A PROSPECTIVE, DESCRIPTIVE STUDY EVALUATING THE EVOLUTION OF COVID-19 ASSOCIATED COAGULOPATHY IN MECHANICALLY VENTILATED, CRITICALLY-ILL PATIENTS USING STANDARD LABORATORY COAGULATION STUDIES AND THROMBOELASTOGRAPHY

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the degree

Masters of Medicine (MMed) in Anaesthesiology

In the publication-ready format, with the title

"THE EVOLUTION OF COAGULOPATHY IN CRITICALLY-ILL COVID-19 PATIENTS: A THROMBOELASTOGRAPHY STUDY"

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Date of submission: 14 June 2021

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TABLE OF CONTENTS

DECLARATION

I, Colette Neethling, hereby declare that the research reported on is based on my independent work and no part of this work has been, is being, or is submitted for any other degree or other university.
I declare that this work has not been reported or published prior to registration for the Masters of Medicine in Anaesthesiology.
This dissertation has been submitted to the Turnitin module and I confirm that my supervisor has seen my report and any concerns revealed by such have been resolved with my supervisor.

Signed by candidate

Colette Neethling
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Date: 14 June 2021

I, Malcolm Miller, hereby declare that the journal we intend to submit to is accredited by the department of higher education and training (DHET). I declare that the candidate is the first author on the manuscript and has contributed the most to the paper. The candidate was involved in the analysis, presentation and interpretation of results. The candidate wrote the protocol and paper under supervision and all author contributions are declared.

Malcolm Miller
Date: 14 June 2021

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The candidate was responsible for the conception and development of the research idea and did the necessary literature review to formulate an appropriate research question. The candidate wrote the protocol under supervision and was responsible for all the data collection and capturing. The candidate was responsible for the write-up of the manuscript under the guidance of the supervisors. The supervisors, Dr Malcolm Miller and Prof Jessica Opie, were involved in the development of the research question and protocol. They provided guidance and support during the data collection period and offered invaluable input in the writing of the final manuscript. Prof Gregory Calligaro assisted with statistical analysis and drafting of digital artwork for the final manuscript.

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FORMAT

This thesis is submitted in the publication-ready format. The manuscript is currently submitted to an international critical care journal, *Critical Care Medicine*, for possible publication. This journal is ISI and DHET approved. The intention is to have the work published either internationally or locally.

ABSTRACT

Objectives: Few studies detail the evolution of Coronavirus disease 2019 (COVID-19) associated coagulopathy in critically-ill patients. We aimed to perform serial thromboelastography (TEG) and laboratory coagulation studies on critically-ill patients with COVID-19 over a 14-day period, comparing variables in 30-day survivors with those in non-survivors.

Design: Prospective.

Setting: Intensive care unit (ICU) in Cape Town, South Africa.

Subjects: Forty patients with severe COVID-19 pneumonia admitted to ICU for mechanical ventilation.

Interventions: None.

Measurements & Main Results: On admission, TEG maximum amplitude (MA) with heparinase correction was above the upper limit of the reference range in 80% of patients while 82.5% presented with absent clot lysis. The functional fibrinogen MA was also elevated above the upper limit of the reference range in 92.5% of patients. All patients had elevated D-dimer and fibrinogen levels, prolonged prothrombin times (PT), normal platelet counts and activated partial thromboplastin times (aPTT). No significant differences in laboratory coagulation studies and TEG analysis were noted between survivors and non-survivors on admission. The heparinase MA decreased significantly with time and normalised in non-survivors on day 14 (p=0.01). The functional fibrinogen MA continued to increase in non-survivors compared to survivors on day 14 however this difference was not statistically significantly (p=0.07). No patients developed disseminated intravascular coagulation (DIC) according to the International Society on Thrombosis and Haemostasis (ISTH) after 14 days, however thrombosis and bleeding were each reported in 7.5% of patients.

Conclusion: Critically-ill patients with COVID-19 admitted to ICU for mechanical ventilation were in a hypercoagulable state as demonstrated by TEG analysis. This state evolved over the 14-day observation period, emphasizing the importance of regular monitoring of coagulation parameters in these patients. A small group developed thrombotic complications despite therapeutic anticoagulation, however a similar proportion suffered a bleeding event, indicating that routine therapeutic anticoagulation should be practiced with caution.

Word Count: 300

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

SARS-CoV-2	: Severe acute respiratory syndrome coronavirus 2
TEG	: Thromboelastography
R-time	: Reaction
K-time	: Kinetic
HMA	: Heparinase maximum amplitude
FFMA	: Functional fibrinogen maximum amplitude
MA	: Maximum amplitude
α- angle	: Alpha
LY-30	: Lysis of clot at 30 minutes
COVID-19	: Coronavirus disease 2019
ICU	: Intensive care unit
PT	: Prothrombin time
aPTT	: Activated partial thromboplastin time
IQR	: Interquartile range
SD	: Standard deviation

PUBLICATION-READY FORMAT

TITLE: The Evolution of Coagulopathy in Critically ill COVID-19 Patients: A Thromboelastography Study

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Conflicts of Interest

None

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Corona virus disease 2019 (COVID-19); thromboelastography (TEG); acute respiratory distress syndrome (ARDS); hypercoagulability; COVID-19 coagulopathy; critically ill

Abstract

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coagulation studies and TEG analysis were noted between survivors and non-survivors on admission. The heparinase MA decreased significantly with time and normalised in non-survivors on day 14 (p=0.01). The functional fibrinogen MA continued to increase in non-survivors compared to survivors on day 14 however this difference was not statistically significantly (p=0.07). No patients developed disseminated intravascular coagulation (DIC) according to the International Society on Thrombosis and Haemostasis (ISTH) after 14 days, however thrombosis and bleeding were each reported in 7.5% of patients.

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Introduction

In December 2019 a pneumonia-like illness emerged in Wuhan, Hubei Province in Central China. This was found to be caused by a novel Corona virus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (1). Coronavirus disease 2019 (COVID-19) has since spread rapidly across the globe, affecting most nations worldwide. At the time of writing, global confirmed cases exceed 162 million with over 3.3 million recorded deaths (2). COVID-19 is associated with a hypercoagulable state characterised by elevated fibrinogen and D-dimer levels (3) and high rates of venous thromboembolism (VTE) in critically-ill patients despite thromboprophylaxis (4-9). The four key mechanisms regarded to be responsible for this prothrombotic state include widespread endothelial damage, activation of the coagulation system and platelets, and suppression of fibrinolysis (10).

The high rates of VTE in this group has led to much controversy regarding the management of their thrombosis risk. In September 2020, the International Society on Thrombosis and Haemostasis (ISTH) subcommittee recommended standard prophylactic dose anticoagulation for all hospitalized COVID-19 patients, escalating to intermediate dosing in the critically ill, and full-dose anticoagulation in the setting of suspected or confirmed VTE (11). Early in the pandemic, a significant relationship between an elevated D-dimer level and

non-survival was identified with utility in predicting the risk of thrombosis, disease severity and outcomes (12,13). The D-dimer, unfortunately, has several limitations due to its poor specificity (14) which has led to the use of viscoelastic tests, such as thromboelastography (TEG), in critically-ill COVID-19 patients.

TEG is a point of care test used to demonstrate overall clotting and fibrinolytic activity of whole blood in vitro. It was first used to identify bleeding abnormalities and guide blood transfusion strategies (14,15). More recently TEG has been validated to identify hypercoagulable states and evaluate risk for thromboembolic events (15,16). Reports of TEG in critically-ill COVID-19 patients admitted to the intensive care unit (ICU) have demonstrated increased clot strength and hypofibrinolysis, and thus a hypercoagulable state (6,17-19). These studies have all evaluated TEG at a single time point during ICU admission. The evolution of the COVID-19 associated coagulopathy over time using TEG has not been fully described. We thus performed serial TEG analysis on critically-ill COVID-19 patients together with laboratory coagulation studies to elucidate the evolution of the COVID-19 associated coagulopathy in an attempt to improve therapy and patient outcomes.

Materials and Methods

Study Design and Subjects

This was a single centre, prospective, descriptive study which included 40 consecutive patients admitted to ICU between July 19, and August 13, 2020 at Groote Schuur Hospital, a tertiary academic center in Cape Town, South Africa. Ethics approval was obtained from the Human Research and Ethics Committee of the Faculty of Health Sciences of the University of Cape Town (HREC 400/2020). Delayed informed consent was obtained for survivors and proxy consent for non-survivors. All patients admitted to ICU during the study period with severe COVID-19 pneumonia, as defined by the World Health Organisation, were eligible for enrolment (20). Study patients were intubated and mechanically ventilated, and had laboratory confirmed SARS-CoV-2 by reverse transcription-polymerase chain reaction test. Patients were excluded if they were younger than 18 years of age, pregnant, known to have active cancer, a bleeding disorder, or chronic anticoagulation/anti-platelet therapy.

Standard of Care

Laboratory coagulation studies for COVID-19 patients admitted to ICU included a D-dimer and fibrinogen level, platelet count, prothrombin time (PT) and activated partial thromboplastin time (aPTT). As per local institutional guidelines, all critically-ill patients received glucocorticoid therapy (6mg dexamethasone IV) once daily and full therapeutic anticoagulation for VTE prevention. Anticoagulation was achieved with enoxaparin 1mg/kg twice daily or unfractionated heparin (UFH) infusion, depending on the individual clinical scenario, and in the absence of contraindications (21). Enoxaparin was monitored using anti-factor Xa levels, targeting 0.6-1.0IU/ml. UFH was monitored targeting an activated clotting time (ACT) of 180-220sec. Screening imaging for VTE was not standard of care, but was performed at the discretion of the treating physician when clinically indicated.

Data and Sample Collection

Laboratory coagulation studies were performed on day 1 of ICU admission and again on day 14 using samples collected from an indwelling arterial line. TEG analysis was performed on days 1, 7 and 14 of ICU admission using blood from 3.2% sodium citrate Vacutainer BD® tubes, as per manufacturers recommendations. TEG analysis was performed within 30 minutes of sample collection and not specifically timed to heparin dosing. The same operator conducted the TEG analysis in all cases to prevent inter-operator variability. Patient information collected included: age, sex, body mass index (BMI),comorbidities, anticoagulation use/dosage, glucocorticoid use/dosage, date of symptom onset and ICU admission. Disease severity scores included ratio of arterial oxygen partial pressure to fractional inspired oxygen ($Pa0_2/Fi0_2$ ratio) to classify severity of acute respiratory distress syndrome (ARDS)(22), the sequential organ failure assessment (SOFA) score to quantify organ involvement (23), and the ISTH disseminated intravascular coagulation (DIC) score to determine presence of DIC (24). Outcomes measured included survival at 30 days, death, bleeding events and thrombotic complications. Bleeding events were included if they met the criteria for major bleeding according to the Control of Anticoagulation Subcommittee of the ISTH (25). Thrombotic complications included those confirmed on imaging studies from computerised tomography scan or ultrasonography, where requested by the treating physician.

Thromboelastography

TEG analysis was performed using the TEG 6 analyser (Haemonetics®, Braintree, MA).

