and the remaining cine-loops of the exam have been rated as compressible by the reviewer and reference standard has confirmed no evidence of DVT for these scans.

The proportion of correctly avoided imaging specialist ultrasound will be reported per study site as:

$$ultrasound_{avoided} = \frac{\#\ true\ negatives}{\#\ total\ scans}$$

- # *true negatives* is defined as the number of scans rated as adequate image quality and all individual cine-loops of the exam have been rated as compressible by the reviewer and SOC has confirmed no evidence of DVT for these scans.
- # *total scans* is defined as the number of all exams in the dataset (complete and incomplete)

Negative-predictive-value and positive-predictive-value

The negative-predictive-value (NPV) and positive-predictive-value (PPV) of ThinkSono Guidance (based on reviews of qualified clinicians) will be reported. We do expect the $PPV_{priority}$ to be higher than the PPV_{triage}.

$$NPV_{triage} = \frac{\#\ true\ negatives}{\#\ compressible\ assessments}$$

$$PPV_{triage} = \frac{\#\ true\ positives}{\#\ incompressible\ assessments}$$

$$PPV_{priority} = \frac{\#\ high\ priority\ clots}{\#\ incompressible\ assessments}$$

- # *true negatives* is defined as the number of scans rated as adequate image quality and all individual cine-loops of the exam have been rated as compressible by the reviewer and SOC has confirmed no evidence of DVT for these scans.
- # *compressible assessments* is the number of all ThinkSono Guidance reviews reported as compressible and adequate quality.
- # *true positives* is defined as the number of scans rated as adequate image quality and at least one individual cine-loop of the exam have been rated as incompressible, and none of the cine-loops is rated as indeterminate by the reviewer and SOC has confirmed evidence of DVT for these scans.
- # *incompressible assessments* is the number of all ThinkSono Guidance reviews reported as incompressible and adequate quality.
- # *confirmed incompressible assessments* is the number of all scans where the reference scan confirmed a DVT and the ThinkSono Guidance reviewer assessed the exam as adequate quality and incompressible.

Meta-analytic NPV/PPV and CIs will be derived from meta-analytic sensitivity/specificity, their confidence intervals and overall study DVT prevalence.

Serial Ultrasound Sensitivity

Clinical practice guidelines for proximal compression ultrasound recommend a repeat scan within a week if the initial scan is negative. [2] This follow-up is intended to identify thrombi that were not detectable at the first visit but subsequently progress to become evident.

In the ThinkSono studies, repeat scanning is not performed as all patients will receive a full-leg duplex scan as their standard of care assessment, leaving no justification for an additional follow-up scan. This is consistent with many prior studies in the field, e.g., Goodacre et al. [3]

Brateanu et al. report that 7% of patients who test negative initially on lower extremity proximal compression ultrasound test positive on a repeat scan. [4]

We estimate the serial ultrasound sensitivity as follows:

$$SUS = \frac{Pr*(Sen+(1-Sen)*Sen)+(1-Pr)*Pd*Sen)}{Pr+(1-Pr)*Pd}$$

where

- SUS = Estimated serial ultrasound sensitivity,
- Pr = Prevalence of proximal DVT,
- Pd = Proportion of initially negative patients who develop DVT by follow-up,
- Sen = Estimated single-scan meta-analytic sensitivity of ThinkSono Guidance.

14. References

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