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TITLE: The Pathogenesis of Post-Traumatic Pulmonary Embolism: A Prospective Multi-center Investigation by the CLOTT Study Group

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14. ABSTRACT Venous thromboembolism, which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially mortal complication after injury in both civilian and military settings. To date, there are no methods that have been definitively demonstrated to prevent post-traumatic pulmonary embolism (PE) which carries a mortality of 11% and is the third leading cause of death following injury. PE is particularly common among combat casualties due to the prevalence of certain risk factors such as multiple amputations, traumatic brain injury, the need for transfusions, and prolonged immobilization during evacuation. In Year 1, all subcontracts were initiated. Protocols, data collection forms and REDCap data entry system were developed. IRB and HRPO approval was attained for 15 of 17 sites participating in CLOTT Part 1. Surgical research associates were trained to screen and enroll subjects. 1,533 subjects were enrolled in CLOTT Part 1. IRB and HRPO approval was attained for 4 of 5 sites for CLOTT Part 2. Surgical research associates were trained in enrolling subjects and conducting research procedures (blood samples for thromboelastography testing. 11 subjects have been enrolled in CLOTT Part 2. There are no significant findings to report at this time.					
15. SUBJECT TERMS Venous thromboembolism, pulmonary embolism, combat casualty, trauma, clots, thromboelastography, fibrinolytic shutdown, clot lysis, surveillance bias					
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YEAR 1 ANNUAL REPORT

1. INTRODUCTION

Venous thromboembolism, which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially mortal complication after injury in both civilian and military settings. To date, there are no methods that have been definitively demonstrated to prevent post-traumatic pulmonary embolism (PE) which carries a mortality of 11% and is the third leading cause of death following injury. PE is particularly common among combat casualties due to the prevalence of certain risk factors such as multiple amputations, traumatic brain injury, the need for transfusions, and prolonged immobilization during evacuation. However, due to the liberal use of computed tomography following injury, many patients are found to have small clots in the chest that may not be PE at all and may in fact not need to be treated. Additionally, recent laboratory investigations suggest that some severely injured patients develop a hypercoagulable state due to failure to break down clot once formed and that platelets contribute to the strength of the clot. This failure of clot lysis may set the stage for true PE events. For Aim 1, patients aged 18-40 years who are admitted to any of 17 major trauma centers will be considered eligible for enrollment. Data will be collected on all patients who develop PE in order to characterize the risk factors for those with symptomatic, central PE versus those with asymptomatic, peripheral thrombi. The safety of observing patients with peripheral thrombi versus treatment (full-dose anticoagulation or placement of a vena cava filter) will be compared. For Aim 2, five trauma centers will enroll a cohort of patients admitted to their intensive care unit and collect blood samples that can be subjected to thromboelastography (TEG) in order to identify patients with failure of clot lysis (fibrinolytic shutdown). The association between fibrinolytic shutdown and the subsequent development of PE will be explored.

2. KEY WORDS

Venous thromboembolism, pulmonary embolism, combat casualty, trauma, clots, thromboelastography, fibrinolytic shutdown, clot lysis, surveillance bias

3. ACCOMPLISHMENTS

- a. What were the major goals of the project?
 - i. Study Specific Aims: (1) To compare the safety of observation versus treatment of asymptomatic peripheral pulmonary clots discovered on computed tomography (CTA) (2) To define the role of post-injury fibrinolysis shutdown in the development of post-traumatic PE.
 - ii. CLOTT Aim 1/Part 1:
 1. Main Hypothesis: Peripheral asymptomatic pulmonary thrombi (PT) seen on chest computed tomography (CTA) can be safely observed without specific treatment.
 2. Secondary Hypothesis: Risk factors for asymptomatic PT will differ from risk factors for symptomatic pulmonary emboli (PE) with or

without associated deep vein thrombosis (VTE).

3. Sub-Aim 1: To compare the safety of observation versus treatment of asymptomatic peripheral pulmonary thrombi discovered on computed tomography of the chest with contrast (CTA)
4. Sub-Aim 2: To evaluate the efficacy of various prophylactic measures in their ability to prevent PE
5. Sub-Aim 3: To determine the magnitude of surveillance bias on the incidence of PE based on the frequency with which chest CTA is utilized.

iii. CLOTT Aim 2/Part 2:

1. Main Hypothesis: Fibrinolytic shutdown after injury will be detected frequently in critically injured patients.
2. Secondary Hypothesis: Fibrinolytic shutdown is associated with an increased incidence of VTE after injury.
3. Sub-Aim 1: To describe the incidence of and the timing for the development of fibrinolytic shutdown in critically injured patients
4. Sub-Aim 2: To identify the risk factors for the development of fibrinolytic shutdown after injury
5. Sub-Aim 3: To investigate the association between fibrinolytic shutdown and the development of DVT and/or PE

b. What was accomplished under these goals?

Major Task 1: Adapt CLOTT protocol for DoD funded status

- Submit protocol to IRB for lead study site, UCSF: CLOTT protocols for Parts 1 and 2 were submitted to the UCSF IRB on August 15th and 22nd 2017, respectively. This was completed prior to the DoD award (as planned).
- Submit lead study site (UCSF) protocols to military 2nd level IRB review (ORP/HRPO): CLOTT protocols for Parts 1 and 2 were submitted to ORP/HRPO for 2nd level review on September 18th and October 6th 2017, respectively.
- Coordinate with sites for IRB protocol submission: CLOTT Part 1 IRB submission materials were distributed to the 16 supporting sites on December 12, 2017. NTI assisted the sites with their local IRB submissions and HRPO application and continuing reviews.
- *Milestone Achieved: Local IRB approval at the lead study site: Part 1 on August 21, 2017 and Part 2 on September 20, 2017*
- *Milestone Achieved: HRPO approval for the lead study site: Part 1 on December 5, 2017; Part 2 on February 3, 2018*
- *Milestone Partially Achieved: Local IRB approval at all sites*
- *Milestone Partially Achieved: HRPO approval for all protocols*

Major Task 2: Subcontract with all study sites

- Verify subaward documents (budgets, budget justifications, salary verification): Completed November 30, 2017
- Submit quarterly progress reports: Ongoing and on schedule for Year 1
- Review quarterly progress report: Ongoing and on schedule for Year 1
- *Milestone Achieved: Subawards issued for all sites – Completed December 21, 2017*

Major Task 3: Patient enrollment

- Educate and train research staff on study protocols and data collection procedures: Study materials (CRF, data definitions, protocols, data dictionary) have been refined. Data entry templates in REDCap are complete. Individual CLOTT kick-off teleconferences were conducted with the sites (February 2 – March 19, 2018). A training webinar for research associates on CLOTT Part 1 was held on March 27, 2018. CLOTT Research Team teleconferences were held to discuss study initiation and processes on January 29, March 28, and March 29. CLOTT Part 2 training on processing TEG assays was conducted on April 9, 2018 at Denver Health. The statement of work estimated that training would be completed by month 3. That target was not met due to delays in hiring and human subjects protections approvals. Training was completed in month 7.
- Identify patients during daily rounds at all 17 sites for study inclusion and collect data during the total length of stay (Aim 1 & Aim 2): UCSF initiated CLOTT Part 1 subject enrollment on March 16, 2018. As of September 29, 2018, fifteen of seventeen sites were enrolling patients for CLOTT Part 1. For CLOTT Part 1, 1,533 subjects have been enrolled. As of September 29, 2018, Four of five sites for CLOTT Part 2 are enrolling patients. For CLOTT Part 2, 11 subjects have been enrolled.
- Draw blood samples for thromboelastography testing (TEG) (Aim 2 only): Ongoing at four of five sites for CLOTT Part 2.
- Complete a duplex venous examination (Aim 2 only): Ongoing at four of five sites for CLOTT Part 2.
- Validate data collected quarterly on a sample of 3% of enrollees: Ongoing
- Coordinate with sites and NTI for monitoring data collection rates and data quality: Ongoing

- c. What opportunities for training and professional development has the project provided?
 - i. Surgical research associates participated in web-based and in-person protocol training.
- d. How were the results disseminated to communities of interest?
 - i. Nothing to report
- e. What do you plan to do during the next reporting period to accomplish the goals?
 - i. In the next quarter, sites pending IRB/HRPO approval for Part 1 and Part 2 will work to finalize approvals. All sites with IRB/HRPO approval for Part 1 will continue enrolling subjects. CLOTT Part 2 sites with IRB/HRPO approval will continue enrolling subjects. Regular investigator/research

team teleconferences will be held to manage research activities at all sites. UCSF will conduct data assurance checks on 3% of completed cases. The research associates will have a monthly teleconference to discuss study issues. Sites will submit quarterly progress reports to the National Trauma Institute. These reports will be compiled and submitted to the Department of Defense as scheduled.