Two TEG reagents were recorded: TEG with citrated kaolin in heparinase which neutralises the effect of heparin and TEG functional fibrinogen, which contains tissue factor and a glycoprotein IIb/IIIa platelet receptor inhibitor to isolate the contribution of fibrinogen to clot strength (26). The citrated kaolin TEG was not included in the analysis due to the use of heparin therapy by all patients. TEG parameters recorded included the R-time, K-time, α-angle, heparinase maximum amplitude (HMA), functional fibrinogen maximum amplitude (FFMA) and clot-lysis at 30 minutes (LY30). **Figure 1** illustrates a standard TEG and functional fibrinogen tracing. Hypercoagulability was defined as an HMA above the upper limit of the reference range (>68mm) (27). Patient parameter values were compared to the reference ranges provided by the TEG 6 operating manual.

Statistical analysis

A statistically significant sample size was calculated prior to commencement of the study using TEG results from critically-ill COVID-19 patients by Mortus et al (19). Statistical analysis was performed using STATA/SE®. Data for descriptive analysis was reported as mean (standard deviation [SD]), median (interquartile range [IQR]) or number (%) as appropriate. Temporal changes in coagulation parameters and disease severity scores over the 14-day observation were presented as median (IQR). Spearman's correlation coefficient (rho) was used to determine the relationship between laboratory coagulation studies and TEG parameters. P-values were calculated using the student t-test, Mann-Whitney U test, χ^2 test or Fisher's exact test as appropriate. A p-value of less than 0.05 was deemed statistically significant.

Results

Forty patients were included in the study. All patients were intubated and mechanically ventilated with median admission SOFA score of 4 (4-6) and PaO_2/FiO_2 ratio 95 (64-124). One patient required renal replacement therapy and one other extracorporeal membrane oxygenation (ECMO). The mean age was 55 years (±8) and 26 patients (65%) were male. Twenty-eight patients (70%) had hypertension, 27 (67.5%) diabetes and 34 (85%) were overweight or obese with a BMI >25kg/m^2 (27). The median time from onset of symptoms to ICU admission was 11.5 days (8-14). All patients received glucocorticoid therapy during their ICU stay. Thirty-nine patients (97.5%) received therapeutic anticoagulation, 37 (92.5%) of those received LMWH and 2 (5%) UFH due to acute renal failure and ECMO therapy respectively. One patient (2.5%) received prophylactic dose heparin, due to a perceived increased bleeding risk by the treating physician.

At 30-day follow up, 6 patients (15%) were still in ICU, one (2.5%) in the medical ward, 6 (15%) had been discharged home and 27 (67.5%) demised with a median time from ICU admission to death of 11 days (4-19). **Figure 2** details the 14-day follow up and 30-day outcomes of study patients. Clinically significant bleeding events occurred in three patients (7.5%) whilst receiving therapeutic anticoagulation. These included pulmonary haemorrhage requiring massive blood transfusion, intracranial haemorrhage leading to brain stem death and epistaxis requiring cauterization (see supplementary figures). Confirmed large vessel thrombotic complications, including pulmonary embolus, cardiac ventricular thrombus and lower limb deep venous thrombosis, occurred in three patients (7.5%) despite therapeutic anticoagulation. All patients with a bleeding or thrombotic event did not survive.

Table 1 displays characteristics, laboratory coagulation and TEG values of study patients on admission. Admission laboratory coagulation studies demonstrated a prolonged PT, elevated D-dimer and fibrinogen level, normal platelet counts and aPTT. The median DIC score on admission was 3 (2-3) with only one patient meeting the ISTH criteria for DIC (24). Admission TEG analysis confirmed a hypercoagulable state, with an HMA above the upper limit of the reference range in 32 (80%) patients and absent clot lysis in 33 (82.5%). FFMA was also above the upper limit of reference range in 37 (92.5%) patients on admission. No significant differences were noted between the survivor and non-survivor groups on admission except for BMI (p=0.02) and urea level (p=0.02). Associations between admission laboratory coagulation studies and TEG analysis were found to be weak to moderate. The HMA correlated with D-dimer level (r=0.39, p=0.01) and platelet count (r=0.54, p<0.001) while FFMA correlated with fibrinogen level (r=0.41, p=0.01).

Of the 40 patients recruited, 11 died within 7 days of ICU admission and therefore could not be followed up over the 14-day observation. **Table 2** details the differences between admission characteristics, laboratory coagulation and TEG values of these 11 patients who demised and the survivors. There were no significant differences between these two groups with the exception of sex (p=0.046), BMI (p=0.002) and PT (P=0.013).

Due to the early deaths and discharges, only 21 of the 40 patients could be evaluated for evolution in coagulopathy over the 14-day observation. **Figure 3** illustrates temporal changes in disease severity scores, laboratory coagulation and TEG values over the 14-day observation for these 21 patients. Overall 30-day survivors and non-survivors are represented as blue and red respectively. No significant differences were noted between the survivors and non-survivors for all timepoints except for aPTT and SOFA on day 14 (p=<0.01, p=0.01 respectively). **Table 3** details coagulation parameters and disease severity scores for these 21 patients at all timepoints. In survivors, disease severity scores such as SOFA (p=<0.01) and $Pa0_2/Fi0_2$ ratio (p=0.02) improved significantly on day 14 when compared to admission. In non-survivors, overall clot strength as denoted by HMA decreased significantly (p=0.01) and returned to normal reference ranges on day 14 while the aPTT prolonged (p=0.01), however always remaining within the normal reference ranges.

Discussion

Critically-ill patients with COVID-19 present with a distinct coagulopathy characterised by an overall hypercoagulable state. In this study which focused on mechanically ventilated patients, TEG analysis clearly demonstrated increased clot strength and hypofibrinolysis in the majority of patients on admission, which is consistent with other TEG studies involving critically-ill COVID-19 patients (6,17-19). This hypercoagulable state evolved over the 14-day observation with overall clot strength returning to normal reference ranges in the non-survivor group. Laboratory coagulation studies revealed markedly elevated D-dimer and fibrinogen levels that are in alignment with published literature demonstrating the prognostic value of these parameters (3,12,13). Although the PT was marginally prolonged throughout, the platelet count and aPTT always remained within the normal reference ranges over the 14-day observation period for both survivors and non-survivors.

Hyperfibrinogenaemia was noted in 36 (90%) patients on ICU admission. On day 14 the median fibrinogen levels decreased from above 5 g/L to 4.95 g/L in survivors. Although this is still elevated, it suggests a diminished inflammatory state when compared to non-survivors where levels persisted above 5 g/L. The elevated fibrinogen levels were found to positively correlate with FFMA, which was also above the upper limit of the reference range in 37 (92.5%) patients on admission. The FFMA continued to rise in non-survivors when compared to survivors, suggesting a persistently unquenched inflammatory state in those who died. In non-COVID trauma patients, fibrinogen contributes approximately 30% to overall clot strength with the remainder

contributed by platelets (29). In this group of critically-ill COVID-19 patients, fibrinogen's contribution to clot strength exceeds the 30% previously reported in non-COVID patients. These findings suggest that fibrinogen, an acute phase reactant, plays a significant role in increased clot strength in critically-ill COVID-19 patients. Hypofibrinolysis was also noted in most patients on admission to ICU. This finding is well reported in the literature and is thought to be due to the suppression of plasmin activity through increased plasminogen activator inhibitor-1 and suppressed urokinase-type plasminogen activator (10)

Normal to elevated platelet counts were present in 36 (90%) patients on admission. Three (7.5%) patients had platelet counts below the lower limit of the reference range and 1 (2.5%) had moderate thrombocytopenia ($<100 \times 10^9$/L), likely due to sepsis related to candidaemia (30). A meta-analysis of 9 studies performed by Lippi et al (31) found that a platelet count below the lower limit of the reference range was associated with a five-fold higher risk of severe COVID-19. They also noted a substantial decrease in platelet counts in non-survivors, reflecting either secondary infection or a platelet-viral interaction. We found platelet counts progressively decreased in both survivors and non-survivors over the 14-day observation, however the change and difference between the two groups were not statistically significantly. Median platelet counts also remained within the normal reference ranges illustrating that thrombocytopenia was not a prominent feature in our cohort. It is of interest however, that the HMA approaches normal reference ranges in non-survivors on day 14 despite a worsening FFMA. Since the platelet count positively correlated with HMA, the normal HMA could be the result of a lower platelet contribution to clot strength. The reason for this finding is unclear, therefore more detailed follow up of platelet function using platelet mapping would better elucidate the underlying mechanism.

Comorbidities such as hypertension (70%), diabetes (67.5%) and obesity (52%) were noted in the majority of patients. This aligns with other studies reporting these risk factors in patients with severe disease, likely due to underlying endothelial dysregulation (32). Endothelial cells, which play an integral role in regulating inflammatory, thrombotic and immune reactions, are disrupted upon invasion by SARS-CoV-2 via the ACE-2 receptor (33). This disruption leads to a severe systemic inflammatory response with an associated coagulopathy (3,10,32-34). All patients presented with severe ARDS (22) and a median admission SOFA of 4. Survivors had a significantly lower SOFA score and an improved $Pa0_2/Fi0_2$ ratio on day 14, signaling clinical

improvement when compared to non-survivors. Large vessel thrombosis was diagnosed in 7.5% of patients despite therapeutic anticoagulation. This is a lower rate of thrombosis compared to previous studies (4-9) and could be for various reasons. Firstly, local guidelines advocated therapeutic anticoagulation for all critically-ill COVID-19 patients (21). Secondly, routine screening for VTE was not standard of care due to resource constraints and infection risks, thus subclinical thromboses may have been missed. Clinically significant bleeding complications were found in the same proportion of patients and correlates with published data. In a retrospective multicenter study by Al-Samkari et al (35), involving 144 critically-ill COVID-19 patients receiving standard dose thromboprophylaxis, 7.6% of patients suffered clinically significant bleeding, an event rate similar to ours. Although DIC was rare in our setting, one patient met the ISTH criteria for DIC on admission. This was likely due to candidaemia (30) and this patient survived. Tang et al (12) initially reported that 71.4% of non-survivors developed DIC after a median time of 4 days after admission. Contrary to this, we recorded no true cases of DIC, nor could we demonstrate an evolution to DIC over the 14-day observation.

The main objective of this study was to describe the evolution of coagulopathy in critically-ill, mechanically ventilated COVID-19 patients using TEG. It was designed with a 14-day follow up to investigate the development of DIC in non-survivors as postulated by Tang et al (12). Although it was not designed to test the utility of TEG in this cohort, we did find the data produced clinically useful. TEG was able to reliably identify a hypercoagulable state and clearly demonstrated the relative contributions of fibrinogen and platelets toward overall clot strength. TEG analysis in those who bled also revealed a hypocoagulable state with an increased propensity toward bleeding, likely from excessive anticoagulation. As TEG analysis was not specifically timed to heparin dosing, the citrated kaolin TEG was often difficult to interpret and therefore omitted from the data analysis. For future studies, standardised timing of TEG analysis to heparin dosing may be useful in identifying those at risk of over anticoagulation and assist in the personalising of anticoagulation therapy. We were unable to demonstrate any significant differences in TEG parameters between survivors and non-survivors at all time points which questions the usefulness of TEG at identifying those at risk of poor outcomes. Although a sample size was calculated, this study was limited because many patients could not be followed up due to early death or discharge. Our laboratory testing of coagulation studies also had limitations since D-dimer and fibrinogen levels could only be reliably measured up to 5.25 mg/L and 5 g/L respectively. Thus, for statistical purposes, all values above the upper measurable limit were reported as 5.25 mg/L and 5 g/L. Therefore, fibrinogen and D-

dimer levels reported here probably underestimate the true results. Further studies should include a larger patient cohort, with more frequent and prolonged follow up of TEG to clearly illustrate the trends identified in this study. The TEG platelet mapping assay would also better elucidate the role of platelets in increased clot strength.

