Assessment with **C**linical **U**ltrasound of **V**enous **EX**cess in Patients Undergoing **R**enal **R**eplacement **T**herapy (**ACUVEX-RRT**)

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CONTENTS

KEY WORDS

Ultrasound, Venous Congestion, Fluid

LIST OF ABBREVIATIONS

A2C	Apical 2 Chamber
A4C	Apical 4 Chamber
AE	Adverse Event
CAG	Confidential Advisory Group
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
ESKD	End-stage Kidney Disease
GAfREC	Governance Arrangement for NHS Research Ethics
HRA	Health Research Authority
HTA	Human Tissue Authority
HV	Hepatic Vein
ICF	Informed Consent Form
IHD	Intermittent Haemodialysis
IVC	Inferior Vena Cava
PI	Principal Investigator
PIS	Participant Information Sheet
PLAX	Parasternal Long-Axis
PSAX	Parasternal Short-Axis
PV	Portal Vein
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
RV	Renal Vein
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
TAPSE	Tricuspid Annular Place Systolic Excursion
TMF	Trial Master File
VEXUS	Venous Excess Ultrasound Assessment

STUDY SUMMARY

STUDY OVERVIEW	
Full title	Assessment of Clinical Utility of Venous Ultrasound in Patients Undergoing Renal Replacement Therapy (ACUVEX-RRT)

Objectives	Primary
	• Measure the effect on a novel ultrasound score to assess venous congestion in response to fluid removal in patients undergoing renal replacement therapy
	
	Secondary
	• Feasibility of performing VEXUS assessment
	  ○ Number of incomplete studies
	  ○ Reasons for incomplete studies
	• To quantify the changes in selected lung ultrasound parameters during fluid removal in patients undergoing intermittent haemodialysis
	• To quantify the changes in femoral vein Doppler signal during fluid removal in patients undergoing intermittent haemodialysis

Type of trial	Single site, prospective, blinded, observational study
Trial design and methods	30 participants with stable end stage kidney disease undergoing outpatient renal replacement therapy Demographics and medical details will be recorded Structured ultrasound assessment will be performed prior to, during and after intermittent haemodialysis session Reasons for not being able to perform examination or poor ultrasound windows will be recorded Fluid removal during the session will be recorded
Health condition(s) or problem(s) studied	Ultrasound assessment of venous system in patients with chronic kidney disease
Target sample size	30
Trial duration per participant:	Duration of intermittent haemodialysis session plus 30 mins pre and post
Main inclusion/exclusion criteria:	Inclusion Criteria • Age ≥18 years • Patient undergoing intermittent haemodialysis who present over their dry weight Exclusion criteria • Previous echocardiographic evidence of right heart dysfunction • Previous nephrectomy or renal transplantation • Previous liver resection or liver transplantation • Known liver cirrhosis

STUDY TIMELINES	
Study Duration/length	6 months
Expected Start Date	01/12/2021
End of Study definition and anticipated date	Last patient completed ultrasound assessment. Estimated 01/12/2022
Key Study milestones	Months 1-3: Recruitment Months 3-5: Data analysis Month 6: Outcome presentation/publication
STORAGE of SAMPLES (if applicable)	
Human tissue samples	N/A
Data collected / Storage	Pseudo anonymised data will be stored for 5 years after study completion in secure filing cabinets in the research team locked room.

1 INTRODUCTION

Fluids are the most commonly administered intravenous therapy in patients on the intensive care unit (ICU), indeed it is a fundamental aspect of critical care. They are primarily used to maintain or increase cardiac output, thereby relieving overt tissue hypoperfusion or hypoxia. There is a growing appreciation that there is significant morbidity and mortality associated with excess fluid administration (Malbrain 2018).

2 BACKGROUND AND RATIONALE

A positive fluid balance in critically ill patients is associated with poorer outcomes in a variety of conditions (Acheampong and Vincent, 2015; Vaara et al, 2012; NHLBI ARDSnet, 2006).

Whilst research mainly focussing on the administration of fluid during the resuscitation and optimisation phase continues to expand, management strategies to detect fluid overload and fluid removal are still sparse (Malbrain 2014). The physiological parameters and monitoring devices have not moved far forward from weighing patients, documenting cumulative fluid balance and clinical examination of oedema (Hoste, 2014). Hence, there is significant variation in practice amongst clinicians with regards to the physiological parameters to monitor fluid status and subsequently guide management (Silversides, 2017).