4. IMPACT

- a. What was the impact on the development of the principal discipline(s) of the project?
 - i. Nothing to report
- b. What was the impact on other disciplines?
 - i. Nothing to report
- c. What was the impact on technology transfer?
 - i. Nothing to report
- d. What was the impact on society beyond science and technology?
 - i. Nothing to report

5. CHANGES/PROBLEMS

- a. Changes in approach and reasons for change
 - i. Nothing to report
- b. Actual or anticipated problems or delays and actions or plans to resolve them
 - 1. Sites for CLOTT Part 2 - February 13, 2018 NTI notified Florence D'Orazi and Rochelle Day of site change on CLOTT Part 2. Scripps decided not to participate. University of Maryland replaced that site. Subcontracts were revised accordingly. Dr. D'Orazi verified that it was not necessary to submit an amended Statement of Work.
 - 2. In the statement of work, we estimated that all sites would have local IRB approval by month 5 and HRPO approval by month six. At the end of Year 1, all 17 CLOTT Part 1 sites had IRB approval. Two sites were under initial review at HRPO. For CLOTT Part 2, four of five sites had IRB and HRPO approval at the end of Year 1. One site was pending IRB approval. There were a couple of factors that slowed the IRB approval process. First, some sites had delays in hiring staff and, therefore, delays in submitting to the IRB. Second, some IRBs expressed concern about the waiver of consent in CLOTT Part 1. Third, some IRBs were concerned about collecting date of birth and date of injury. Fourth, some IRBs wanted Data Use Agreements to be executed with UCSF before giving IRB approval.
 - 3. Subject enrollment was delayed as a result of issues described above.
- c. Changes that had a significant impact on expenditures
 - i. Nothing to report

- d. Significant changes in use o care of human subjects, vertebrate animals, biohazards, and/or select agents
 - i. Nothing to report

6. PRODUCTS

Several documents were created for training purposes regarding TEG quality control and lab procedure Standard Operating Procedures:

- a. Clinical report forms, data definitions, and data dictionary for Part 1 and Part 2
- b. Data entry templates in REDCap
- c. CLOTT Part 1 training webinar
- d. CLOTT Part 2 Laboratory Standard Operating Procedures
- e. Research Lab Quality Control Standard Operating Procedures
- f. CLOTT Part 2 TEG Set-up Guide

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- a. Individuals who have worked on the project:

Prime Award at National Trauma Institute

Name	Project Role	Nearest person month worked	Contribution to the project
Mary Knudson	Principal Investigator	1	Oversight of entire project (in addition to the effort on the UCSF subaward)
Eric Vittinghoff	Biostatistician	1	Biostatistical support for the entire project (in addition to the effort on the UCSF subaward)
Ernest Moore	Co-Investigator	1	Lead site investigator for Part 2 (in addition to the effort on the Denver Health subaward)
Michelle Price	Project Manager	2	Oversight and management of daily project activities across 17 data collection sites
Lizette Villarreal	Research Coordinator	1	Assists with regulatory oversight and coordination; maintains research materials; assists with DoD report submissions
Amy Flores	Project Support	1	Manage subawards

Other Collaborating Organizations

Site	Institution	PI
1	UC San Francisco	Mary Knudson
2	Christiana Healthcare	Mark Cipolle
3	Medical College of Wisconsin	David Milia
4	Medical University of South Carolina Charleston	Bruce Crookes
5	Johns Hopkins University	Elliot Haut
6	UTHSC Houston	Michelle McNutt
7	University of Florida Health - Jacksonville	Andrew Kerwin
8	University of Florida – Gainesville	Alicia Mohr
9	Oregon Health and Science University	Laszlo Kiraly
10	Denver Health Medical System	Ernest Moore
11	University of Utah	Raminder Nirula
12	Lancaster General Hospital	Frederick Rogers
13	Stanford University	David Spain
14	University of Maryland-R. Adams Cowley Shock Trauma	Brandon Bruns
15	UC San Diego-Hillcrest	Todd Costantini
16	Massachusetts General Hospital	George Velmahos
17	Scripps Mercy Hospital	Michael Sise

8. SPECIAL REPORTING REQUIREMENTS

- a. Quad Chart – Attached

9. APPENDICES

- a. PowerPoint presentations attached

The Pathogenesis of Post-Traumatic Pulmonary Embolism: A Prospective Multi-center Investigation by the CLOTT Study Group

ERMS/Log Number: BA160400

Award Number: W81XWH-17-1-0673

PI: Mary Knudson

Org: National Trauma Institute

Award Amount: \$4,262,854



Study

1. To compare the safety of observation versus treatment of asymptomatic peripheral pulmonary clots discovered on computed tomography (CTA).
2. To define the role of post-injury fibrinolysis shutdown in the development of post-traumatic PE.

Approach

This is a multi-center, prospective, observational trial performed at 17 level I trauma centers. All injured civilian adult patients in the age range of 18-40 years will be screened and those who are found to have PE on a CTA will be enrolled. Data will be collected and uploaded into REDCap to characterize the risk factors for those with symptomatic, central PE versus those with asymptomatic, peripheral thrombi. Furthermore, five of these trauma centers will enroll a cohort of patients admitted to their ICU and collect blood samples that can be subjected to thromboelastography (TEG) in order to identify patients with failure of clot lysis (fibrinolytic shutdown).

Activities	CY	18	19
Adapt CLOTT Protocol for DoD Funded Status			
Subcontract with all study sites			
Patient enrollment			
Data Analysis and Knowledge Translation			

Updated: 10/24/2018

Landmark Clinical Trial of Post-Traumatic Pulmonary Embolism Begins Enrolling Patients

UCSF Department of Surgery at Zuckerberg San Francisco General - by Richard Barg - July 02, 2018



Peggy Knudson, MD

The CLOTT (Coalition of Leaders in Thromboembolism) study group, led by trauma surgeon [M. Margaret "Peggy" Knudson, M.D., FACS](#), has begun enrolling patients in a landmark clinical trial looking at the treatment and prevention of post-traumatic pulmonary embolism. The study, which includes investigators at 17 Level 1 trauma centers, is funded by a \$4.25M grant from the Defense Medical Research and Development Program (DMRDP).

Dr. Knudson, the study's principal investigator, is a professor of surgery and member of the UCSF Department of Surgery at Zuckerberg San Francisco



Goals/Milestones

CY18 Goal – Adapt Protocol

- ☒ Obtain IRB and HRPO approval for lead site
- ☐ Obtain IRB and HRPO approval for all sites

CY18 Goal – Subcontracts

- ☒ Sub Awards issued for all sites

CY18 and 19 Goal – Patient Enrollment

- ☐ Aim 1 enrollment completed (n=9,000)
- ☐ Aim 2 enrolment completed (n=800)

CY19 Goal – Data Analysis and Knowledge Translation

- ☐ Analyze data
- ☐ Disseminate findings

Budget Expenditure to Date

Projected Expenditure: \$2,155,129

Actual Expenditure: \$832,933

Demographic and Admission Clinical Characteristics

Record ID

Study ID.

(Please enter your two digit site specific code (provided durring initial institutional account set-up) and a four digit study specific number for this patient (determined by individual site).
Ex: 99-0044 (site = 99, pt # 0044))

Date and Time of Admission

Demographics Information

Date of Birth

Sex

☐ Female ☐ Male

Race/Ethnicity

- ☐ Caucasian
☐ African American
☐ Hispanic/Latino
☐ Asian
☐ Pacific Islander
☐ Native American
☐ Unknown Ethnicity/Other

Insurance Status

- ☐ Uninsured
☐ Private
☐ Medicaid
☐ Medicare
☐ Other

Height in meters

(1 meter = 39.37 inches)

Weight in kilograms

(1 Kg = 2.2 pounds)

Admission Vital Signs

NOTE: Please enter FIRST vital signs if patient was initially admitted to an outside hospital before being admitted to your institution.

Systolic Blood Pressure

Pulse Rate

Temperature (Celsius)

(Temp in Celsius at admission)

Admission Glasgow Coma Scale Score

Injury Characteristics

Mechanism of Injury

☐ Blunt ☐ Penetrating

Mode of Blunt Injury

- ☐ Motor Vehicle Accident
- ☐ Motorcycle Accident
- ☐ Pedestrian Struck
- ☐ Bicycle Crash
- ☐ Assault
- ☐ Fall from Height
- ☐ Other blunt (describe below)

Other Blunt Injury

Mode of Penetrating Injury

- ☐ Gunshot Wound
- ☐ Stab Wound
- ☐ Shotgun Wound
- ☐ Other penetrating (describe below)

Other Penetrating Injury

Transfusion of Cells or Procoagulants in first 24 hours

Units FFP administered

Units PRBC administered

Units platelets administered

Units whole blood administered

Units cryoprecipitate administered

Units PCC administered

PCC Product Name

Units TXA administered

- ☐ 1 gram bolus
- ☐ 1 gram infusion
- ☐ None

Date and Time of Administration of 1st Dose of TXA

Units rFVIIa administered

Date and Time of Administration of 1st Dose of rFVIIa

Admission Laboratory Data (If Available)

Date and Time of Admission Blood Draw	
Admission INR	
Admission PT	
Admission PTT	
Admission Platelet Count	
Admission Fibrinogen	
Admission Lactate	
Admission Base Deficit	

Hospital Day 1 Laboratory Data (If Available)

Date and Time of Hospital Day 1 Blood Draw	
Hospital Day 1 INR	
Hospital Day 1 PT	
Hospital Day 1 PTT	
Hospital Day 1 Platelet Count	
Hospital Day 1 Fibrinogen	

Hospital Day 2 Laboratory Data (If Available)

Date and Time of Hospital Day 2 Blood Draw	
Hospital Day 2 INR	
Hospital Day 2 PT	
Hospital Day 2 PTT	
Hospital Day 2 Platelet Count	
Hospital Day 2 Fibrinogen	

Hospital Day 3 Laboratory Data (If Available)

Date and Time of Hospital Day 3 Blood Draw _____

Hospital Day 3 INR _____

Hospital Day 3 PT _____

Hospital Day 3 PTT _____

Hospital Day 3 Platelet Count _____

Hospital Day 3 Fibrinogen _____

Operative Procedures

Operative procedures in first 24 hours

 (Please list all operative procedures requiring general anesthesia in the first 24 hours of the patient's hospital course)

Pre-Existing Risk Factors for VTE

History of Deep Vein Thrombosis ☐ Yes ☐ No

History of Pulmonary Embolism ☐ Yes ☐ No

Inferior vena cava filter in place at time of admission ☐ Yes ☐ No

Taking medication that interferes with clotting at time of admission ☐ None
☐ warfarin
☐ Xa Inhibitor
☐ Direct Thrombin Inhibitor
☐ Antiplatelet or 325mg Aspirin

History of or current known cancer ☐ Yes ☐ No

Currently pregnant or recently post-partum ☐ Yes ☐ No

Taking hormone replacement therapy (HRT) ☐ Yes ☐ No

Taking hormonal birth control ☐ Yes ☐ No

Inflammatory Bowel Disease ☐ Yes ☐ No

Injury Severity and Discharge Data

Date of Discharge	
Disposition at Discharge	☐ Alive ☐ Dead
Date of Death	
Cause of Death	
Length of ICU stay (days)	 (If the patient is in the ICU for any part of the 24 hour day, it is counted as 1 ICU day.)
Ventilator Days	
Ventilator Free Days	
Please list codes for all complications the patient experienced during care for their injuries:	
(Codes provided in the Vermont Performance Improvement Manual)	(Separate each code with a comma; enter "NONE" if none; Definitions of complications can be found in the Vermont Performance Improvement Manual (VPIM); Please use codes only for data entry.)