Conclusion

Our study demonstrated that patients with severe COVID-19 pneumonia admitted to ICU for mechanical ventilation were in a hypercoagulable state as evidenced by TEG analysis. This hypercoagulable state was predominantly due to increased clot strength, mainly from the contribution of fibrinogen and evolved over the 14-day observation. Although a small proportion of patients developed radiologically confirmed thrombosis despite therapeutic anticoagulation, an equal proportion developed severe bleeding complications. Therefore, caution is needed in the routine use of therapeutic anticoagulation in these patients.

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TABLES AND FIGURES

FIGURE 1: Thromboelastography tracing

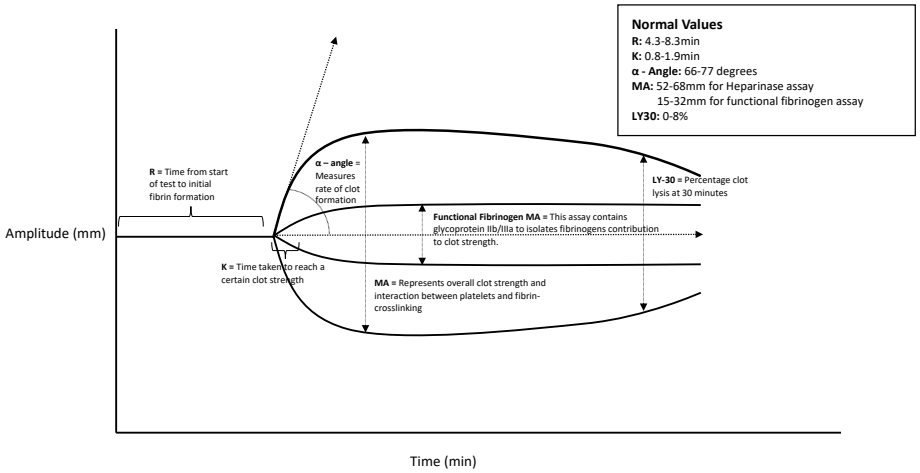


Figure 1: Diagram illustrating a heparinase and functional fibrinogen thromboelastography tracing with all measured parameters and normal reference ranges. R = reaction, K = kinetic, α = alpha, MA = maximum amplitude, LY-30 = lysis of clot at 30minutes.

FIGURE 2: Study cohort flow chart

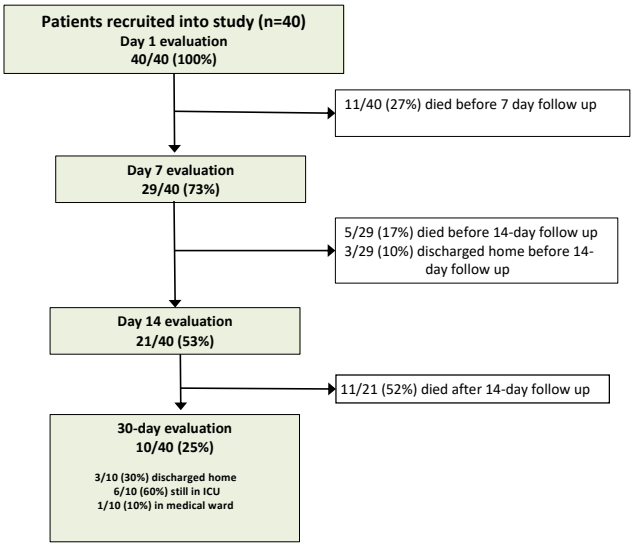


Table 1: Clinical characteristics, laboratory coagulation studies and thromboelastography parameters for study patients on admission to the intensive care unit.

Variable on admission	Normal reference ranges	Total (N=40)	30-day Survivor (N=13)	30-day Non-survivor (N=27)	P value
Age, years (SD)		55 (±8)	52 (±9)	56 (±8)	0.09
Sex					0.08
Female n (%)		14 (35)	7 (54)	7 (26)	....
Male n (%)		26 (65)	6 (46)	20 (74)	....
Comorbidities					
Hypertension n (%)		28 (70)	9 (69)	19 (70)	0.94
Diabetes n (%)		27 (68)	8 (62)	19 (70)	0.58
BMI (kg/m²)					0.02
Normal weight (18-25) n (%)		6 (15)	0 (0)	6 (22)	....
Overweight (>25 and <30) n (%)		13 (33)	2 (15)	11 (41)	....
Obese (>30) n (%)		21 (52)	11 (85)	10 (37)	....
Disease Severity Scores					
SOFA score (IQR)		4 (4-6)	4 (4-4)	4 (4-6)	0.55
$Pa0_2/Fi0_2$ ratio (IQR)	200 < - ≤ 300 Mild ARDS 100 < - ≤ 200 Moderate ARDS ≤ 100 Severe ARDS	95(64-124)	95 (60-103)	96 (66-130)	0.61
DIC score (IQR)	<5 not suggestive of DIC ≥ 5 is suggestive of DIC	3 (2-3)	3 (2-3)	3 (2-4)	0.55
Laboratory Values					
Platelet count, X 10^9/L (IQR)	171-388	354 (267-448)	352 (263-466)	356 (270-438)	0.86
Urea, mmol/L (IQR)	2.1-7.1	9.5 (7.3-11.6)	7.7 (5.8-8.5)	10.2 (9.1-13.0)	0.02
Creatinine, μmol/L (IQR)	64-104	72 (61.5-117.0)	67 (64-81)	85 (61-136)	0.32
Prothrombin time, s (IQR)[a]	11-12.5	13.7 (13.0-15.3)	13.3 (12.8-13.5)	14.2 (13.2-15.7)	1.00
Activated partial thromboplastin time, s (IQR)	25.1-36.5	30.1 (28.6-32.8)	29.9 (28.9-32.6)	30.2 (28.4-32.8)	1.00
D-Dimer, mg/L (IQR)	<0.25	1.2 (0.6-3.1)	0.9 (0.6-2.5)	1.4 (0.6-4.0)	1.00
Fibrinogen, g/L (IQR)	2-4	5 (5-5)[b]	5 (5-5)[b]	5 (5-5)[b]	0.59
TEG Heparinase					
R-time, min (IQR)	4.3-8.3	7.7 (5.8-9.8)	7.7 (7.5-8.2)	7.8 (5.8-10.7)	0.87
K-time, min (IQR)	0.8-1.9	1.1 (0.9-1.7)	1.1 (0.9-1.4)	1.2 (0.9-1.8)	0.46
α-angle, degree (IQR)	64-77	75.4 (69.6-77.9)	75.0 (71.3-78.9)	75.9 (69.6-77.9)	0.87
Max Amplitude, mm (IQR)	52-68	70.3 (68.5-72.1)	71.1 (69.5-72.6)	70.2 (68.5-71.7)	0.30
LY-30, % (IQR)	0-8	0 (0)	0 (0-0.1)	0 (0)	0.70
TEG Functional Fibrinogen					
Max Amplitude, mm (IQR)	15-32	47.0 (41.2-52.6)	48.3 (41.4-50.4)	44.9 (40.2-52.6)	0.88

Table 1. Demographics, laboratory coagulation studies and thromboelastography (TEG) analysis for all study patients on admission to the intensive care unit (ICU). Differences between admission characteristics for overall 30-day survivors (N=13) and non-survivors (N=27) is shown with corresponding p-value in parenthesis. Data are reported as mean (±SD), median (IQR), n (%). Normal reference ranges provided.

[a] PT laboratory control for the duration of the study was 11.7sec.

[b] Value is above the upper measurable limit of fibrinogen in local laboratory.

Table 2: Clinical characteristics, laboratory coagulation studies and thromboelastography parameters of study patients on admission to the intensive care unit, comparing the 30-day survivors to the patients who demised within 7 days.

Variable on admission	Normal reference ranges	30-day Survivor (N=13)	Died before 7 days (N=11)	P value
Age, years (SD)		52 (±9)	57 (±9)	0.171
Female, n (%)		7 (54)	1 (9)	0.046
Comorbidities				
Hypertension, n (%)		9 (69)	7 (64)	0.556
Diabetes, n (%)		8 (62)	8 (73)	0.444
Overweight, (BMI >25kg/m^2) n (%)		2 (15)	6 (55)	0.055
Obese, (BMI >30kg/m^2) n (%)		11 (85)	2 (18)	0.002
Disease Severity Scores				
SOFA score (IQR)		4 (4-4)	5 (4-7)	0.360
PaO_2/FiO_2 ratio (IQR)		95 (60-103)	101 (81-122)	0.450
DIC score (IQR)		3 (2-3)	3 (3-4)	0.113
Laboratory Values				
Platelet count, x 10^9/L (IQR)	171-388	352 (263-466)	358 (255-438)	0.776
Urea, mmol/L (IQR)	2.1-7.1	7.7 (5.8-8.5)	9.3 (6.1-12.8)	0.296
Creatinine, µmol/L (IQR)	64-104	67 (64-81)	65 (56-136)	0.943
Prothrombin time, s (IQR) [a]	11-12.5	13.3 (12.8-13.5)	15.0 (13.6-15.8)	0.013
Activated partial thromboplastin time, s (IQR)	25.1-36.5	29.9 (28.9-32.6)	30.2 (28.7-33.3)	0.809
D-Dimer, mg/L (IQR)	<0.25	0.9 (0.6-2.5)	3.0 (0.9-5.3)	0.096
Fibrinogen, g/L (IQR)	2-4	5 (5-5)[b]	5 (5-5)[b]	0.399
TEG Heparinase				
R time, min (IQR)	4.3-8.3	7.7 (7.5-8.2)	6.6 (5.4-9.7)	0.579
K time, min (IQR)	0.8-1.9	1.1 (0.9-1.4)	1.0 (0.8-2.0)	0.830
α-angle, degree (IQR)	64-77	75.0 (71.3-78.9)	77.3 (66.6-78.7)	0.679
Maximum amplitude, mm (IQR)	52-68	71.1 (69.5-72.6)	70.5 (69.1-71.7)	0.503
LY-30, % (IQR)	0-8	0 (0-0.1)	0 (0-0.6)	0.529
TEG functional fibrinogen				
Max Amplitude, mm (IQR)	15-32	48.3 (41.4-50.4)	42.1 (39.4-49.1)	0.353

Table 2 Admission demographics, laboratory coagulation studies and thromboelastography (TEG) analysis for the overall 30-day survivors compared to the early death group (those that died before the 7-day evaluation). Differences between the two groups are shown with p-value in parenthesis.

[a] PT laboratory control for the duration of the study was 11.7sec.

[b] Value is above the upper measurable limit of fibrinogen in local laboratory.