Our understanding of haemodynamic management of patients continues to evolve (de Chambrun, 2020) alongside a greater appreciation of the role of right heart dysfunction and venous congestion in organ malperfusion. The utility of ultrasound such as echocardiography and lung ultrasound to guide fluid management is also increasing (Monnet, 2006; Volpicelli, 2020).

However, such ultrasound examination and protocols have tended to focus on fluid responsiveness and cardiac systolic dysfunction rather than diastolic dysfunction, fluid excess and venous congestion per se.

Recently, Beaubien-Souligny and colleagues developed the Venous Excess Ultrasound Score (VEXUS) which involves a structured ultrasound evaluation of venous congestion (Beaubien-Souligny, 2020). The scoring system has been shown to predict the incidence of acute kidney injury in the post-cardiac surgery patient population. The same group has also published early work have shown that femoral vein Doppler analysis is an easily accessible method to assess right ventricular dysfunction and venous congestion (Denault, 2020).

Despite its sound physiological rationale, studies exploring the validity of the score outside the cardiac surgery population has been limited (Spiegal, 2020). Furthermore, these studies excluded patients with established renal dysfunction/failure.

Ultimately, the physiological importance of venous congestion in organ malperfusion as well as the clinical implications and utility of this assessment in the critical care setting requires further investigation.

Patients undergoing intermittent haemodialysis are mostly in established end-stage kidney disease (ESKD). The reason this group were selected for this study is that the population is more homogenous compared to patients presenting with acute kidney failure. Furthermore, they are more likely to be

fluid overloaded (index condition) at the outset of the intervention. Optimising fluid balance in such patients, whilst challenging, is potentially beneficial as it reduces myocardial stretch and remodelling. During the treatment period, the majority of these patients will have fluid removed through the extra-corporeal circuit. This would allow for the assessment of the ultrasonographic appearance in response to this (Karatala, 2020).

3 Objectives

3.1 Primary objectives

To measure the efficacy of a novel ultrasound score (VEXUS) in detecting changes in venous congestion during fluid removal in patients undergoing intermittent haemodialysis

3.2 Secondary Objectives

Feasibility of performing VEXUS assessment

- Number of incomplete studies
- Reasons for incomplete studies

To quantify the changes in selected lung ultrasound parameters during fluid removal in patients undergoing intermittent haemodialysis

To quantify the changes in femoral vein Doppler signal during fluid removal in patients undergoing intermittent haemodialysis

4 STUDY DESIGN

4.1 Overview

A prospective, blinded, observational study. Patients undergoing intermittent haemodialysis will be imaged using echocardiography, lung ultrasonography, femoral vein and intra-abdominal ultrasound in order to quantify VEXUS scores at three time points during the dialysis session. The change in VEXUS score with fluid removal will be the primary end point of the study

4.2 Setting

Outpatient haemodialysis unit

4.3 Population

Adult patients with end stage renal failure undergoing intermittent haemodialysis

4.3.1 Inclusion Criteria

- Age ≥18 years
- Presenting for intermittent haemodialysis
- In excess of dry weight prior to the dialysis session

4.3.2 Exclusion Criteria

- Previous echocardiographic evidence of right heart dysfunction

- Previous nephrectomy or renal transplantation
- Previous liver resection or liver transplantation
- Known liver cirrhosis
- Unable or unwilling to give informed consent

4.4 Co-enrolment

Co-enrolment is permitted for both observational and interventional studies

4.5 Screening

Potential participants will be identified when presenting for their routine hospital clinic visits or during an inpatient admission. Members of the site staff (direct care team) will pre-screen and screen for potential eligible study participants using the inclusion/exclusion criteria. Screening logs will be kept on the secure renal research study hard drive and will be encrypted for confidentiality. All eligible and ineligible patients, plus those declining to participate will be logged on the secure screening log. Patients who fulfil the inclusion criteria will have their eligibility confirmed by the research team. After confirming eligibility, eligible patients will be approached by an appropriately trained member of the clinic team to ascertain interest in entering the study. This individual will give a comprehensive verbal explanation of the study. Time for questions throughout the discussion will be given and questions adequately addressed. Potential participants will be given enough time to reflect on the patient information sheet (PIS), which will be provided during the initial discussion with the patient.