Abbreviated Injury Scale Scores and Injury Severity Scores

Injury Severity Score	
Maximum Head AIS	
Maximum Chest AIS	
Maximum Abdomen AIS	
Maximum Extremity AIS	
Maximum Face AIS	
Maximum Face AIS	
Probability of survival (Ps) Using the TRISS methodology	
Trauma Mortality Prediction Model Score	

Angel Catheter Placement and Removal

Was an angel catheter placed during this hospital stay?	
☐ Yes	
☐ No	
Date and Time of Placement of Angel Catheter	
Date and Time of Removal of Angel Catheter	

Rationale for Placement of Angel Catheter (select any/all that apply)

- ☐ Unable to receive full-dose anticoagulation with known DVT
- ☐ Unable to receive chemical prophylaxis
- ☐ Temporary protection during surgical procedure
- ☐ Other

Describe other rationale for placement of angel catheter:

VTE and Risk Factor Data

VTE Risk Assessment

VTE Risk Factors (check all that apply)

- ☐ Closed head injury with intracranial hemorrhage OR suspected diffuse axonal injury (Head AIS $\geq$ 3)
- ☐ Spinal cord injury with neurological deficit or paralysis
- ☐ Shock on Admission (Systolic BP < 90)
- ☐ Major chest injury (Chest AIS $\geq$ 3)
- ☐ Pelvic fracture
- ☐ Mechanical ventilation for >3 days
- ☐ Major venous injury requiring repair/ligation
- ☐ Long-bone fracture of lower extremity above ankle
- ☐ Femoral venous catheter
- ☐ Central line
- ☐ Any operative procedure under general anesthesia
- ☐ Major Abdominal Injury (AIS $\geq$ 3)
- ☐ Active infection
- ☐ None

Chest Injury Location

- ☐ R chest
- ☐ L chest

Lower Extremity Injury Location

- ☐ R leg
- ☐ L leg

Femoral Venous Catheter Location

- ☐ R groin
- ☐ L groin

Central line location

- ☐ R Subclavian
- ☐ L Subclavian
- ☐ R Internal jugular
- ☐ L Internal jugular
- ☐ R Peripherally inserted central catheter (PICC)
- ☐ L Peripherally inserted central catheter (PICC)

Active infection description

(Surgical site infection: within 30 days of procedure as defined by TQIP)

- ☐ Urinary tract infection
- ☐ Pneumonia
- ☐ Surgical site infection
- ☐ Intra-abdominal abscess
- ☐ Septicemia
- ☐ Other

Surgical site infection description

(Superficial: skin/subcutaneous tissues; Deep: muscular and fascial involvement, but not in an organ space)

☐ Superficial (skin/subcutaneous)☐ Deep (muscle/fascial)

Describe other active infection

VTE Prophylaxis

Patient received mechanical prophylaxis during hospital stay (Intermittent compression device)

(Mechanical prophylaxis includes lower extremity foot or calf intermittent compression devices. Support stockings DO NOT count.)

☐ Both legs☐ R Leg only☐ L Leg only☐ None

Patient received pharmacologic VTE prophylaxis during hospital stay

☐ Yes ☐ No

(Pharmacologic prophylaxis: drug has been ordered and patient has received at least one dose.)

Date pharmacological VTE prophylaxis initiated

Date pharmacological VTE prophylaxis discontinued

Rationale for INITIALLY withholding pharmacologic VTE prophylaxis

(See VPIM 998.11 and 998.12 for definitions of hematoma and hemorrhage.)

☐ Patient was minimally injured☐ Patient was ambulating and without significant VTE risk factors☐ Patient was discharged before prophylaxis administration☐ Patient was at risk for further bleeding☐ Patient was recovering from intracranial hemorrhage☐ Discontinued for complication of pharmacologic prophylaxis (hematoma or hemorrhage)☐ Patient received therapeutic VTE treatment☐ Other (please describe below)

Describe rationale for withholding pharmacologic prophylaxis

Agent of pharmacologic prophylaxis:

☐ Heparin☐ Enoxaparin☐ Other prophylaxis agent

Prophylactic SQ heparin dose and frequency

☐ 5000 u BID☐ 5000 u TID☐ Other (enter amount below)

Describe other dose and frequency of prophylactic SQ Heparin

Prophylactic enoxaparin dose and frequency:

☐ 30 mg BID☐ 40 mg daily☐ Other (enter amount below)

Describe other dose and frequency of prophylactic Enoxaparin

List name, dose, and frequency of other chemical prophylactic agent administered

(note (Name, Dose, Frequency))

Did the patient miss (or have held) any doses of pharmacologic prophylaxis during their hospital stay?

☐ Yes ☐ No

Why was the pharmacologic prophylaxis held/missed

- ☐ Operative/IR procedures
- ☐ Concern for bleeding
- ☐ Bleeding Complication
- ☐ Medication administration error
- ☐ Patient refused
- ☐ Other (describe below)

Please describe other rationale for missed chemical prophylaxis doses

Total number of pharmacological prophylaxis doses missed during patient's hospital stay

Complications attributed to pharmacologic VTE prophylaxis

- ☐ None
- ☐ Wound hematoma
- ☐ Hemorrhage from a recent wound
- ☐ Increased or new bleeding at site of solid organ injury
- ☐ Increased or new intracranial bleeding
- ☐ Evidence of Gastrointestinal bleeding
- ☐ Evidence of Genitourinary bleeding
- ☐ Heparin induced thrombocytopenia (HIT)
- ☐ Other

Describe complication from pharmacological VTE prophylaxis

Was chemical prophylaxis changed during patient's hospital stay?

☐ Yes ☐ No

Date of change of chemical prophylaxis regimen

Please provide rationale for changing of chemical prophylaxis:

IVC Filter Insertion and Rationale

Prophylactic inferior vena caval filter inserted during any part of hospital stay

☐ Yes ☐ No

Date of prophylactic IVC filter insertion

Type of IVC filter placed

IVC filter placed by:

- ☐ Trauma Surgeon (Trauma Service)
☐ Radiologist (Interventional Radiology Service)
☐ Vascular Surgeon (Vascular Service)

Rationale for prophylactic IVC filter insertion (can not receive pharmacologic prophylaxis because...)
(Choose all that apply.)

- ☐ Neurotrauma
☐ Repeat OR trips anticipated
☐ Spinal cord injury with paralysis
☐ Persistent coagulopathy
☐ Solid Organ Injury
☐ Spine fracture
☐ Other (please describe below)

Describe rationale for prophylactic IVC filter insertion (not otherwise listed above)

Was retrieval of an inferior vena caval filter attempted during this hospitalization?

- ☐ Never placed
☐ No
☐ Yes

If IVC filter retrieval was attempted, it was:

- ☐ Unsuccessful, patient refused
☐ Unsuccessful, failed to retrieve filter
☐ Technical success WITHOUT complications
☐ Technical success with a complication

VTE Surveillance and Diagnosis

Duplex ultrasound exam performed during hospital stay

☐ Yes ☐ No

Date of duplex ultrasound exam

Was this a surveillance exam?

- ☐ Yes
☐ No

Rationale for ordering exam (check all that apply):

- ☐ RUE swelling
- ☐ LUE swelling
- ☐ RLE swelling
- ☐ LLE swelling
- ☐ Fever of unknown origin
- ☐ RUE pain
- ☐ LUE pain
- ☐ RLE pain
- ☐ LLE pain
- ☐ Other (describe below)

Describe other rationale for ordering duplex ultrasound exam:

Duplex Ultrasound exam results

- ☐ No clot detected
- ☐ R brachial vein
- ☐ L brachial vein
- ☐ R axillary vein
- ☐ L axillary vein
- ☐ R subclavian vein
- ☐ L subclavian vein
- ☐ R tibial or peroneal vein clot
- ☐ L tibial or peroneal vein clot
- ☐ R below knee popliteal vein clot
- ☐ L above knee popliteal vein clot
- ☐ R femoral vein clot
- ☐ L femoral vein clot
- ☐ R iliac vein clot
- ☐ L iliac vein clot

Was the exam limited by wound dressings, external fixators, or other factors?

- ☐ Yes
- ☐ No

CT scan ordered during hospital stay?

- ☐ Yes
- ☐ No

CT ordered for surveillance or due to symptoms?

- ☐ Surveillance
- ☐ Symptomatic

VTE discovered on CT scan?

- ☐ Yes
- ☐ No

Location of VTE discovered on CT scan

Date of VTE diagnosis from CT Scan

How was DVT treated?

- ☐ Observation only
- ☐ IV Heparin drip
- ☐ Therapeutic anticoagulation with enoxaparin
- ☐ other anticoagulant
- ☐ conversion to Coumadin
- ☐ insertion of therapeutic IVC filter

Please describe other anticoagulant for treatment of DVT

Rationale for insertion of therapeutic IVC Filter

- ☐ Pt not a candidate for full-dose anticoagulation
☐ Bleeding complications with attempted anticoagulation
☐ Other (please describe)

Please describe other rationale for insertion of therapeutic IVC filter

CTA and PE findings

Did patient undergo INITIAL chest CTA on admission?

- ☐ Yes
☐ No

What were the findings of the admission chest CTA?

Did patient undergo subsequent CTA exams?

- ☐ Yes
☐ No

Date of CTA exam

Rationale for obtaining CTA

- ☐ Suspected PE
☐ Retained hemothorax
☐ pneumonia evaluation
☐ pneumothorax evaluation
☐ other

Symptoms of suspected PE:

- ☐ Shortness of breath/tachypnea
☐ O2 saturation decrease (5% from baseline)
☐ Tachycardia (>100 bpm)
☐ Chest pain
☐ PaO2 < 80 OR PaCO2 < 35
☐ Fever

Please describe other rationale for obtaining CTA exam:

Clots seen on CTA?