Figure 3: Temporal changes in laboratory coagulation studies, thromboelastography parameters and disease severity scores over the 14-day follow up

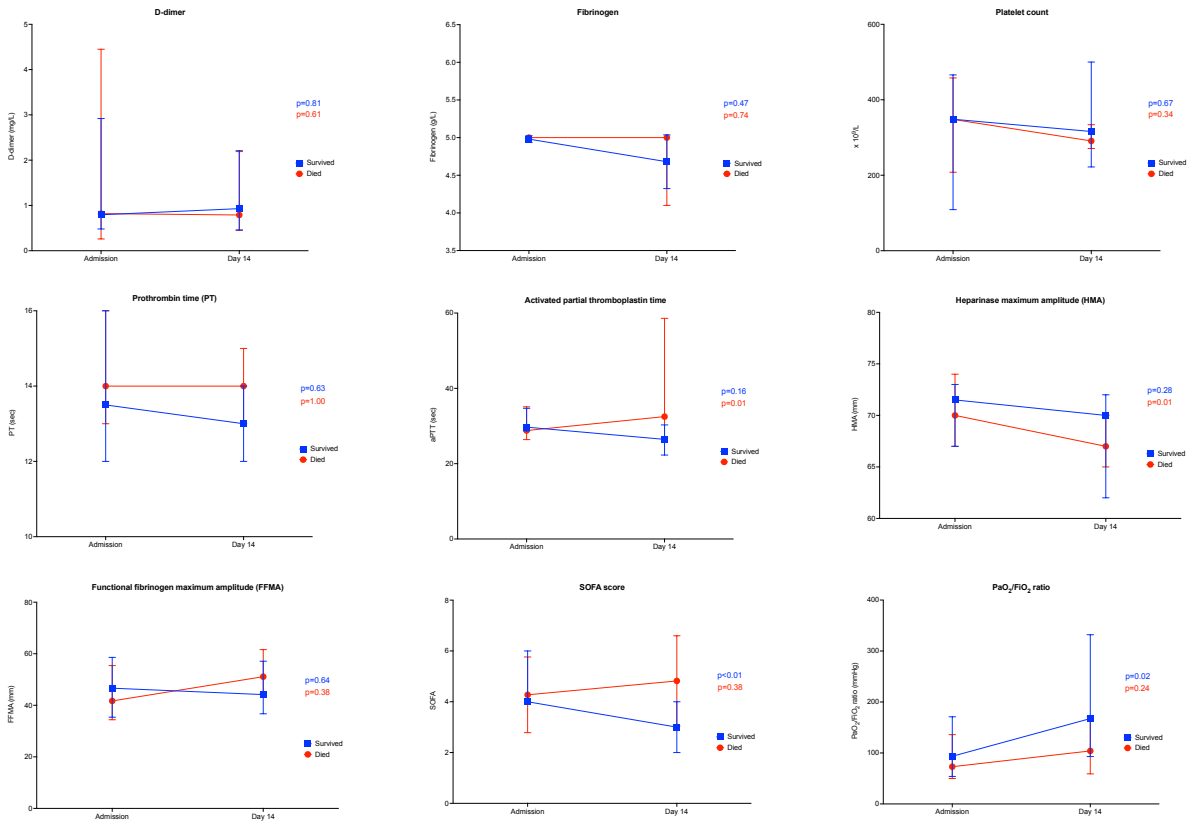


Figure 3: Temporal changes in laboratory coagulation studies, thromboelastography (TEG) parameters and disease severity scores over the 14-day observation. Differences in admission and day 14 median values for survivors (N=10) and non-survivors (N=11) are represented as blue and red respectively with p-values provided.

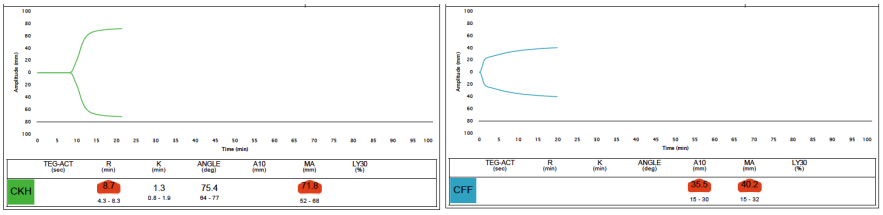
TABLE 3: Laboratory coagulation studies, thromboelastography parameters and disease severity scores over the 14-day observation

Parameter	**Normal reference ranges**	**Survivors (N=10)**			**Non-survivors (N=11)**			**P-value**		
		Day 1	*Day 7*	*Day 14*	*Day 1*	*Day 7*	*Day 14*	*Day 1*	*Day 7*	*Day 14*
D-dimer, mg/L (IQR)	<0.25	0.80 (0.5-2.46)		0.93 (0.7-1.77)	0.82 (0.44-3.1)		0.79 (0.47-2.17)	0.88		0.94
Fibrinogen, g/L (IQR)	2-4	5 (5-5)		4.95 (4.5-5)	5 (5-5)		5 (5-5)	1.00		1.00
Prothrombin time, s (IQR)	11-12.5	13.45 (12.9-13.8)		12.8 (12.5-13.9)	14 (12.8-15)		14 (13.4-14.7)	0.36		0.12
Activated partial thromboplastin time, s (IQR)	25.1-36.5	29.7 (28.9-32.6)		26.45 (22.4-28.6)	28.8 (27.2-32.7)		32.5 (27.8-54.4)	0.45		<0.01
Platelet count, $X10^9/L$ (IQR)	171-388	348.5 (223-418)	342.5 (209-444)	316 (261-429)	348 (208-458)	334 (311-432)	291 (271-334)	0.76	0.50	0.39
HMA, mm (IQR)	52-68	71.3 (68.5-72.6)	72.3 (69.5-72.8)	70.05 (66.1-72.3)	70.1 (68.2-71.8)	71.3 (69.9-72)	67.3 (65.1-69.4)	0.62	0.46	0.19
FFMA, mm (IQR)	15-32	46.65 (41.2-57.3)	51.95 (43.1-56.7)	44.15 (36.9-50.6)	41.7 (35.5-53.7)	54.4 (45.6-60.4)	51.1 (48.5-59.9)	0.70	0.40	0.07
SOFA (IQR)		4 (4-6)	4 (3-4)	3 (2-4)	4 (3-4)	4 (3-6)	5 (3-6)	0.37	0.29	0.01
$Pa0_2/Fi0_2$ ratio (IQR)		94 (60-126)	106.5 (77-142)	168 (129-215)	73 (57-130)	93 (73-120)	104 (68-146)	0.80	0.48	0.06

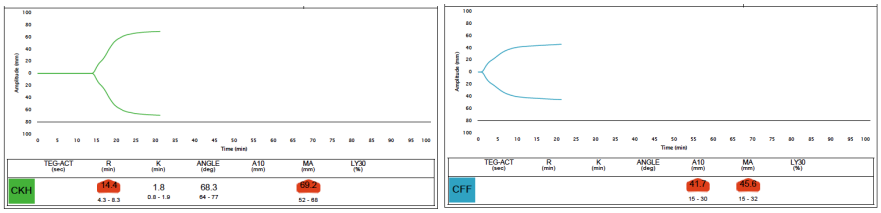
Table 3: Differences between survivors (N=10) and non-survivors (N=11) at all time points are shown with p-values in parenthesis.

SUPPLEMENTARY FIGURES

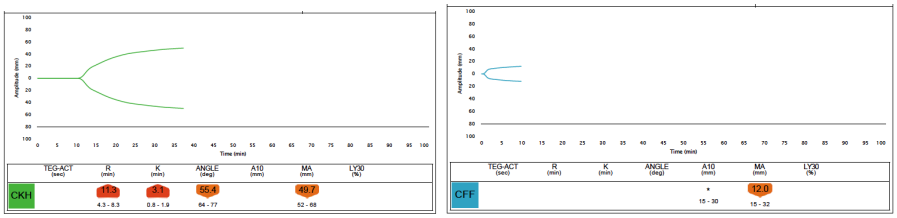
Figure 1: Detailed thromboelastography tracings for the pulmonary haemorrhage patient



Day 1 TEG tracing



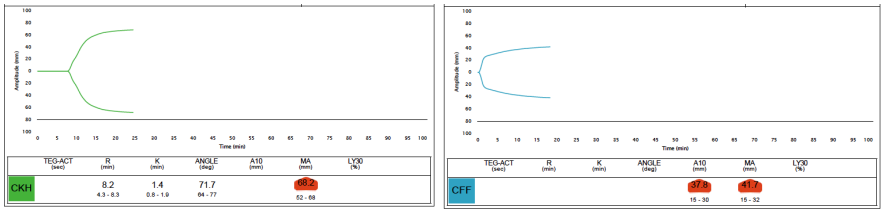
Day 7 TEG tracing



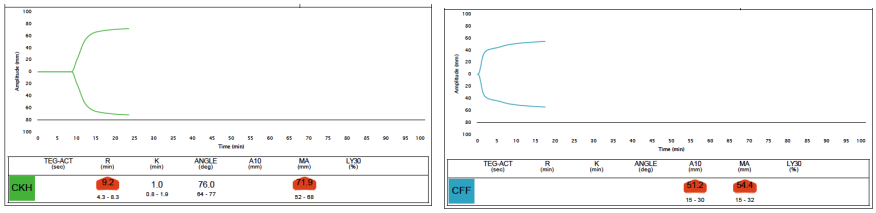
Day 14 TEG tracing

Figure 1: Detailed thromboelastography (TEG) tracings for the patient that suffered a pulmonary haemorrhage on day 10 of admission. All anticoagulation was subsequently stopped. CKH=citrated kaolin in heparinise, CFF=citrated functional fibrinogen. Normal reference ranges as provided by the TEG 6s operating manual.

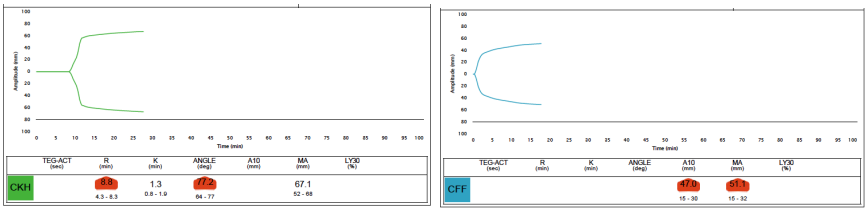
Figure 2: Detailed thromboelastography tracings for the epistaxis patient



Day 1 TEG tracing



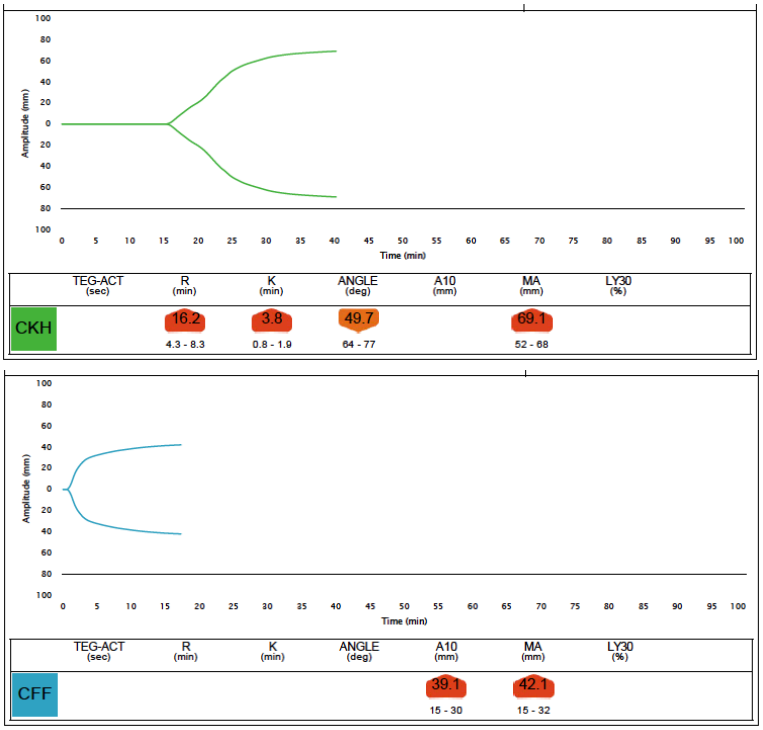
Day 7 TEG tracing



Day 14 TEG tracing

Figure 2: Detailed thromboelastography (TEG) tracings for the patient that suffered epistaxis on day 16 of admission. All anticoagulation was subsequently stopped. CKH=citrated kaolin in heparinise, CFF=citrated functional fibrinogen. Normal reference ranges as provided by the TEG 6s operating manual.