4.6 Recruitment and Consent

Initial information in the form of a verbal briefing and a written participant information sheet will be provided to all eligible patients identified at screening. Patients will signal their potential willingness to participate in the study at this meeting. After a cooling off period of at least 24 hours potential participants will be approached at the next study session to provide informed written consent.

In gaining consent from the participant, we will ensure that the participant is able to:

1. Understand the purpose and nature of the research
2. Understand what the research involves including potential benefits and burden
3. Understand that the alternative to taking part is for them to receive standard medical care and that this is not affected by participation
4. Retain information long enough to make an effective decision
5. Make a free choice

It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

Non-English speakers will be offered the opportunity to participate with a translator if available.

4.7 Data collection

Data collection in the form of the acquisition of ultrasound images as well as documentation of fluid removal and basic haemodynamic parameters will take place at 3 time points ;

1. Immediately prior to commencement of dialysis
2. At a point approximately mid-way through the dialysis procedure
3. Immediately following the end of the dialysis procedure

4.8 Ultrasound assessment

Ultrasound assessment (including transthoracic echocardiography) will be performed using an Affiniti Ultrasound System (Philips, UK). Participant dignity will be maintained at all times, and all imaging performed behind screens, curtains or in a side room on the dialysis unit.

In order to reduce bias during analysis all images will be de-identified and assigned a randomised alphanumeric code at the time of recording. Identification of video sequences and images will be possible by reference to a study database which will indicate the patient and timepoint relating to each video /image.

4.8.1 Echocardiography

Two-dimensional echocardiography will be performed on each study subject at the bedside and stored for offline analysis. Patients should be positioned in the left lateral position for optimal image-acquisition. However, this is not always possible in which case, the best-possible position will be used, and attempts made to achieve usable images. Standard parasternal long-axis (PLAX), parasternal short-axis (PSAX), apical 2-chamber (A2C) and 4-chamber (A4C) views will digitally recorded for off-line analysis.

Recorded parameters will focus on right ventricular function and volume. Recorded parameters will include:

- Right ventricular volume
- Right ventricle: left ventricle ratio
- Tricuspid annular plane systolic excursion (TAPSE)
- Right ventricular S'
- Right atrial volume
- Peak tricuspid regurgitation velocity

4.8.2 Lung

Lung ultrasound will be performed using previously described protocols (Volpicelli). The chest wall is divided into eight areas (two anterior and two lateral areas per side), and two scans obtained for each area with the patient in the supine position. The anterior zone of the chest wall is designated from the sternum to the anterior axillary line and was then divided into upper and lower halves (from the clavicle to the third intercostal spaces and from the third space to the diaphragm). The lateral zone is positioned from the anterior axillary line to the posterior axillary line and was also divided into the upper and lower.

Recorded parameters at each area will include:

- Presence/absence of pleural sliding
- Presence/absence of pleural effusions
- Presence/absence of lung consolidation
- Number of B-lines per rib space

4.8.3 Abdominal

Assessment of the inferior vena cava (IVC), portal, hepatic and splenic vein will be performed.

The IVC will be measured in its intrahepatic portion in either longitudinal or transverse orientation.

The hepatic vein flow will be imaged using a phased-array or curvilinear transducer as it drains into the IVC. The use of colour Doppler to help identify and aid optimal placement of pulsed-wave Doppler for analysis will be utilised.

Portal vein Doppler assessment will be performed using a phased-array or curvilinear transducer positioned in a right posterior-axillary coronal view in the 9th to 11th intercostal spaces. The portal vein is identified by its position with confirmation using pulsed-wave Doppler mode to differentiate portal venous flow signature (monophasic to biphasic) from the pattern seen in the hepatic artery (sharp systolic upstroke) and the hepatic veins (triphasic). Blood flow velocity in the portal vein usually ranges from 10 to 30 cm/s, so Doppler scale will be adjusted to obtain the best velocity differentiation with minimal noise (usually in the 20–40 cm/s or 0.2–0.4 m/s range).

The peak (VMax) and the minimum velocities (VMin) during the cardiac cycle will be recorded. The pulsatility fraction (PF) will be subsequently calculated as follows:
PF% = 100 (VMax -VMin/Vmax)

Intrarenal Doppler assessment will be performed using pulsed wave Doppler waveform at the corticomedullary junction. The peak (VMax) and the minimum arterial velocities (VMin) during the cardiac cycle will be recorded. The renal arterial resistive index (RI=(VMax–VMin)/VMax) will be calculated.