- ☐ Yes ☐ No

Location of CT-PA discovered thrombus:
((check all that apply))

- ☐ R main pulmonary artery
☐ L main pulmonary artery
☐ R lobar artery
☐ L lobar artery
☐ R segmental artery
☐ L segmental artery
☐ R sub-segmental artery
☐ L sub-segmental artery

Treatment of Pulmonary Clots

How was pulmonary clot treated?

- ☐ Observation only
- ☐ IV Heparin drip
- ☐ Therapeutic anticoagulation with enoxaparin
- ☐ other anticoagulant
- ☐ insertion of therapeutic IVC filter

Please describe other anticoagulant for treatment of pulmonary clot

Rationale for insertion of therapeutic IVC Filter

- ☐ Pt not a candidate for full-dose anticoagulation
- ☐ Bleeding complications with attempted anticoagulation
- ☐ Other (please describe)

Following insertion of the therapeutic IVC filter, please list any complications (specific to the actual insertion of the device)

(Within 24 hours of insertion)

- ☐ None
- ☐ Local Hematoma
- ☐ Local hemorrhage requiring TRANSFUSION
- ☐ Local hemorrhage requiring PROCEDURE
- ☐ DVT at insertion site
- ☐ IVC occlusion
- ☐ Device misplacement
- ☐ Other (please describe below)

Describe insertion site complication

TEG

Record ID _____

Patient ID _____

Informed Consent Obtained

☐ Yes

☐ No

PLEASE NOTE: The following laboratory values will be collected at the following intervals: 6 hours; 12 hours; 24 hours; 48 hours; 72 hours; 120 hours (5 days); and 168 hours (7 days).

Blood Draw Date and Time _____

Citrated Rapid TEG

ACT _____

MA _____

R _____

K _____

Angle _____

TMA _____

G _____

LY30 _____

CL30 _____

LY60 _____

CL60 _____

MRTG _____

TMRTG _____

TG _____

MRL _____

TMRL _____

L _____

Citrated Kaolin TEG

ACT	_____
MA	_____
R	_____
K	_____
Angle	_____
TMA	_____
G	_____
LY30	_____
CL30	_____
LY60	_____
CL60	_____
MRTG	_____
TMRTG	_____
TG	_____
MRL	_____
TMRL	_____
L	_____

Citrated Kaolin TEG with tPA

ACT	_____
MA	_____
R	_____
K	_____
Angle	_____
TMA	_____
G	_____
LY30	_____
CL30	_____
LY60	_____
CL60	_____

MRTG	
TMRTG	
TG	
MRL	
TMRL	
L	

Citrated Native TEG

ACT	
MA	
R	
K	
Angle	
TMA	
G	
LY30	
CL30	
LY60	
CL60	
MRTG	
TMRTG	
TG	
MRL	
TMRL	
L	

Citrated Native TEG with tPA 75 ng/ml

ACT	
MA	
R	
K	
Angle	

TMA	
G	
LY30	
CL30	
LY60	
CL60	
MRTG	
TMRTG	
TG	
MRL	
TMRL	
L	

Citrated Native TEG with tPA 150 ng/ml

ACT	
MA	
R	
K	
Angle	
TMA	
G	
LY30	
CL30	
LY60	
CL60	
MRTG	
TMRTG	
TG	
MRL	
TMRL	
L	

Vte And Risk Factor Data

DVT Surveillance

PLEASE NOTE: For patients enrolled in this substudy, there is only ONE required surveillance ultrasound exam on Hospital Day 3. Data for this ultrasound exam will be collected at the 72 hour time point with pertinent laboratory data for that interval.

Date of duplex ultrasound exam _____

Rationale for ordering exam (check all that apply):

- ☐ RUE swelling
- ☐ LUE swelling
- ☐ RLE swelling
- ☐ LLE swelling
- ☐ Fever of unknown origin
- ☐ RUE pain
- ☐ LUE pain
- ☐ RLE pain
- ☐ LLE pain
- ☐ Other (describe below)

Describe other rationale for ordering duplex ultrasound exam: _____

Duplex Ultrasound exam results

- ☐ No clot detected
- ☐ R brachial vein
- ☐ L brachial vein
- ☐ R axillary vein
- ☐ L axillary vein
- ☐ R subclavian vein
- ☐ L subclavian vein
- ☐ R tibial or peroneal vein clot
- ☐ L tibial or peroneal vein clot
- ☐ R below knee popliteal vein clot
- ☐ L above knee popliteal vein clot
- ☐ R femoral vein clot
- ☐ L femoral vein clot
- ☐ R iliac vein clot
- ☐ L iliac vein clot

Was the exam limited by wound dressings, external fixators, or other factors?

- ☐ Yes
☐ No

How was DVT treated?

- ☐ Observation only
- ☐ IV Heparin drip
- ☐ Therapeutic anticoagulation with enoxaparin
- ☐ other anticoagulant
- ☐ conversion to Coumadin
- ☐ insertion of therapeutic IVC filter

Please describe other anticoagulant for treatment of DVT _____

Rationale for insertion of therapeutic IVC Filter

- ☐ Pt not a candidate for full-dose anticoagulation
- ☐ Bleeding complications with attempted anticoagulation
- ☐ Other (please describe)

Please describe other rationale for insertion of therapeutic IVC filter



CLOTT

Laboratory Procedures

First, Turn on both centrifuges to allow to cool down

Bring all reagents out of refrigeration and allow to reach room temperature
Check reagent expiration dates

The following reagents are required at each time point:

QTY 1: Kaolin Vial

QTY 1: tPA vial (high dose, 75 ng in vial, Red label)

CaCl₂

Once the centrifuge has reached the programmed temperature (4°C)
blue top citrate tube (on ice) are placed in centrifuge and spin cycle begun

Turn on Teg analyzers and open the Teg Analytical software

Check the balance bubble on the top of the analyzers to verify they are balanced

Use "site Administrator" as the user and "teg" as the password (lowercase)

CLOTT TEG Databases will be created differently depending on what works best for you site,
Denver Health will create a separate database for each individual patient and will contain every
TEG tracing for all time-points for each individual patient.

Log in as "operator" using your personal password
Click on the Teg icon at the upper right of the screen
Follow instructions on screen to perform the e-test

The patient's study ID will be entered into the TEG software, either type in the
Study ID in the "patient name" field or select the study ID from the drop down by selecting
the arrow to the right of the "patient name" field

Do not enter any PHI in the TEG software

For "sample description" field, enter the information in **EXACTLY** the following format:

Time point (Hour 6, Hour 12, Hour 24 etc.)

For channel 2: add " + tPA 150" after the time point. Be sure to insert a space before and after
the "+" -example: "Hour 6 (space) + (space) tPA 150"

THIS SCREENSHOT IS AN EXAMPLE OF HOW CLOTT DESCRIPTIONS SHOULD LOOK:
(Note that Channel 3 is selected)

Channel	Patient name	
ST	Sample description	
1	C-001	
CK - C	Hour 6	
2	C-001	
CK - C	Hour 6 + tPA 75	
3	** Select **	
-- - No		
4	** Select **	
-- - No		
5	** Select **	
-- - No		
6	** Select **	
-- - No		
7	** Select **	
-- - No		
8	** Select **	
-- - No		
Active	Pending	Selected

Seat all channels with cups and pins

Place cup and pin in the carrier

Hold one hand on the top of the analyzer, slide the carrier up and push the bottom button at least twice to attach the pin to the analyzer

Lower the carrier (now only containing the cup) to just above the magnetic tray below

Push the cup firmly into the carrier

All the tests that are performed on this bank of TEG analyzers use blood from a [blue top citrate](#) tube so all channels require 20 mL of CaCl₂ to counteract the citrate preservative.

The TEG Channels on the primary bank of analyzers will always be set-up the same way:

1 Citrated Kaolin (CK)

2 Citrated Kaolin (CK)

In this channel, indicate " + tPA 150" in the sample description field

The following reagents and materials will be used for the TEG analysis

1 CK Citrated Kaolin Channel

Use [Blue top Citrate Tube](#)

20 mL CaCl₂

One Kaolin vial

340 mL whole blood

2 CK Citrated Kaolin with tPA 150 Use [Blue top citrate Tube](#)

20 mL CaCl₂

1 Kaolin vial (same vial as used on channel 2)

One tPA 75 ng vial

340 mL whole blood

All TEG assays that are run from the [blue top citrate tube](#) require 20 mL CaCl₂ in the cup

Run all research lab assays in the order as described on the following pages

1 CK Citrated Kaolin

Use [Blue top Citrate Tube](#)

20 mL CaCl₂ in the cup

1 mL whole blood into the Kaolin vial

Invert the vial gently 10 times

340 mL from the vial into the cup

Mix 3 times with the pipette, activate channel by pushing F10

2 CK Citrated Kaolin with 75 ng/mL

tPA Use [Blue top Citrate Tube](#)

20 mL CaCl₂ in the cup

Pipette 500 mL from the Kaolin vial into the tPA 150 vial

Invert this vial gently 10 times

340 mL from the vial into the cup

Mix 3 times with the pipette, activate channel by pushing F10

The **OPENED** blue top citrate tube (used for TEG assays) and the **UNOPENED** blue top citrate tube may now be placed in the centrifuge to spin for Platelet Poor Plasma following your specific site's specifications.

DIRECTIONS FOR PLATELET POOR PLASMA (Following Denver Health's Processing SOPs)

The same instructions apply for processing all tubes. *Note, your specific site may do this differently*

First Spin:

Large Centrifuge: 1,000g / 15 Min / 4°C

After the program is complete the centrifuge will beep

Carefully draw off the plasma into an Eppendorf tube (do not disturb the red cells on the bottom)

Second Spin:

Micro Centrifuge: 12,600g / 6 Min / 4°C

After the program is complete the centrifuge will beep

Carefully draw off the plasma into an Eppendorf tube

These are aliquotted in 500mL volumes in as many aliquots as you can make. Any left-over plasma can be put into the last tube and noted in the Sample Tracking Log as **500+**

As soon as complete, immediately put in the liquid nitrogen to flash-freeze or into the -80 freezer depending on your site's specifications.