Figure 3: Detailed thromboelastography tracings for the intracranial haemorrhage patient



Day 1 TEG tracing

Figure 3: Detailed thromboelastography (TEG) tracings for the patient that suffered an intracranial haemorrhage on day 2 of admission. All anticoagulation was subsequently stopped and life support withdrawn. CKH=citrated kaolin in heparinise, CFF=citrated functional fibrinogen. Normal reference ranges as provided by the TEG 6s operating manual.

APPENDICES

APPENDIX 1: DATA CAPTURING SHEET

Admission data collection form

Patient Sticker	**Participant Study Code** [_][_][_][_][_][_]
	Date [_][_]/[_][_]/[2][0]
	Day in ICU [_][_]
	Date of Symptom onset [_][_]/[_][_]/[2][0]

Age	[_][_]					
Sex	Male [_]	Female [_]	Other [_]			
Race	Black [_]	White [_]	Coloured [_]	Indian [_]	Other [_]	
Estimated weight	[_][_][_]kg		**Estimated height**	[_][_][_]cm		
BMI	[_][_]					
Comorbidities	Hypertension	[_]				
	Diabetic	[_]				
	Coronary Artery Disease	[_]				
Thromboprophylaxis	LMWH	[_]	Dose	[_][_][_]mg	[_][_]	
	UF boluses	[_]	Dose	[_][_][_][_]IU	[_][_][_]	
	UF Infusion	[_]	Dose	[_][_][_][_]IU/hr		
	None	[_]				
Therapies	Immune modulators	[_]				
	Antivirals	[_]				
	Steroids	[_]				
	Proton Pump Inhibitors	[_]				
SOFA Score	[_][_]		**P:F Ratio**	[_][_][_]		
DIC Score	[_][_][_]					

Clinically suspected or confirmed thrombotic event in past 7 days	DVT	[_]
	PE	[_]
	Thrombosed ECMO catheter	[_]
	Thrombosed Dialysis catheter	[_]
	Myocardial Infarction	[_]
	Stroke	[_]
	Acute Limb Ischaemia	[_]
Was this event confirmed with imaging?		
Clinically significant bleeding episode event in past 7 days	Epistaxis	[_]
	Haematuria	[_]
	Intracranial Haemorrhage	[_]
	Intrapulmonary Haemorrhage	[_]
	UGIB	[_]
	LGIB	[_]
	Surgical sites	[_]
	Wounds	[_]
	Central Lines	[_]
Were blood products transfused for the bleeding episode?	RBC	[_]
	FFP	[_]
	Cryoprecipitate	[_]
	Platelets	[_]
Was this event confirmed with imaging?		

Fibrinogen		**TEG Kaolin**		**TEG Heparinase**		**TEG Functional fibrinogen**	
D-Dimer		**R Time**		**R Time**		**R Time**	
PT		**K Time**		**K Time**		**K Time**	
aPTT		**α angle**		**α angle**		**α angle**	
Platelet		**MA**		**MA**		**MA**	
Urea		**LY30**		**LY30**		**LY30**	
Creatinine							

Day 7 and 14 Follow up

Participant Study Code [_][_][_][_][_][_]
Day in ICU [_][_]

Thromboprophylaxis

LMWH	[_]	Dose	[_][_][_]mg	[_][_]
UF boluses	[_]	Dose	[_][_][_][_]IU	[_][_][_]
UF Infusion	[_]	Dose	[_][_][_][_]IU/hr	
None	[_]			

Therapies

Immune Modulators	[_]
Antivirals	[_]
Steroids	[_]
Proton Pump Inhibitors	[_]

SOFA Score [_][_] **P:F Ratio** [_][_][_]
DIC Score [_][_][_]

Clinically suspected or confirmed thrombotic event in past 7 days?

DVT	[_]
PE	[_]
Thrombosed ECMO catheter	[_]
Thrombosed Dialysis catheter	[_]
Myocardial Infarction	[_]
Stroke	[_]
Acute Limb Ischaemia	[_]

Was this event confirmed with imaging? _____

Clinically significant bleeding episode in past 7 days?

Epistaxis	[_]
Haematuria	[_]
Intracranial Haemorrhage	[_]
Intrapulmonary Haemorrhage	[_]
UGIB	[_]
LGIB	[_]
Surgical sites	[_]
Wounds	[_]
Central Lines	[_]

Were blood products needed for bleeding episode?

RBC	[_]
FFP	[_]
Cryoprecipitate	[_]
Platelets	[_]

Was this event confirmed with imaging? _____

Fibrinogen		**TEG Kaolin**		**TEG Heparinase**		**TEG Functional fibrinogen**	
D-Dimer		**R Time**		**R Time**		**R Time**	
PT		**K Time**		**K Time**		**K Time**	
aPTT		**α angle**		**α angle**		**α angle**	
Platelet		**MA**		**MA**		**MA**	
Urea		**LY30**		**LY30**		**LY30**	
Creatinine							

APPENDIX 2: CONSENT FORM

Groote Schuur Hospital Patient Information and Consent Form

Thromboelastography in Critically Ill Patients with Covid-19

Principle Investigator
Dr Malcolm Miller
Co-Investigators
Dr Colette Neethling
Prof Jessica Opie

What is Groote Schuur Hospital and what is this study about?
Groote Schuur Hospital (GSH) is the chief academic hospital for the University of Cape Town. This means that along with being your primary hospital where you seek treatment, it is also an academic institution where young doctors are being trained. The University of Cape Town is a well-known research hospital and therefore you as a patient play a critical role in developing our research. Research is important to understand disease processes and therefore to manage them better.

The aim of this study is to better understand Covid-19 so that we can manage patients better in the future. The novel severe acute respiratory coronavirus 2 (SARS-COV-2) was first detected in Wuhan, China and has since then spread to 213 countries. Patients admitted to the intensive care unit (ICU) have shown a high mortality rate and this proves an area for future improvement. One of the causes of mortality in patients admitted to ICU is thrombotic complications. This is when a blood clot obstructs the blood flow to a vital organ and causes it to dysfunction. We aim to assess the coagulation status of patients admitted to ICU with Covid-19 so we can better understand what drives this propensity to clot. If we can understand what happens we can better understand why and in future we can institute better management protocols.

What will this involve from me?
We would like to perform some blood tests on you to assess your coagulation system. The coagulation system is a complex system of cells, proteins and processes that dictate your bodies ability to form clots and breakdown clots in response to tissue damage. We have reason to believe based on early studies from China and Italy that patients with Covid-19 have an over active coagulation system that leads to inappropriate and excessive clot formation.

What we need from you is a sample of your blood in order to perform these coagulation tests. Most of these tests are already performed routinely and we will be adding more sophisticated testing to understand your global coagulation status.
These added, sophisticated blood tests, will be performed on left over samples of your routine blood tests therefore no extra blood will need to be sampled from you. All blood tests in ICU are sampled from an indwelling arterial line which will cause no added harm or discomfort to you. Your coagulation status and disease severity will be monitored on day 1 in ICU and again on day 7 and 14.

Are there any risks involved?
This is a prospective, descriptive study. This means that we will only be describing what we find on your blood results and describing your outcomes and risk factors. We will not be altering your therapy in any way and whether you agree to participate or not it will have no effect on your treatment in ICU. All information that we gather will be de-identified and your personal details will be kept confidential at all times. Your identity will only be known by the researchers listed above and we take an oath to protect and safeguard your identity at all times. Blood sampling for the added tests will not be necessary as we will be using a small volume (0.4ml) of your left-over blood to perform the test. This is very low risk to you as the participant.

Are there any benefits of participating?
There is no immediate benefit to you as a patient as this is merely a descriptive study where we describe what we see. However, your participation is invaluable and will assist us in better understanding this disease which

will assist us in treating patients better in the future. This is a pandemic and timeous knowledge acquisition and sharing is important for us to improve outcomes for the critically ill.

What are the costs involved?
There is no cost to you as the individual as all testing that is not deemed routine is being funded.

What happens if I refuse to participate?
All participation in this study is voluntary. You are free to decide whether you want to take part in this study or not. Not participating will not impact your current management at all. You are allowed at any point to withdraw your participation in the study and the UCT FHS Human Research Ethics Committee can be contacted on 021 406 6338 in case you have any questions regarding your rights and welfare as a research subject in this study.

What happens to the samples?
Some of your blood will be sent off to the National Health Laboratory Service (NHLS) for testing, this is part of routine care. These samples will then be discarded once the test has been performed. Tests that are deemed part of routine care will have the results made available on the NHLS system for your physician to see.
A small amount of your blood will be used to run the Thromboelastography (TEG). This blood will be obtained from left-over samples. TEG is a point of care test that reports on your bloods global ability to form a clot and is not considered standard routine care. The results of this test will be available on the machine itself. The researchers are the only people who are allowed to operate the machine and the results will only be viewed by them. Once all the data is captured electronically, this information will be deleted from the TEG machine. The sample used to run the TEG is immediately discarded.

Who will have access to information about me and my blood results?
As mentioned above, blood results that are deemed routine and ordered by your treating physician will be made available on the NHLS website. This is routine standard of care for all inpatients. Blood tests that aren't deemed routine and are needed for research purposes will only be accessible to the research team listed above. On enrolment into the study we will be capturing your details and demographics and after that your information will be de-identified with the use of a study code. The researchers will be the only individuals who will have access to your information and this will be kept safely locked away at all times.

Who has allowed this research to take place?
This research has been reviewed by the Anaesthesia Departmental Research Committee and has been deemed important and clinically relevant. This research has also been approved by the Human Research Ethics Committee of the University of Cape Town and has been deemed ethical, safe and that patients' rights have been respected.

Compensation in event of adverse effects ?
This is a descriptive study which means we are just describing your blood results, risk factors and outcomes. This study poses no harm to you that could cause grievous bodily damage or psychological effect and therefore compensation is not deemed necessary.