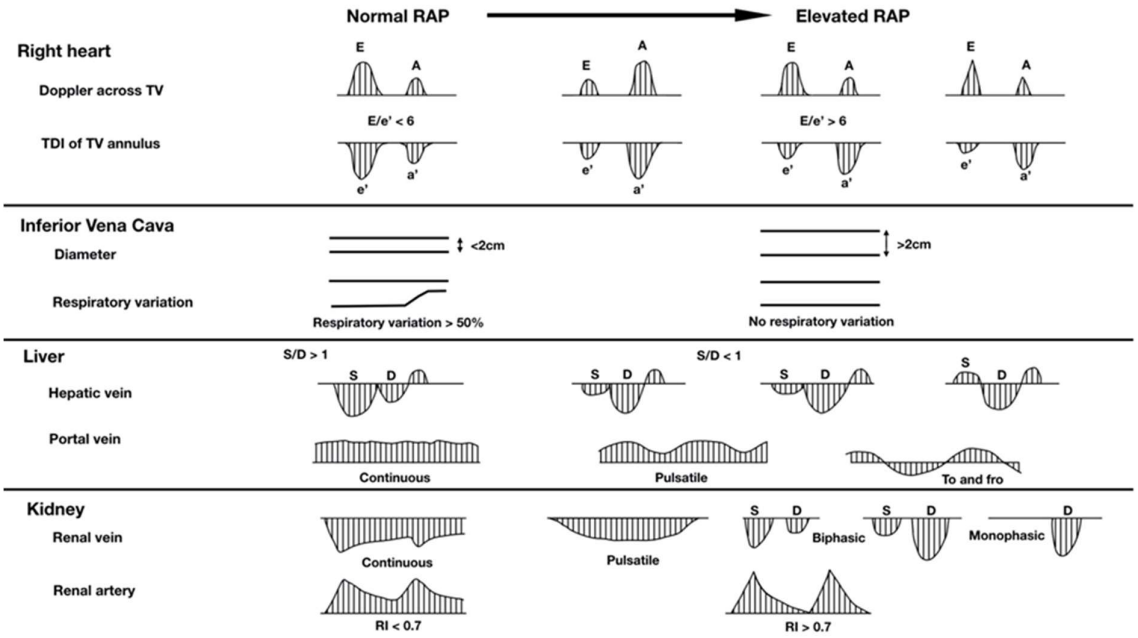
Components and grading of the Venous Excess Ultrasound Score (VEXUS) is shown in Table 1 below.

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
IVC	< 5 mm with respiratory variation	5-9 mm with respiratory variation	10-19 mm with respiratory variation	>20 mm with respiratory variation	20 mm with minimal or no respiratory variation
Hepatic vein	normal S-wave > D-wave	S-wave < D-wave with antegrade S-wave	S-wave flat or inverted or biphasic trace		
Portal Vein	< 0.3 pulsatility index	0.3-0.49 pulsatility index	0.5-1.0 pulsatility index		
Renal doppler	continuous monophasic/pulsatile flow	dis-continuous biphasic flow	dis-continuous monophasic flow (diastole only)		
VEXUS score	IVC grade < 3, HD grade 0, PV " grade 0 (RD grade 0)	IVC grade 4, but normal HV/PV/RV patterns.	IVC grade 4 with mild flow pattern	IVC grade 4 with severe flow pattern	

			abnormalities in HV/PV/RV	abnormalities in HV/PV/RV	

Table 1. Grading table for assessment of Venous congestion with point-of-care ultrasound VEXUS = venous congestion assessment with ultrasound (adapted with permission from reference 3). IVC – inferior vena cava; HV – hepatic vein; PV – portal vein; RV – renal vein

Assessment of splenic vein flow will be done with a phased array or curvilinear transducer positioned in the left posterior-axillary position in the 9th to 11th intercostal spaces to obtain a coronal view of the spleen. The position of the splenic vein in the hilum can be confirmed by pulsed-wave Doppler. The normal waveform is negative (blood directed away from the probe) and monophasic or biphasic. An image of the pulsed-wave Doppler waveform can be obtained after adjusting scale (20–40 cm/s) and gain to optimize velocity differentiation.



4.8.4 Femoral Vein

Femoral vein ultrasound will be performed with the patient should be lying supine in a horizontal position, less than 20°, as changes in intra-abdominal pressure while sitting might alter Doppler patterns of pulsatile flow. The common femoral vein (CFV) is located inferior to the ileo-inguinal ligament and medial to the common femoral artery. Care should be taken to correctly identify the CFV and not one of its tributaries, such as the saphenous vein.