DATA ENTRY TEG

The results are displayed on the screen and can be printed out for convenience

To print: select a tracing, select "report" icon, and after on screen report is generated, select "print"

STUDY DATABASES

Results from TEG tracings should be put into the REDCap database

CLOTT SOP			
STUDY LOCATION:	Denver Health and Hospital Authority and University of Colorado-Denver		
SOP TITLE:	Quality Controls-Trauma Research Laboratory		
SOP DATE:	4/2/2018	SOP VERSION:	1

PURPOSE: This Standard Operating Procedure (SOP) describes the processes and procedures for completing quality controls on equipment in the Trauma Research Laboratory.

POLICY: The research coordinator and research assistants will understand the proper policies and procedures for performing quality controls (QCs) on all laboratory equipment and for maintaining, cleaning, and troubleshooting machines on a weekly basis.

RESPONSIBILITY: All CLOTT Study research personnel

PROCEDURE:

1. TEG machines need QCs run weekly to maintain their effectiveness, precision, and accuracy.

- a. TEG QCs involve the following checks:
 - a. Ensure the analyzer is level
 - b. Clean the column of any dried blood
 - c. Ensure the ribbon cable is fully inserted into the connectors on the back of the carrier and that the ribbon has no kinks in it.
 - d. Ensure the temperature reading is 37.0 ± 0.5 (or within half a degree of the set point to which the temperature was adjusted).
 - e. Perform an eTest, and ensure the *Min* and *Max* fields values that display fall between the acceptable range of 1800 and 2300. The ideal reading is between 1950 and 2050.
 - f. Check the Level I and Level II reference ranges
 - g. Run Level I controls and Level II controls
 - h. Level I and Level II Troubleshooting

2. For detailed instructions on performing each of the above tasks, see the corresponding letter below.

- a. To ensure the analyzer is level:
 - i. Adjust the front and back leveling legs until the bubble is centered within the smallest circle on the leveling bubble on the top of the analyzer.
- b. If the column is dirty (dried blood, etc.), clean the column of any dried blood:
 - i. Use the dental mirror located in the supply cabinet to visualize the column. If there is any dried blood on it, the column must be cleaned.
 - ii. Get a Q-tip or cotton swab and Hydrogen Peroxide. Dip the Q-tip in the peroxide and, using a little force, clean the inside of the column until there is no blood on it.
 - iii. Dry the column, and ensure there is no blood remaining
- c. To ensure the ribbon cable is fully inserted into the connectors

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- i. The writing on the ribbon cable should be facing upward toward the column.
 - ii. Check that there are no kinks and that the cables are not twisted.
 - iii. If there are twists or kinks in the ribbon, it should be replaced.
- d. To ensure the temperature reading is correct
 - i. Check that “Bad” does not appear on the temperature controller and that the temperature reading is 37.0 ± 0.5 (or within half a degree of the set point to which the temperature was adjusted).
 - ii. For temperature troubleshooting information, see below:

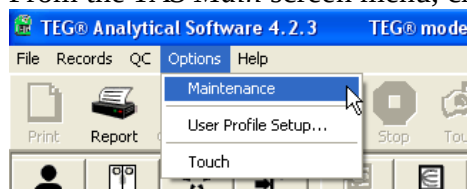
Temperature errors

Problem	Possible cause	Recommended action
<i>The temperature readout is flashing “BAD.”</i>	The ribbon cable is loose.	Check that the ribbon cable connections between the carrier and the analyzer are tight.
	The ribbon cable and/or carrier is dirty.	Clean the carrier and ribbon cable with alcohol.
	The carrier or ribbon cable is damaged or defective.	Contact TEG System Technical Support.
<i>The temperature is high or there is a jump in temperature.</i>	The ribbon cable is loose.	Check that the ribbon cable connections between the carrier and the analyzer are tight.
	The ambient temperature is fluctuating.	Make sure that the analyzer is not in front of a window or by an air duct.
	There is a loose connection inside the temperature controller.	Contact TEG System Technical Support.
	The temperature controller is defective.	Contact TEG System Technical Support.
<i>The temperature stays at room temperature and will not heat up to 37.0 degrees.</i>	The ribbon cable is loose.	Check that the ribbon cable connections between the carrier and the analyzer are tight.
	The ribbon cable and/or carrier is dirty.	Clean the carrier and ribbon cable with alcohol.
	The carrier or ribbon cable is defective.	Contact TEG System Technical Support.
	The temperature controller is defective.	Contact TEG System Technical Support.

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<i>The temperature readout is not at 37.0 degrees $\pm$ 0.5.</i>	The temperature set point was changed.	Reset the set point to 37.0 degrees.
---	--	--------------------------------------

- e. To perform an eTest:
- Log into the TEG software (TAS)
 - From the *TAS Main* screen menu, choose **Options > Maintenance**

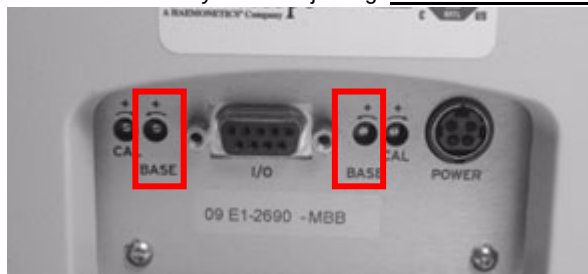


- The *Maintenance* screen appears with the **Daily Maintenance** tab selected by default. Select a row for a connected channel and click **eTest**. Repeat for all connected channels.
- On the analyzer(s), move the levers to Test
- Check the *Min* and *Max* fields to make sure the values that display fall between the acceptable range of 1800 and 2300. The ideal reading is between 1950 and 2050. Print out the eTest (if it needs to be calibrated, print the report out after calibrating), and file it in the binder in the lab.
 - If the eTest min/max values are not in the acceptable range, see below:**

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Adjusting the eTest Baseline

1. Make sure the **Daily Maintenance** tab is displayed in the TEG Analytical Software and that eTest has been performed on the channel.
2. Without moving the analyzer, locate the potentiometer adjustment screw labeled BASE on the back of the analyzer (USE THE DENTAL MIRROR) that corresponds to the channel that you are adjusting. **NEVER ADJUST THE CAL SCREW!**



3. Use the trimmer adjustment tool (the blue screw-driver tool in the study cabinet) to turn the BASE screw in one of the following directions:
 - In the direction of the arrow to *increase* the eTest reading.
 - In the opposite direction of the arrow to *decrease* the reading.

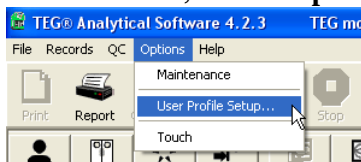
Wait 15 seconds to allow the readings to stabilize after each adjustment.
4. Adjust the BASE screw to bring the eTest *Min* value between 1950 and 2050.
5. Repeat steps 1-4 for each channel that is being adjusted

Note: If the eTest baseline still remains out of range after adjusting the potentiometer adjustment screw(s), contact TEG System Technical Support.

- vi. To print the eTest:
 - i. Click "Report"
 - ii. Enter the date you are running QC's
 - iii. Press "Print"
 - iv. Write the bank of the TEG machines on the top of the page along with your initials, and file it in the binder on the counter.

f. Checking or changing reference ranges (new lot numbers) before running a Level I and/or a Level II sample:

- i. From the TAS Main screen, choose **Options > User Profile Setup**.



- ii. In the User Profile Setup screen, click the **Normal values** tab.

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- iii. In the Select Sample type drop-down list, select the sample type for which you want to update reference ranges.
- iv. Using the information provided in the insert, complete the following fields for each test parameter:

Field	Description
Low Value	Click this field and enter the corresponding number for each test parameter.
High Value	Click this field and enter the corresponding number for each test parameter.

- v. Click **Done**.

g. Running Controls

- i. Reconstitute one vial of Level I control material. Follow the instructions on the product insert in the control kit.
- ii. In the *TAS Main* screen, click . The *TEG* screen displays.
- iii. Complete the following fields in the two channel sections that correspond to the analyzer:

CHANNEL: Already pre-filled
ST: Select “L1-Level I control”
Patient Name: Type the lot number of the vial
Sample description: Enter the date (MM/DD/YYYY) and your initials

- iv. Load the cups and pins
- v. Pipette 20 microliters of calcium chloride (CaCl₂) into each cup.

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- vi. Pipette 340 microliters of reconstituted Level I control into each cup.
- vii. Quickly but carefully raise the carriers until they are flush with the bottom of each column.
- viii. Move the levers to Test
- ix. Press F10 on the computer

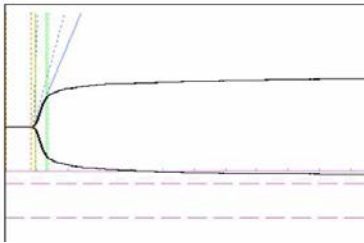
Running Level II controls: Follow steps i-ix in section “g,” but use the Level II reagents. Remember to ensure the control ranges for the lot number are correct (follow section “f”)

- h. Level I and Level II troubleshooting:

Quality control (Level I and Level II) sample errors

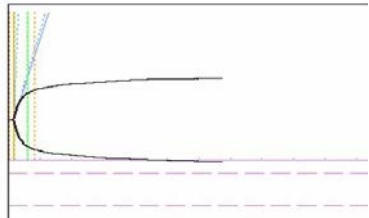
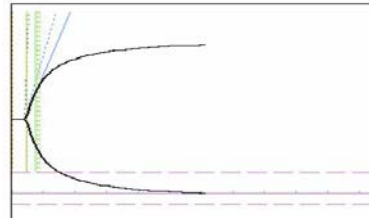
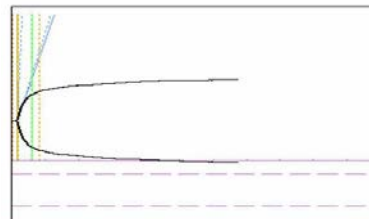
Problem	Possible cause	Recommended action
<i>The quality control samples are missing.</i>	The database was closed and all the QC samples were transferred to the QC	From the <i>TAS Main</i> screen menu, choose QC > Go To to open the QC database.
	The software is configured to transfer the samples after they terminate, so it is possible that the samples transferred without the database being	From the <i>TAS Main</i> screen menu, choose QC > Go To to check if the samples transferred.
<i>When trying to enter a new lot number the screen to enter a new patient appears.</i>	The sample type was not set to L1 or L2.	From the <i>TAS</i> screen, go to the sample type (ST) field and select either L1 or L2 , whichever is appropriate.