What if I have any questions?
If you have any questions regarding the study, you are welcome to contact the research con-investigator listed below

Dr Colette Neethling
Department of Anaesthesia and Perioperative Medicine
Groote Schuur Hospital
Tel: 0716718719

If you have any questions regarding your rights and welfare you are welcome to contact the UCT FHS Human Research Ethics Committee
Tel: 021 406 6338

Groote Schuur Hospital Consent Form
Thromboelastography in Critically Ill Patients with Covid-19

I, _____ (name of participant) have had the research explained to me. I understand all risks involved and have had all my questions and concerns addressed satisfactorily.

- ☐ I agree to participate in the study
- ☐ I agree to have my blood taken for analysis
- ☐ I would like to know the results of my blood tests
- ☐ I would like my results shared with my treating physician

I understand that I can change my mind at any point and can withdraw myself from the study at no detriment to myself. The relevant people to contact in this event has been made know to me.

_____ _____
Participant Name (or name of legal representative/proxy) Date

_____
Participant Signature (or signature of legal representative/proxy)

I certify that I have followed the study SOP to obtain consent from the participant and S/he understands the nature and purpose of the study and consents. S/He has been given the opportunity to ask questions and all questions have been answered satisfactorily.

_____ _____
Name of person taking consent Date

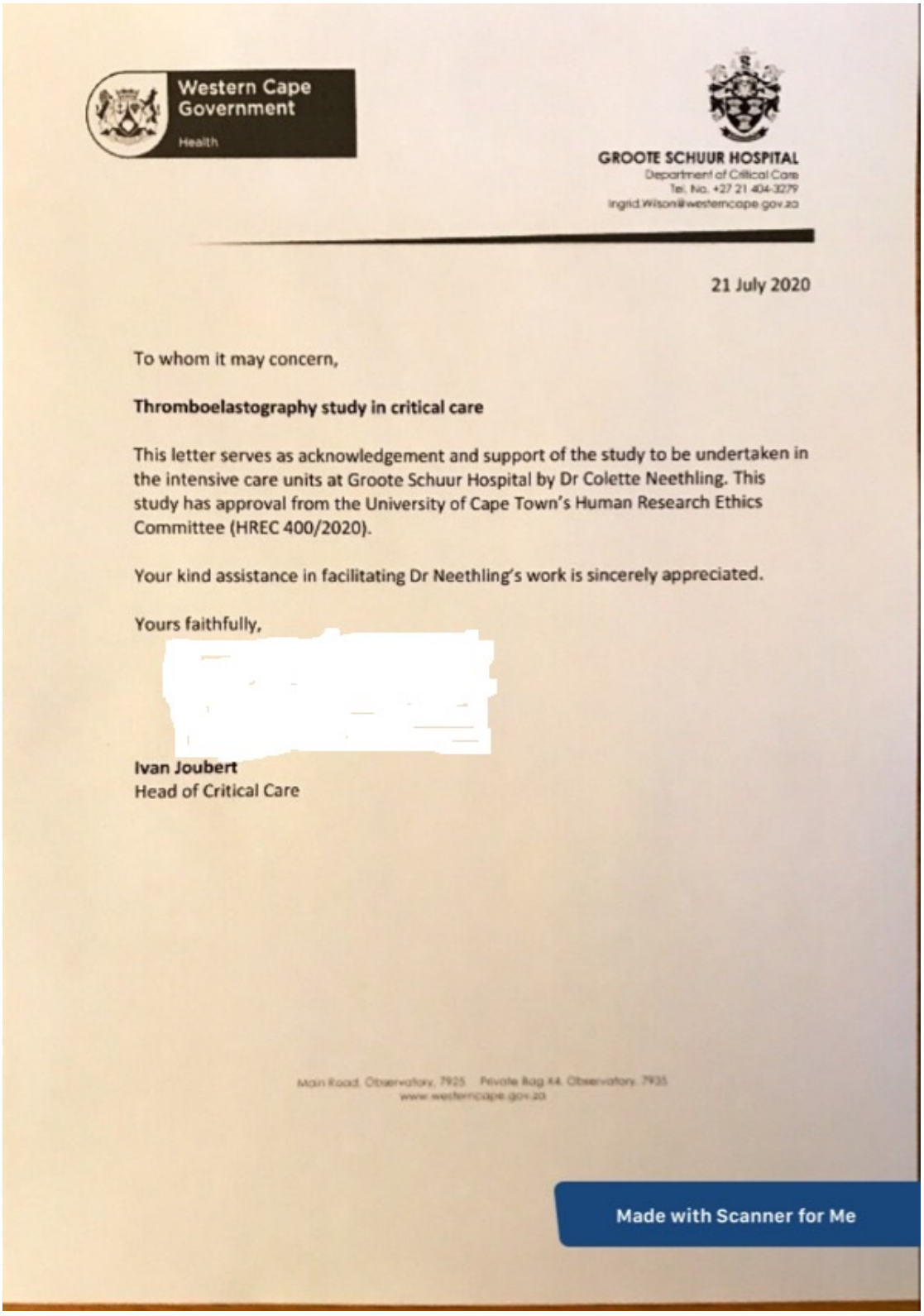
_____
Signature

A witness can be any member of healthcare staff who is not involved in the study.

_____ _____
Witness Name Date

_____
Witness Signature

APPENDIX 3: PERMISSION TO PERFORM STUDY IN ICU



Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Department of Critical Care
Tel. No. +27 21 404-3279
Ingrid.Wilson@westerncape.gov.za

21 July 2020

To whom it may concern,

Thromboelastography study in critical care

This letter serves as acknowledgement and support of the study to be undertaken in the intensive care units at Groote Schuur Hospital by Dr Colette Neethling. This study has approval from the University of Cape Town's Human Research Ethics Committee (HREC 400/2020).

Your kind assistance in facilitating Dr Neethling's work is sincerely appreciated.

Yours faithfully,

Ivan Joubert
Head of Critical Care

Main Road, Observatory, 7925 Private Bag X4, Observatory, 7935
www.westerncape.gov.za

Made with Scanner for Me

APPENDIX 4: PERMISSION TO PERFORM STUDY AT GROOTE SCHUUR HOSPITAL

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
e-mail: *Bernadette.Eick@westerncape.gov.za*

Dr Malcolm Miller
DIVISION OF CRITICAL CARE

E-mail: Malcolm.Miller@uct.ac.za / neethling.colette@gmail.com

Dear Dr Miller,

RESEARCH PROJECT: Thromboelastography In Critically Ill Patients With COVID-19 (MMed Dr Colette Neethling)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 July 2021.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) Confidentiality must always be maintained.
d) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
m) Kindly submit a copy of the publication or report to this office on completion of the research.
n) At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 24 July 2020

C.C. Mr. L. Naidoo, Dr S. Peter, Professor I. Joubert

G46 Management Suite, Old Main Building,
Observatory 7925
Tel: +27 21 404 6288 fax: +27 21 404 6125

Private Bag X,
Observatory, 7935
www.westerncape.gov.za/health

APPENDIX 5:

a. HUMAN RESEARCH ETHICS APPROVAL LETTER

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

15 July 2020

HREC REF: 400/2020

Dr M Miller
Division of Critical Care
D-12 NGSH
Email: malcolm.miller@uct.ac.za
Student: neethling.colette@gmail.com

Dear Dr Miller

PROJECT TITLE: THROMBOELASTOGRAPHY IN CRITICALLY ILL PATIENTS WITH COVID-19- MMED CANDIDATE-DR COLETTE NEETHLING

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study, subject to the following: -

1. Every effort is made to achieve proxy consent.
2. That each waiver of consent for a participant that passes on as discussed with the HREC.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020.

Approval is granted for one year until the 30 July 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Dr Colette Neethling will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

b. MOTIVATION AND APPROVAL TO INCREASE SAMPLE SIZE

UNIVERSITY OF CAPE TOWN

Department of Anaesthesia and Perioperative Medicine

Faculty of Health Science,
Anzio Road, Observatory
Western Cape, South Africa 7925
Telephone: (021) 406-6143

Professorial Staff:

JLC Swanevelder MB ChB, MMed (Anes) (U Stell), FCA (SA), FRCA (Hon)
Head of Department
Email: justiaan.swanevelder@uct.ac.za
BM Biccard MBChB (UCT), FFARCSI, FCA (SA), MMedSci, PhD
2nd Chair of Anaesthesia
Email: bruce.biccard@uct.ac.za
Administrative Officer: C Wyngaard, Email: cheryl.wyngaard@uct.ac.za

Re: HREC 400/2020 Minor Amendment to Research Protocol : Increase sample size

Dear Professor Blockman,

We have had the pleasure of commencing the aforementioned study and recruitment has been going very well.

We write to you in connection with increasing our study ***sample size*** from ***33*** to ***40.***
Our primary study objective was to assess coagulation status of patients with severe COVID pneumonia using standard coagulation studies and Thromboelastography (TEG). Our aim was to describe the coagulation status on admission and the evolution over time with a day 7 and 14 follow up. We met with a biostatistician during the planning phase of this study to determine a well powered sample size. According to the table below and available funding and resources, a sample size of 33 seemed appropriate and well powered.

Unfortunately, due to the high mortality rate of patients with severe COVID pneumonia admitted to ICU, a large portion of our patients have been lost to follow up. This creates concern as the number of patients reaching day 14 of follow up falls outside of the sample size reference ranges recommended by our statistician. Thus far 31 patients have been enrolled of which 11 have passed away before the day 7 and 14 follow ups could be conducted. Based on this, roughly 36% of patients will not be able to be followed up. This means that with a sample size of 33 and the current loss to follow up rate, we will have approximately 21 patients survive to the day 14 follow up. From the literature we know that the MA and LY30 are the greatest predictors of outcome in these patients and therefore it would be ideal to have at least 24 to 32 patients reach the day 14 mark. In order to reach this we need to increase our sample size to atleast 38 in order to meet the minimum sample size of 24 on day 14.

With the above statistical support we therefore request to ***increase the sample size from 33 to 40***

Sample Size Calculation based on article by Mortus et al.

Thromboelastography			
Parameter	Mean (SD)	Ref range mean	Sample size
R	10 (11)	6 (4-8)	62
K time		2.5 (1-4)	
Alpha angle	60 (23)	60.5 (47-74)	27
MA	67 (17)	64 (55-73)	18
LY30	0.9 (1.8)	4 (0-8)	24
Thromboelastography with heparin correction			
R	6 (2.7)	6 (4-8)	17
K time		2.5 (1-4)	
Alpha angle	73 (10)	60.5 (47-74)	16
MA	74 (10)	64 (55-73)	10
LY30	2.1 (3.7)	4 (0-8)	32

Warm Regards

UNIVERSITY OF CAPE TOWN | FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS006: Protocol Amendment

HREC office use only (FWA00001637; IRB00001938)		
☑ Approved	☑ Type of review: Expedited	☐ Full committee
This serves as notification that the changes and documentation described below are approved.		
Signature HREC Chairperson/ Designee		Date 25/8/20

Note: All major amendments must include a **Local PI Synopsis** justifying the changes for the amendment. Please note that incomplete amendment submissions will not be reviewed.

Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown.

Comments from the HREC to the Principal Investigator:
Note: The approval of this protocol amendment does not grant annual approval. Please complete the FHS016 / FHS017 form for annual approval at least one month before study expiration.