Once identified, 2D and colour flow Doppler will be used to assess the presence of a normal or abnormal velocity. In a resting, spontaneously breathing subject, a normal spectral Doppler profile of CFV velocity is unidirectional (antegrade), with a mean velocity around 10 cm/s.

Time taken for all assessments will be recorded.

4.9 Outcome measures

Changes in ultrasound measures during the course of the intermittent haemodialysis session will be analysed.

4.10 Data collection

Data will be collected by local investigators. Only data as set out on the CRF will be collected for this study.

4.11 Data management

All participant data collected will be entered onto a paper CRF before being transferred to an electronic spreadsheet. The PI will oversee and be responsible for data collection, quality and recording.

Security of the electronic spreadsheet is through restricted access permission. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act.

5 ADVERSE EVENTS AND INCIDENT REPORTING

It is expected that patients may experience adverse events as part of renal replacement therapy itself and should follow normal reporting procedures. The use of ultrasound has an established safety profile and it is not expected to have a direct causal effect leading to adverse events.

6 STATISTICS AND DATA ANALYSIS

6.1 Data analysis

A random number generator (Rstudio) will be used to assign each ultrasound sequence for each study. A series of database will be used to ensure that the researcher assessing the scans are blinded to the patient and the time point that the image was acquired. All images will be assessed offline by trained operators.

6.1.1 Analysis of abdominal ultrasound

Ultrasound images of IVC, HV, PV and RV will allow for the calculation of the VEXUS score as shown in table 1.

6.1.2 Analysis of echocardiography

Ultrasound images obtained will allow for the assessment of right ventricular size and function (systolic and diastolic).

6.1.3 Analysis of lung ultrasound

Ultrasound images obtained will allow for the calculation of a lung aeration score as shown in Table 2 (ref).

Points for each lung zone	Pattern	Degree of lung aeration
0 point	Normal aeration	Horizontal A-line (no more than 2 B-line)
1 point	Moderate loss of aeration	Multiple B-lines

2 points	Severe loss of aeration	Multiple coalescent B-lines
3 points	Complete loss of aeration	Lung consolidation or pleural effusion

Table 2: Lung aeration score

6.1.4 Analysis of femoral vein ultrasound

Ultrasound images obtained will allow for the assessment of the presence of absence of abnormal venous flow.

6.2 Statistical analysis

VEXUS scores will be presented as Median (IQR) for both the pre and post time haemodialysis time points. Difference between these groups will be assessed using Mann-Whitney tests.

Continuous data will be presented as the means ± SDs, and dichotomous data will be presented as numbers and percentages. Comparisons will be conducted using the t-test and nonparametric test for continuous variables that are and are not in normal distribution, respectively. The chi-squared test or Fisher's exact test will be used for categorical variables, where appropriate. The relationships among continuous variables will be analysed by Pearson correlation analysis.

Correlation between change in cumulative fluid balance and venous pulsatility fraction will be assessed using Spearman correlation test.

A two-sided $P<0.05$ will be considered statistically significant.

7 STUDY SCHEDULE

Enrolment process: Participants will be approached in outpatient haemodialysis unit by the clinical team and provided with a patient information sheet (PIS). Participants who meet the inclusion and exclusion criteria for the study will not require any further screening prior to involvement in the study. Participant will be requested to provide written consent.

Follow up: None, unless required following an Adverse Event. In such cases, the follow up will be as determined by the Principal Investigator.

Participant withdrawal criteria and procedures: If a participant wishes to withdraw their consent their information will be destroyed.

End of the study: The end of the study will occur after the final patient is recruited and final ultrasound assessment performed.

Table 1: Schedule of Assessments

	Screening	Study visit
Visit No	**1**	**2**
Window of flexibility for timing of visits:	e.g +/- 2 days	
Informed Consent		X
Medical History		X
Vital Signs		X
Eligibility confirmation		X
Ultrasound assessment		X
Adverse Events Review		X

8 PATIENT AND PUBLIC INVOLVEMENT (PPI)

The study protocol will be reviewed by patient representatives.

9 SPONSORSHIP AND FUNDING

The study is co-sponsored by King's College London and King's College Hospital NHS Foundation Trust.