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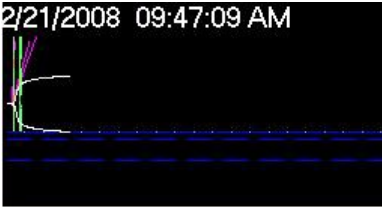
One or more parameters are out of range.	Consider the following common causes: 6. Hardware problems. 7. Quality control sample problems. 8. Operator error.	Do the following: 1. Check the temperature (refer to "Temperature errors" on page A-18). 2. Ensure the analyzer is level. 3. Rerun the control sample: - Make sure the cups and pins are loaded correctly (refer to "Loading and Ejecting Cups and Pins" on page 7-14), avoiding contamination of their surfaces. - Reconstitute a new vial of quality control material, carefully following the instructions on the
Elongated R time. 	The analyzer is out of spec.	Contact TEG System Technical Support.
	The carrier is not raised.	Make sure the carrier is fully raised.
	Calcium and or/activator were pipetted or reconstituted incorrectly or	Prepare another sample and rerun the test.
	The cup/and or pin were loaded incorrectly.	Make sure the cup and pin are pushed firmly into place (refer to "Loading and
	The sample temperature is incorrect.	Check the temperature (refer to "Temperature errors" on page A- 18).
Shortened R time. 	Pipetting was inaccurate and/or the sample was prematurely activated.	Prepare another sample and rerun the test.
	The sample temperature is incorrect.	Check the temperature (refer to "Temperature errors" on page A- 18).

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<i>K is out of range.</i> 	Calcium and or/activator were dispensed incorrectly or are contaminated.	Prepare another sample and rerun the test.
	The sample temperature is incorrect.	Check the temperature (refer to "Temperature errors" on page A- 18).
<i>Angle is out of range.</i> 	The analyzer is out of spec.	Contact TEG System Technical Support.
	There was an electrical disruption to the analyzer.	Rerun the test.
	The sample temperature is incorrect.	Check the temperature (refer to "Temperature errors" on page A- 18).
<i>MA is out of range.</i> 	The analyzer is out of spec.	Contact TEG System Technical Support.
	The carrier is not flush with the lower column.	Ensure that the carrier is fully raised.
	The cup and/or pin were loaded incorrectly.	Make sure the cup and pin are pushed firmly into place (refer to "Loading and Ejecting Cups and Pins" on
	The analyzer is not level.	Use the bubble level at the top of the analyzer and the leveling feet to ensure that the analyzer is level.
<i>MA in one channel is out of range after running multiple control samples.</i>	The analyzer is out of spec.	Contact TEG System Technical Support.
<i>The MA in both channels is either low or high.</i>	The analyzer is not level.	Use the bubble level and the leveling feet to ensure the analyzer is level.
<i>R and Angle are out of range, MA is within limits.</i>	The sample temperature is incorrect.	Check the temperature (refer to "Temperature errors" on page A- 18).
<i>R in one channel is very short and the MA is very large, while the MA in the other channel is very small.</i>	The analyzer is not level.	Use the bubble level at the top of the analyzer and the leveling feet to ensure that the analyzer is level.

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SOP TITLE:	Quality Controls-Trauma Research Laboratory		
SOP DATE:	4/2/2018	SOP VERSION:	1

Parameter values are out of range according to the insert, but not according to the software.	For R and K, TAS may be reporting the units in millimeters (mm) and the insert reports the units in minutes or seconds.	Convert the mm to minutes, remembering that 2mm=1 minute . Convert the mm to seconds if this is the protocol at your site.
	You may have used a new lot that has different reference ranges.	Enter the current reference ranges from the product insert into TAS.
Unexpected tracing for Level I. 	Level I control was placed in the sample cup but "L2" was selected as the sample type in the software.	Do the following: 1. Confirm that the wrong sample type was selected in the software. 2. Select the correct sample type.
Unexpected tracing for Level II. 	Level II control was placed in the sample cup but "L1" was selected as the sample type in the software.	Do the following: 1. Confirm that the wrong sample type was selected in the software. 2. Select the correct sample type.

3. Other Weekly Quality Control Tasks

- a. Liquid Nitrogen Check
 - i. Check the level of liquid nitrogen. Note the level of the liquid nitrogen on the QC Log hanging on the bulletin board.
- b. Checking Lab Refrigerators
 - i. Check the refrigerators in the lab to ensure they are functioning properly. If they are not, take immediate action.
- c. Checking Lab Freezers
 - i. Check the freezers in the freezer room to ensure they are functioning properly. If they are not, take immediate action.
- d. Fill out the chart in the lab
 - i. Record that you performed each of the above tasks on the QC chart. Be sure to note any inconsistencies, defects, machine failures, etc.

4. Important Contacts

CLOTT SOP			
STUDY LOCATION:	Denver Health and Hospital Authority and University of Colorado-Denver		
SOP TITLE:	Quality Controls-Trauma Research Laboratory		
SOP DATE:	4/2/2018	SOP VERSION:	1

- a. TEG
 - o TEG® System Technical Support is available 24 hours per day, 7 days per week at 1-800-GET-A-TEG® (800-438-2834).
- b. Biomed (for lab freezers)
 - o Ext. 22425 or 303-826-4142

CLOTT

TE

1

CK

Citrated Kaolin

Use **Blue top Citrate Tube**

20 mL CaCl₂ in the cup

1 mL whole blood into the Kaolin vial

Invert the Kaolin vial gently 10 times

340 mL from the vial into the cup

Mix 3 times with the pipette, activate channel by pushing F10

2

CK

Citrated Kaolin with tPA 150

Use **Blue top Citrate Tube**

20 mL CaCl₂ in the cup

Use the same kaolin vial as from channel 2 (660 mL remaining)

Take 500 mL from the Kaolin vial and place in the tPA 37.5 ng

Invert this vial gently 10 times

340 mL from the tPA vial into the cup

Mix 3 times with the pipette, activate channel by pushing F10

G Setup Guide

g)
3 / 500 mcL vial

The Pathogenesis of Post- Traumatic Pulmonary Emboli

THE CLOTT STUDY GROUP

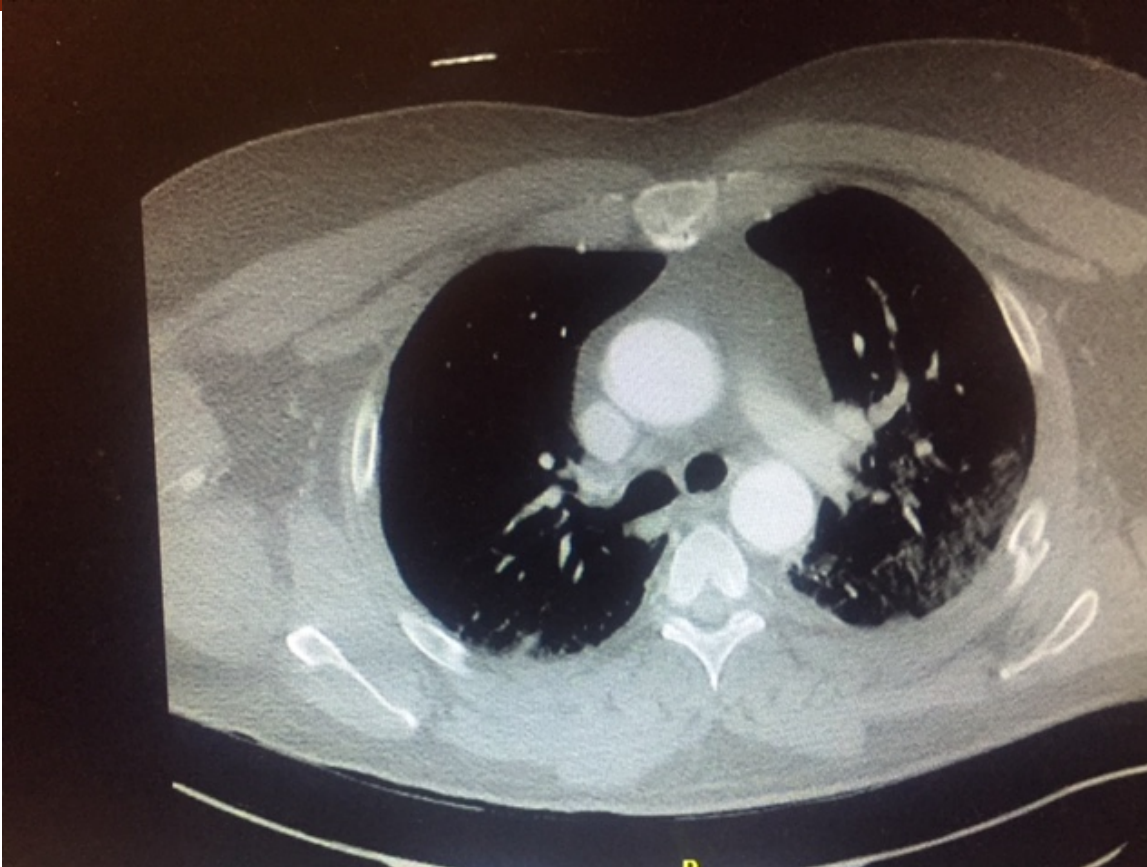


A CASE IN POINT

- 42 y/o “large” man: MCC-hit several cars, separated from bike
- BP normal on arrival, tachycardic
- Multiple open fractures, bilateral acetabular fxs; femur fx
- Degloving injuries: abdominal wall, lower extremity
- CT Head: DAI, subarachnoid hemorrhage
- CT Chest on admission: **right rib fxs 1-7; left 8-10**
- Multiple filling defects: right upper lobe, left segmental upper and lower lobes: “thrombi”
- Hypoxia during initial operating room procedures