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	17 August 2020		
HREC REF Number	HREC 400/2020		
Protocol title	Thromboelastography in Critically Ill Covid-19 Patients		
Protocol number (if applicable)			
Principal Investigator	Dr Malcolm Miller		
Department / Office Internal Mail Address	Department of Critical Care, D12 Groote Schuur Hospital malcolm.miller@uct.ac.za		
1.1 Is this a major or a minor amendment? (see FHS005bp) Major (tick box) Minor (tick box)		☐ Major	☒ Minor
1.2 Does this protocol receive US Federal funding?		☐ Yes	☒ No

1.3 If the amendment is a major amendment and receives US Federal Funding, does the amendment require full committee approval? **Note:** Any protocol amendments for **Full Committee** review MUST be submitted on the monthly HREC submission dates. (**Please email an electronic copy to** hrec-enquiries@uct.ac.za)	☐ Yes	☐ No

2. List of Proposed Amendments with Revised Version Numbers and Dates

Please itemise on the page below, all amendments with revised version numbers and dates, which need approval. This page will be detached, signed and returned to the PI as notification of approval. Please add extra pages if necessary.
1. Increase Sample size from 33 to 40 patients.

3. Protocol status (tick ✓)

☒	Open to enrolment
☐	No participants have been enrolled
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☐	Research-related activities are complete, data analysis only

4. Proposed changes will affect: (tick ✓ all the categories that apply)

	Protocol
☐	Study objectives, design (including investigator's brochure, clinical activities, study length)
☐	Study instruments, questionnaires, interview schedules
☒	Sample size
☐	Recruitment methods
☐	Eligibility criteria (inclusion and exclusion criteria)
☐	Drug/device (composition, amount, schedule, route of administration, combination with other drugs/devices, safety information)
☐	Data collection/ analysis
☐	Principal Investigator. (Please attach revised conflict of interest and PI declaration statements. Refer: sections 7 and 8.4 in the New Protocol Application Form FHS013)
☐	Consent form and information sheet
☐	Recruitment materials (e.g. advertisements)
☐	Administrative (e.g. change in sponsor's name, change in contact information)
☐	Other. Please specify:

4.1 In your opinion, will there be any **increase** in risk, discomfort or inconvenience to participants?	☐ Yes	☒ No
If yes, please provide a detailed justification/explanation:		

4.2 What follow-up action do you propose for participants who are already enrolled in the study?	
☐	Inform current participants as soon as possible
☐	Re-consent current participants with revised consent/assent forms (append)
☒	No action required
☐	Other. Please describe:

5. Detailed description of the change(s)

Please attach, for each amendment, a summary of all changes which clearly indicates:

I. Old wording (e.g. ~~strikethrough~~ text, CHANGED FROM and CHANGED TO)

II. New wording (e.g. *italicized*, **bold**, tracked)

III. Detailed rationale/ justification/ explanation for each change

6. Ethics Review Levy – cost including vat

Cost for Major Amendments - R3 691.20

(Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from charges)

For invoicing purposes, please provide:	
Sponsor's name	
Contact person	
Address	
Telephone number	
Email Address	

7. Signature

My signature certifies that I will maintain the anonymity and/ or confidentiality of information collected in this research. If at any time I want to share or re-use the information for purposes other than those disclosed in the original approval, I will seek further approval from the HREC.

Signature of PI		Date	17 August 2020

c. MOTIVATION AND APPROVAL TO WAIVE CONSENT

UNIVERSITY OF CAPE TOWN

Department of Anaesthesia and
Perioperative Medicine

Faculty of Health Science,
Anzio Road, Observatory
Western Cape, South Africa 7925
Telephone: (021) 406-6143

Professorial Staff:

JLC Swanevelder MB ChB, MMed (Anes) (U Stell), FCA (SA), FRCA (Hon)
Head of Department
Email: justiaan.swanevelder@uct.ac.za
BM Biccard MBChB (UCT), FFARCSI, FCA (SA), MMedSci, PhD
2nd Chair of Anaesthesia
Email: bruce.biccard@uct.ac.za
Administrative Officer: C Wyngaard, Email: cheryl.wyngaard@uct.ac.za

RE: Permission to waive consent for 4 participants HREC 400/2020

Dear Professor Blockman,

With reference to the aforementioned study, we initially requested to waive consent of non-survivors and to obtain delayed consent from survivors. The reason for this request was due to the fact that patients admitted to ICU are already intubated and ventilated and remain in a comatose state for weeks. We motivated that the study was low risk to the participant and results of the study carried great social value. HREC approval was subsequently granted on the proviso that *every effort should be made to achieve proxy consent*. In the event that this is not possible, *each waived consent of patients that pass on should be discussed with the HREC*.

In our study *"Thromboelastography in Critically Ill COVID-19 Patients"* we have obtained informed consent from 36 of the 40 potential participants. Due to the high mortality rate and unique circumstances surrounding the pandemic, majority of consent was afforded by the next of kin/proxy telephonically. In the event that the patient survived their illness, delayed informed consent was obtained directly from the patient in person.

There are 4 patients that meet the inclusion criteria that we would like to include in the study but we were unable to get in contact with any of the family members during their brief stay in ICU. The telephone numbers provided in the folder were either incorrect, not functional, or there was never any answer.

We tried on numerous occasions to contact the family of these 4 participants and we have also searched for alternative numbers in records and clinicom after their passing.

All 4 of these patients were intubated prior to admission to ICU and therefore consent was not possible from the patient themselves. Since admission, calls to family listed as next of

kin in their file were contacted to no avail. The 4 patients had a very brief stay in our ICU's and passed away a few short days after admission.

We therefore motivate to have consent waived for the above 4 participants as the risks to the patient and their families are very low.

Efforts to contact family for delayed consent will continue, but in the likely event that that is not possible we request a waiver. Should a waiver not be granted we will exclude the 4 patients from the descriptive study.

Warm Regards

Dr Malcolm Miller (Principal Investigator)

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

29 September 2020

HREC/REF: 400/2020

Dr M Miller
Department of Anaesthesia and Perioperative Medicine
Ward D 23 NGSH
Email: malcolm.miller@uct.ac.za

Dear Dr Miller

Project Title: THROMBOELASTOGRAPHY IN CRITICALLY ILL PATIENTS WITH COVID-19- MMED CANDIDATE-DR COLETTE NEETHLING

Thank you for your letter to the Faculty of Health Sciences Human Research Ethics Committee (HREC).

The Ethics Committee has granted **permission to waive consent** for the following 4 participants:
-Participant codes:

- TCOV01
- TVOV05
- TCOV08
- TCOV26

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Hrec/ref:400/2020sa

APPENDIX 6: INSTRUCTIONS TO AUTHORS FOR CRITICAL CARE MEDICINE

Critical Care Medicine is an international, peer-reviewed journal that is interested in publishing the highest quality scientific studies in the field of critical care medicine. Studies may include basic, translational, clinical, and implementation science that bear on the field. Approximately 20% of the original manuscripts submitted to the journal are accepted for publication.

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Each manuscript submission should designate one corresponding author and all contributing authors. The number of authors should be restricted to only those persons who have truly participated in the conception, design, execution, and writing of the manuscript. Authors must disclose any potential financial or ethical conflicts of interest regarding the contents of the submission **on the title page of the manuscript.**

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"Conflicts of Interest and Source of Funding." For example:

Conflicts of Interest and Source of Funding: "Author A" has received honoraria from "Company 1." "Author B" is currently receiving a grant (#12345) from "Organization Y," and is on the speaker's bureau for "Organization X"–the CME organizers for Company 1. The remaining authors have disclosed that they do not have any conflicts of interest.

Human and Animal Subjects. All studies of human subjects must contain a statement within the Materials and Methods section indicating approval of the study by the Institutional Review Board (or institutional review body) that subjects have signed written informed consent, or that the Institutional Review Board waived the need for informed consent. ***Before*** **your submission can be sent out for peer review, it is necessary that you address this issue of institutional review approval.** This is in accordance with the International Committee of Journal Editors uniform requirements for manuscripts submitted to biomedical journals. Please see http://www.icmje.org for more details. All animal studies must contain a statement within the Materials and Methods section confirming approval by the Institutional Animal Care and Use Committee and that the care and handling of the animals were in accord with National Institutes of Health guidelines or other internationally recognized guideline for ethical animal treatment.

Statistical Review. Any study containing quantitative data and statistical inference should be reviewed by a consultant with formal statistical training and experience.

Although this journal does not provide specific guidance on statistical reporting, compliance with generally accepted recommendations (e.g., Bailar JC III, Mosteller F: Guidelines for statistical reporting in articles for medical journals: Amplifications and explanations. *Ann Intern Med* 1988; 108:266-273) is suggested.

Clinical Trials. This journal has adopted the definition and recommendations of the International Committee of Medical Journal Editors (see http://www.icmje.org) pertaining to registration of clinical trials. All clinical trials must be registered.

A clinical trial is any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention and a health outcome. Health-related interventions are those used to modify a biomedical or health-related outcome; examples include drugs, surgical procedures, devices, behavioral treatments, educational programs, dietary interventions, quality improvement interventions, and process-of-care changes. Health outcomes are any biomedical or health-related measures obtained in patients or participants, including adverse events. This journal exempts trials in which the primary goal is to determine pharmacokinetics from the registration requirement.

This journal accepts registration in any registry that is a primary register of the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/network/primary/en/index.html) or in ClinicalTrials.gov (http://ClinicalTrials.gov), which is a data provider to the WHO ICTRP. The registration number and registry name must be included with the manuscript submission.

MANUSCRIPT PREPARATION

Manuscripts must conform to *Critical Care Medicine* Instructions for Authors and/or the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," which can be found on the International Committee of Medical Journal Editors web site, www.icmje.org. Manuscripts must be double-spaced with pages numbered consecutively, beginning with the title page. Each paragraph should be indented with a tab. The text portion of each manuscript should be in Microsoft Word format, including references and figure legends. Figures can be saved in .tif or .eps format in 300 DPI or higher. Tables should be submitted as Microsoft Word files; spreadsheets are not acceptable. Figures should be saved as separate files and uploaded after the text upload is complete. Specific guidelines for figure formatting are found on the Editorial Manager® home page. **Documents submitted in .pdf format are not acceptable.**

When uploading the text, tables, and figures into Editorial Manager®, there is the option of entering files for review and files for production. Files for review are viewable by the editorial staff, the editor, and the reviewers. These documents should include all text, tables, and figures, as well as any special referenced material. Files for production are only seen by the editorial staff and will not be seen by reviewers.