The research costs for the study have been supported by a grant from the European Society of Intensive Care Medicine and International Fluid Academy. The study funding has been reviewed by the KCH R&I Office and deemed sufficient to cover the requirements of the study.

10 DATA HANDLING AND MANAGEMENT

The study complies with the principles of the Data Protection Act, 2018. At all times researchers will act to preserve the confidentiality of patient identifiable data.

Patients will be de-identified by allocation of a unique study number and collected data will be referred to this study number rather than to personal identifiable information. Personal data, including full name, contact details, date of birth and NHS number will be required to successfully follow-up enrolled patients and will be linked to collected data on a separate electronic spreadsheet. Only members of the immediate research team will have access to personal identifiable data. Personal data will not be retained after follow up is complete and will be deleted at this time. The research team will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified.

All physical data, such as Clinical Report Forms & Consent Forms will be securely stored in a locked research office.

All electronic data will be maintained on a secure electronic database accessible only by members of the research team.

De-identified data will be retained indefinitely within the sponsors institution.

11 MATERIAL/SAMPLE STORAGE

No samples will be stored from the study.

12 PEER AND REGULATORY REVIEW

The study has been presented at the UK Critical Care Research Group meeting 2021. The feedback, comments and suggestions from this has been incorporated into the study.

The study protocol will be reviewed by patient representatives.

The study was deemed to require regulatory approval from the following bodies (list). Each approval will be obtained before the study commences.

- HRA
- REC

13 MONITORING AND AUDITING

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

The Chief Investigator will inform the sponsors should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

14 TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study.

All staff performing the ultrasound scans have completed established national critical care ultrasound accreditation and regular perform critical care ultrasound as part of their clinical duties for at least 5 years. Further training specifically in performing VEXUS was undertaken with colleagues who developed the original protocol. Prior to starting the study, all staff would have performed a minimum of 10 VEXUS scans.

Appropriate training records will be maintained in the study files.

15 INDEMNITY ARRANGEMENTS

KCH will provide NHS indemnity cover for negligent harm, as appropriate and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Trust will only extend NHS indemnity cover for negligent harm to its employees, both substantive and honorary, conducting research studies that have been approved by the R&D Department. The Trust cannot accept liability for any activity that has not been properly registered and Trust approved. Potential claims should be reported immediately to the R&I Office

16 ARCHIVING

During the study, all data will be kept securely and confidentially at the Research office. After the study has ended, paper data recording sheets, the Trial Master file and patient consent forms will be archived at a long-term storage facility for 5 years. Data spreadsheets will be encrypted, name and

contact details removed, and stored on a private research team folder with limited access. Ultrasound images shall be maintained on a secure electronic database accessible only by members of the research team.

17 PUBLICATION AND DISSEMINATION POLICY

The research team plans to disseminate the study research findings in the following settings:

- Conference presentation of study process and results at the European Society of Intensive Care Medicine annual conference
- Publication of results in a critical care, circulation or ultrasound specific recognised impact journal.

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19 APPENDICES

Appendix 1: PROTOCOL VERSIONS

Versions No	Version Date	Status
1	27/8/21	Current

Appendix 2: Case Report Form

Pt details

Echocardiographic measures

Right ventricular assessment	
TAPSE	
Right ventricular:left ventricular base ratio	
Right ventricular S’	

Lung ultrasound

	Findings				
Probe position	Lung sliding (Y/N)	B lines (>2)	Consolidation/collapse	Pleural Effusion (Y/N)	Other
Right upper anterior					
Right lower anterior					
Right upper lateral					
Right lower lateral					
Left upper anterior					
Left lower anterior					
Left upper lateral					
Left lower lateral					

Abdominal ultrasound

	Findings		
IVC			
Assessable	Yes	No	
(>2cm)	Yes	No	
Hepatic vein			
Assessable	Yes	No	

Doppler	Normal	Mildly abnormal	Severely abnormal
Portal vein			
Assessable	Yes	No	
Doppler	Normal	Mildly abnormal	Severely abnormal
Renal Vein			
Assessable	Yes	No	
Doppler	Normal	Mildly abnormal	Severely abnormal
Renal Artery			
Assessable	Yes	No	
Doppler	Normal	Mildly abnormal	Severely abnormal
Splenic vein			
Assessable	Yes	No	
Doppler	Normal	Mildly abnormal	Severely abnormal

Femoral Vein

Findings		
	Right	Left
Assessable	Yes/No	Yes/No
Pulsatile	Yes/No	Yes/No