Initial CTA

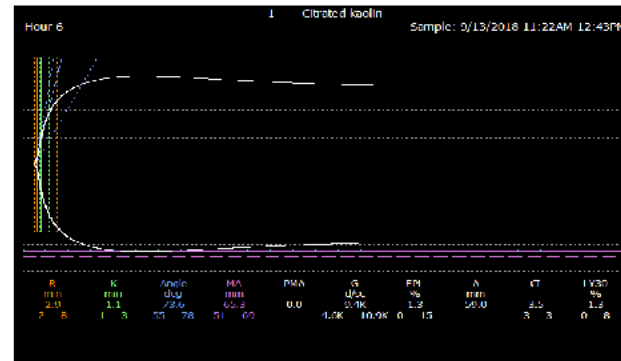
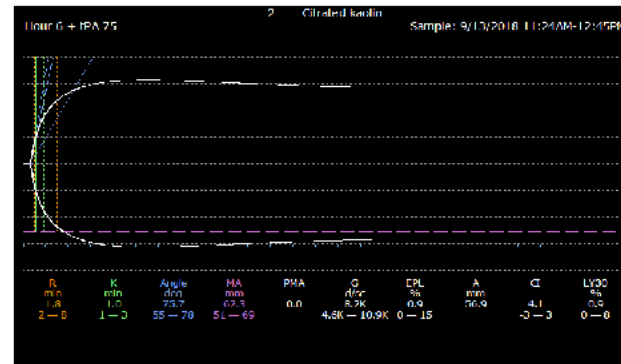


Duplex of lower legs (limited)-negative; left axillary clot



Initial TEG images: kaolin and TPA

■



Timeline: CLOTT Grant

- Grant submitted through BAA process: August 2016
- Received funding announcement: April 2017 (score 2/5)
- Contract sent to NTI/official start date: **September 30, 2017**
- IRB approved at UCSF (both Parts): September 2017
- HRPO approved UCSF application Part 1: November 2017
- Executed contract NTI-UCSF: November 2017
- HRPO approved UCSF application Part 2: February 2018
- Hiring of UCSF CRC, CRF perfected/REDCap (Jan-March)
- First patient enrolled at UCSF: March 19, 2018
- CRC Training Sessions via UCSF webinar and Denver hands-on



Background/Scientific Rationale: Part 1

- The incidence of pulmonary clots continues to rise despite VTE prophylaxis
- Many of these clots are discovered incidentally in asymptomatic patients with the liberal use of CTA of the chest
- There is an association between chest trauma and pulmonary clots
- These clots may be primary thrombi and not embolic
- Observed in both civilian and military trauma patients



Study Hypotheses/Aims: Part 1

- Main Hypothesis: Peripheral asymptomatic pulmonary thrombi (PT) seen on chest computed tomography can be safely observed
- Secondary Hypothesis: Risk factors for asymptomatic PT will differ from risk factors for symptomatic PE with or without deep vein thrombosis (DVT)
- Aim 1: To compare the safety of observation versus treatment of asymptomatic peripheral pulmonary thrombi discovered on CTA
- Aim 2: To evaluate the efficacy of various prophylactic measures in their ability to prevent PE
- Aim 3: To determine the magnitude of surveillance bias on the incidence of PE based on the frequency of chest CTA utilization



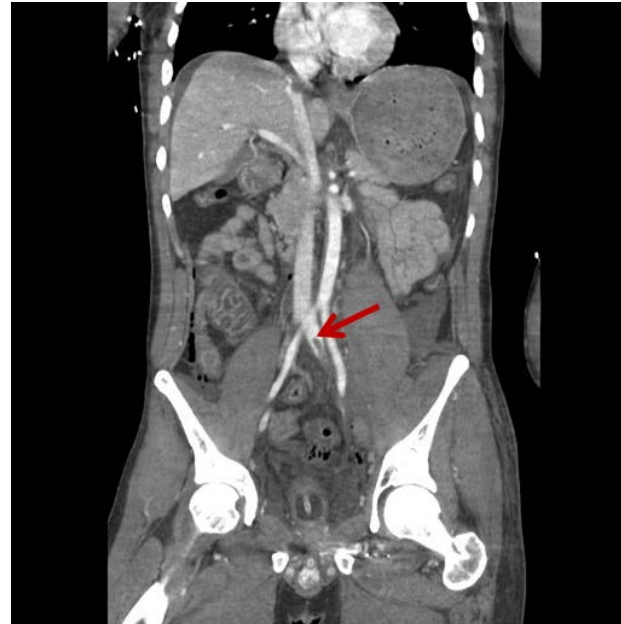
Study Design: Part 1

- Pragmatic, prospective, multi-center, observational study (2 years)*
- ALL Injured patients with identifiable risk factors for VTE enrolled
- **Must meet age range of combat eligible (18-40 years)**
- Data collected on CRF previously designed
- Entered into UCSF REDCap
- VTE risk factors: fractures, major injuries to abdomen, chest, head, spine; venous injuries, shock, ventilator dependence
- **Extensive data: VTE prophylaxis drugs, doses, missed doses etc.**
- Assess the reason for obtaining CTA where PT discovered!!
- Treatment of PT left to the treating physician
- * One year no-cost extension allowed



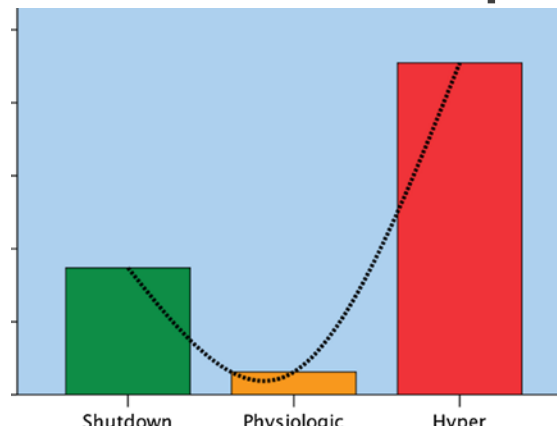
Outcomes of Interest: Part 1

- Major outcome of interest: the presence, extent and location of any clot seen on CTA
- Secondary outcome: presence of DVT in association with PT
- Secondary outcome: the frequency of obtaining chest CTA at each center (surveillance bias)



Background Part 2

- Patients who are coagulopathic after injury are also more likely to develop VTE (Knudson et al J Trauma 1992)
- Recent studies using TEG have demonstrated that critically injured patients frequently exhibit inability to **lyse clot** (Moore et al)
- Both coagulopathic and hyper-coagulable states associated with increased mortality
- The degree of lytic failure can be quantified by TPA-TEG assays



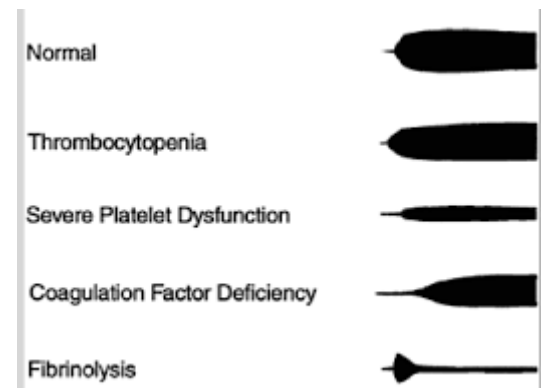
Study Hypothesis and Aims: Part 2

- **Main Hypothesis:** Fibrinolytic shutdown after injury will be detected frequently in critically injured patients
- **Secondary Hypothesis:** Fibrinolytic shutdown is associated with an increased incidence of VTE after injury
- **Aim 1:** To describe the incidence of and the timing for the development of fibrinolytic shutdown in critically injured patients
- **Aim 2:** To identify the risk factors for the development of fibrinolytic shutdown after injury
- **Aims 3:** To investigate the association between fibrinolytic shutdown and the development of DVT and/or PE



Study Design: Part 2

- Patients evaluated at 5 CLOTT centers with coag research labs
- Eligible patients: admitted to ICU with major risk factors
- Serial blood draws for standard and specialized TPA TEG studies over 7 days
- Single surveillance duplex exam: DVT
- Same CRF as in Part 1 with addition of lab values
- Blood samples stored for PAI-1 levels and other studies



Human Subjects Protection Update – September 2018

- **CLOTT Part 1 – Fifteen sites have IRB and DoD Human Research Protection Office (HRPO) approval. Two sites have IRB and are pending HRPO approval.**
- **CLOTT Part 2 – Four sites have IRB and HRPO approval. One site is pending IRB and HRPO approval**
- **All CLOTT sites have Data Transfer Use Agreements in place with UCSF**

Enrollment At One Year: Part 1

- | Center | # Enrolled | # Completed |
|------------------------|------------|-------------|
| UCSF | 147 | 51 |
| U Texas Houston | 234 | 0 |
| U. Maryland | | |
| UCSD | 70 | 10 |
| Stanford | 33 | 31 |
| Denver | 167 | 67 |
| Utah | 77 | 71 |
| U. Florida Gainesville | 58 | 50 |
| MC Wisconsin | 3 | 1 |
| Scripps | 122 | 0 |
| Christianacare | 30 | 11 |