MANUSCRIPT CONTENT

Title Page. The title page should contain 1) the title; 2) first name, middle initial, and last name of each author; 3) highest academic degrees, fellowship designations, and institutional affiliation for each author; 4) name of the institution(s) where the work was performed; 5) the address for reprints and a statement regarding whether reprints will be ordered; and 6) financial support used for the study, including any institutional departmental funds. The authors should also provide six key words for indexing, using terms from the Medical Subject Headings list of *Index Medicus*. **Structured abstracts are required for all manuscripts (except editorials, letters, and book reviews) submitted to *Critical Care Medicine*.**

Editorial Manager® will prompt authors to input the above information into specific fields as they are submitting their manuscript. Authors should also upload their title page and structured abstract with the body of the manuscript. It is also important to note that if there is formatted text or Greek letters or symbols in the title or abstract, special coding is necessary and the Character Palette in Editorial Manager® will need to be used. *It is not necessary to code special characters and formats in the actual manuscript.*

Abstracts. Abstracts should be no more than 300 words in length and must have the following headings: Objective, Design, Setting, Patients (for Clinical Investigations) or Subjects (for Laboratory Investigations), Interventions, Measurements and Main Results, and Conclusions. Review Articles, Special Articles, and Case Reports should use these headings in the abstract: Objective, Data Sources, Study Selection, Data Extraction, Data Synthesis, and Conclusions. For details regarding the preparation of structured abstracts, refer to the *American Medical Association Manual of Style, Tenth Edition* (pp. 20–23).

Text Material. The text should be written in standard scientific English. Authors should carefully proofread their text prior to submission. Text that is poorly written will lead to summary rejection. The text should be organized into the following sections: Introduction, Materials and Methods, Results, Discussion, and Conclusions followed by Acknowledgments, References, Figure Legends, and Tables. Secretarial and editorial assistance are not acknowledged. Results may be presented in the text, in the figures, or in the tables. The Discussion section should interpret the results without unnecessary repetition. References to related studies should be included in the text section.

In addition, the following should be observed:

- Abbreviations should be minimized and avoided wherever possible. The full term for which an abbreviation stands should be used at its first occurrence in the text unless it is a standard unit of measure. The abbreviation should appear in parentheses after the full term. Abbreviations should not be in the title, figure legends, or table titles.

- Do not use values that are more significant than your analysis is capable of accurately measuring (e.g., Pao_2 84 torr [11.2 kPa], not 83.7 torr).

References. All references should be cited in sequential order in the text and typed on a separate sheet of paper. References should be identified in text, tables, and legends by full-size Arabic numerals on the line and in parentheses. **Do not** use wordprocessing footnote, endnote, or paragraph numbering functions to make a list of references. Titles of journals should be set in italics and abbreviated according to the style used in *Index Medicus*. If journal titles are not listed in *Index Medicus,* they should be spelled out. Unpublished data or personal communications should be noted parenthetically within the text but not in the References section. Inclusive page numbers (e.g., p. 1-10) should be used for all references. Listed below are samples of standard references; however, a complete listing of references can be found on the International Committee of Medical Journal Editors web site, www.icmje.org.

Standard Journal Article: Bone RC, Fisher CJ, Cemmer TP, et al: Sepsis syndrome: A valid clinical entity. *Crit Care Med* 1989; 17:389-393

Standard Book with Authors: Civetta JM, Taylor RW, Kirby RR: Critical Care. Third Edition. Philadelphia, Lippincott, Williams & Wilkins, 1996

Standard Book with Editors: Norman IJ, Refern SJ (Eds): Mental Health Care for Elderly People. New York, Churchill Livingstone, 1996

Standard Chapter in a Book: Phillips SJ, Whisnant JP: Hypertension and stroke. *In*: Hypertension: Pathophysiology, Diagnosis and Management. Second Edition. Laragh JH, Brenner BM (Eds). New York, Raven Press, 1995, pp 465-478

Standard Web Site/Electronic Format: Marion DW, Domeier R, Dunham CM, et al: Practice management guidelines for identifying cervical spine injuries following trauma. Available at: http://www.east.org. Accessed July 1, 2000

Equations. Equations should be created as normal text or as images. The use of equation editors or utilities may not convert correctly during the manuscript submission process and their use is discouraged.

Tables and Figures. The number of figures and tables should be appropriate for the length of the manuscript and **should not exceed** a total of 5 figures and tables (e.g., 3 figures and 2 tables); additional figures and tables can be submitted as Supplemental Digital Content. Tables should be numbered consecutively with no A or B add ons. All tables expanding more than 8 columns wide and 40 rows in length must be submitted as Supplemental Digital Content. Tables that are found to be too extensive to fit on a single printed page will be sent back to the author to reclassify as Supplemental Digital Content. Materials reproduced from another published source must be labeled "Reproduced with permission from… ." In addition, a letter granting permission to reproduce the materials from the copyright holder must be received by SCCM when the manuscript is submitted for review. If the manuscript is accepted for publication, it will not be able to be printed unless this permission letter has been submitted. Adapted figure or table materials must be labeled "Adapted with permission from… ." Letters of permission are also required for adapted materials. A sample of a permission request can be found on Editorial Manager® in the instruction section.

Tables. Tables expanding more than 8 columns wide and 40 rows in length should be submitted as Supplemental Digital Content. If, when processing your manuscript, we find that your tables do not comply, the manuscript will be sent back for correction. Every table submitted must have applicable table headings and a table title (a short and to the point explanation of what the table is and not a full description, that should be reserved for the text). Do not use tabs to create tables and do not use table editors. Table building utilities will convert, providing that no special images were inserted. Do not reiterate tabular data in the text. Do not use abbreviations in table titles. Do not use all capital letters in table headings and text. Do not use center, decimal tab, and justification commands. Do not use spaces to separate columns. Use a single tab, not a space, on either side of the ± symbol. Do not underline or draw lines within tables. Footnoted information should be referenced using italicized, superscript, lower case letters (i.e., $^{a, b}$) in alphabetical order (reading from left to right). Avoid lengthy footnotes and insert descriptive narratives in the text or in the Supplemental Digital Content as appropriate.

Figures.
A) Creating Digital Artwork

1. Learn about the publication requirements for Digital Artwork: http://links.lww.com/ES/A42

2. Create, scan, and save your artwork and compare your final figure to the Digital Artwork Guideline Checklist (below).

3. Upload each figure to Editorial Manager® in conjunction with your manuscript text and tables.

B) Digital Artwork Guideline Checklist

Here are the basics to have in place before submitting your digital art:

- Artwork should be saved as .tif or .eps files.
- Artwork is created as the actual size (or slightly larger) it will appear in the journal. (To get an idea of the size images should be when they print, study a copy of the journal to which you wish to submit. Measure the artwork typically shown and scale your image to match.)
- Crop out any white or black space surrounding the image.
- Diagrams, drawings, graphs, and other line art must be vector or saved at a resolution of at least 1200 dpi.
- Photographs, radiographs, and other halftone images must be saved at a resolution of at least 300 dpi.
- Photographs and radiographs with text must be saved as postscript or at a resolution of at least 600 dpi.
- Each figure must be saved and submitted as a separate file. Figures should not be embedded in the manuscript text file.

Remember:

- Cite figures consecutively in your manuscript.
- Number figures in the figure legend in the order in which they are discussed.
- Upload figures consecutively to the Editorial Manager® Web site and number figures consecutively in the Description box during upload.

For captions and variables within a figure, use Helvetica (or Arial) font, if possible, in upper and lower case letters. Radiographic prints must have arrows (if applicable) for clarity. Color photographs will occasionally be published in the journal if use of color is vital to making the point; authors will be charged the cost of color reproduction. Figures that do not conform to these specifications will be sent back to the corresponding author for correction. All abbreviations used in the figure must be spelled out in the legend.

Figure legends should contain enough information for the reader to understand the illustration without referring to the text, but should be concise and should not repeat information already stated in the text. Figure legends should be typed on a separate page. Figures must be referenced sequentially in the text. Authors must assume charges for changes made to figures after manuscripts are accepted.

Units of Measure. Authors should provide units of measurement in SI units. Authors should refer to the *American Medical Associa-*

tion Manual of Style, Tenth Edition (p 787) for details regarding SI units for laboratory data. Where customary or conventional units of measurements are clinically more familiar—such as hemodynamic measurements for pressure (typically reported in mm Hg) and gas tension measurements (typically reported in torr), the SI value and SI units should be reported in parentheses (e.g., Pao_2 84 torr [11.2 kPa]). The units of vascular resistance are dyne.sec/cm^5.

Manufacturer. Provide in parentheses the model number, name of manufacturer, their city, and state or country, for all equipment described in the paper.

Drug Names. Only generic drug names should be used. Trademark or brand names should not be used except in specific cases where the brand name is essential to reproduce or interpret the study. These exceptions should be noted in accompanying correspondence. The manufacturer with the city, state, and country must be provided for any brand name drugs.

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Original Articles. These include randomized controlled trials, intervention studies, laboratory and animal research, outcome studies, cost-effectiveness analyses, and case-control series. The objective and hypothesis of these articles should be clearly stated. Information should be included about study design and methodology, including study setting and time setting; participants, including inclusion and exclusion criteria; any interventions; main outcome measures; main study results; discussion that puts the results in the context of other published literature; and conclusions. The recommended length for original manuscript is 3000 or fewer (12 or fewer typed, double-spaced pages), not including references, tables, or figures. Original articles should include not more than 5 tables and figures in total (e.g., 3 figures and 2 tables) and not more than 50 references. Additional figures, tables, and explanatory material should be submitted as Supplemental Digital Content, as noted above. Authors should include the word count on the title page.

Review Articles. These consist of critical assessment of literature and data pertaining to clinical topics. In these review articles, emphasis should be placed on cause, diagnosis, therapy, prognosis, and prevention. Information concerning the type of study or analysis, population, intervention, and outcome should be included for all data used. The selection process used for all data should be described using standard methodologies. Meta-analyses will be considered as review papers. Review articles should not exceed 3000 words (12 typed, double-spaced pages) and should include not more than a total of 5 figures and tables (e.g., 3 figures and 2 tables). Additional figures, tables, and explanatory material should be submitted as Supplemental Digital Content, as noted above. Authors should include the word count on the title page.

Brief Reports. These should be short reports of original studies or evaluations. They should contain a short, structured abstract and no more than 10 references and 1 to 2 figures or tables. Brief Reports should be no more than 1500 words (6 typed, double-spaced pages). Authors should include the word count on the title page.

Case Reports. Case reports will be considered for publication only rarely, and then only if the case is unique with respect to the problem or novel with respect to management. Case reports should be approximately less than 2000 words (up to 8 typed, double-spaced pages). They must include a structured abstract. The number of references, tables, and figures should be appropriate for the overall length of the paper. In general, no more than 2 tables or 2 figures are necessary.

Letters to the Editor. Letters to the Editor are encouraged. Letters must specifically address a recent article published in *Critical Care Medicine* and may not report any new, unreviewed data. They should be no more than 500 words (2 typed, double-spaced pages) with 5 references.

Invited Editorial. These represent commentaries addressing newly published articles in the journal and are by invitation only. Invited editorials should be no more than 1500 words (6 typed double-spaced pages) with a maximum of 15 references and a maximum of 2 figures and/or tables. See "Writing Editorials for *Critical Care Medicine*" on the main Editorial Manager® login page under Files and Resources.

Invited Viewpoint. These represent opposing positions taken in a point/counterpoint format and are by invitation only. Suggestions for topics and presenters for point/counterpoint segments may be submitted to journals@sccm.org. Suggestions will be reviewed by the editors. Invited viewpoints should be no more than 1500 words (6 typed double-spaced pages) with a maximum of 25 references and a maximum of 3 figures and/or tables.

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All manuscripts will be reviewed by Editorial Board members or consultants selected by the

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