Enrollment at One year: Part 1

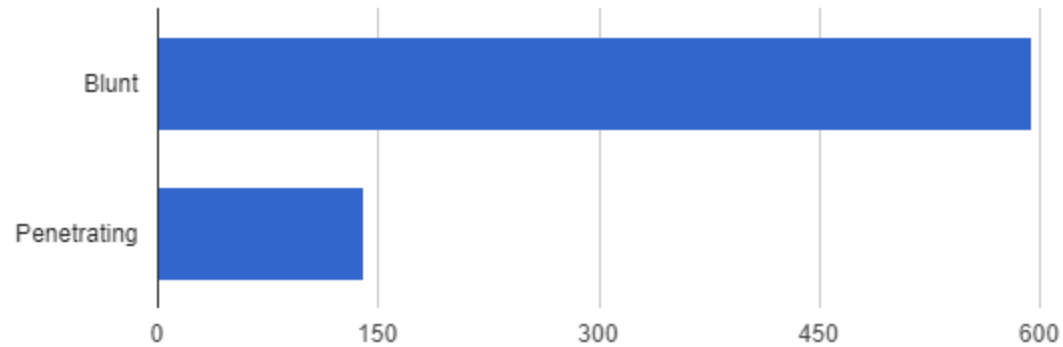
Center	# Enrolled	# Completed-REDCap
Hopkins		
U. Florida-Jacksonville	83	76
Lancaster General	62	41
MGH	21	10
Oregon HSC	73	0
MUSC		
Total # Patients	1,180	419



- Note: Four/five sites have started enrollment into Part 2
- Requires patient/family consent; limited TPA supply until recently



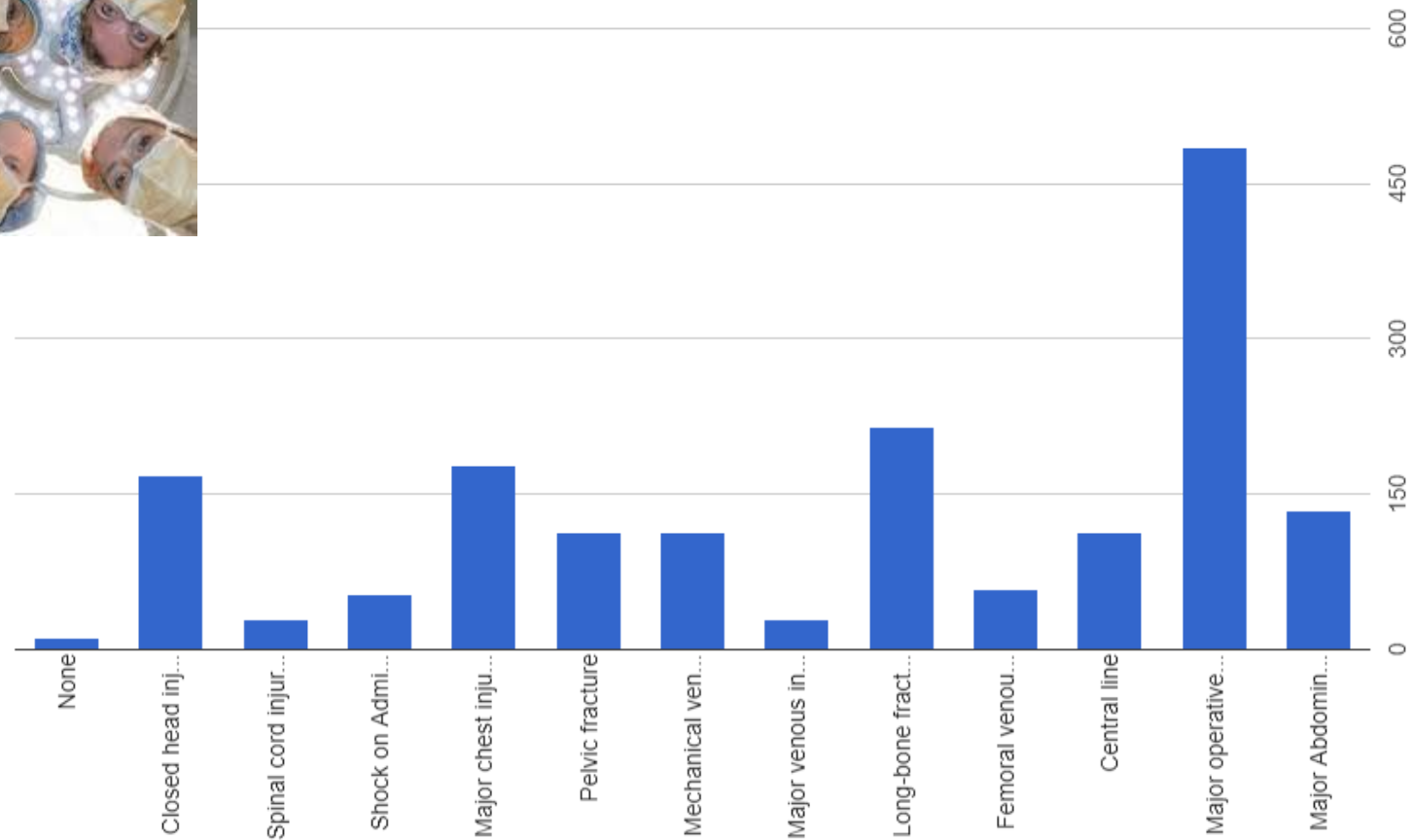
Preliminary Data: Mechanism of Injuries



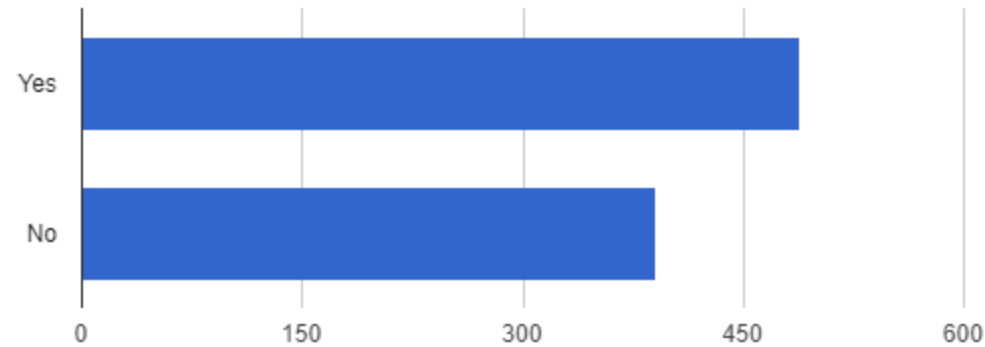
81% Blunt; 60% of penetrating: Firearms



VTE Risk Factors



Number of patients missing at least one dose



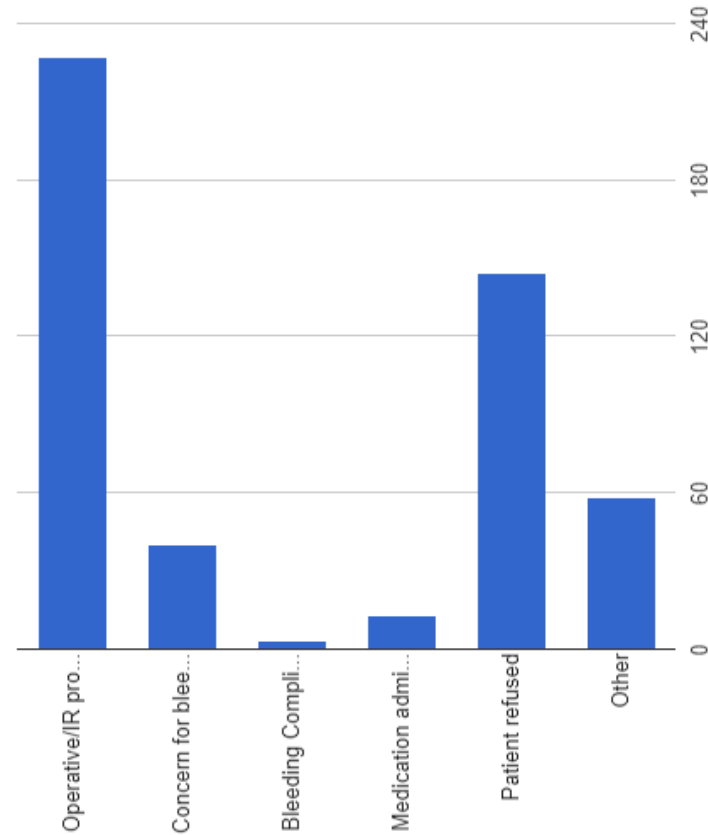
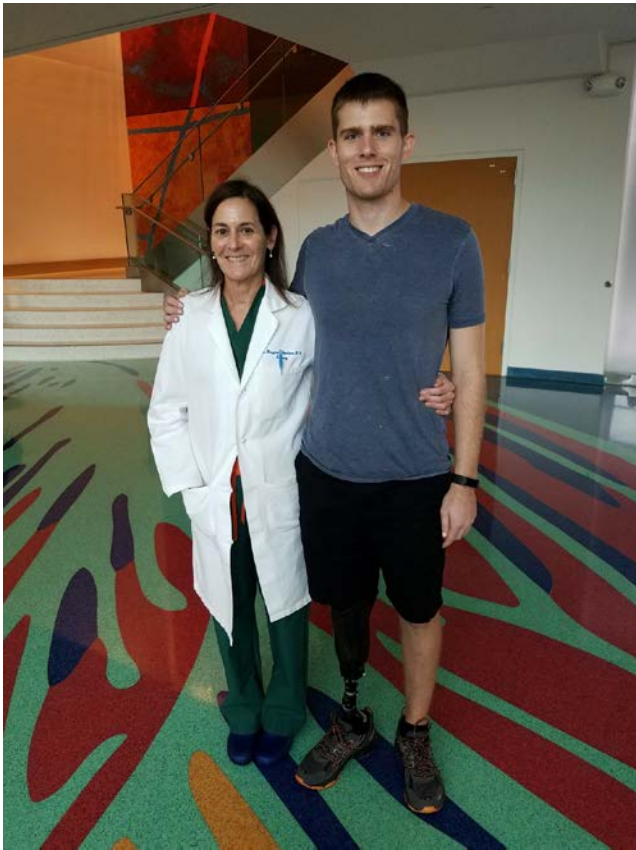
Complications with Inferior Vena Cava filter?

- Fracture or Migration of the IVC Filter
- Perforation of Heart, Lung, or Vena Cava
- Hemorrhage



Received chemical prophylaxis (87% enoxaparin)
Over 80% missed at least one dose
9 prophylactic filters

Reasons for holding chemical prophylaxis



DVT Data

Based on 1030 patients with data entered

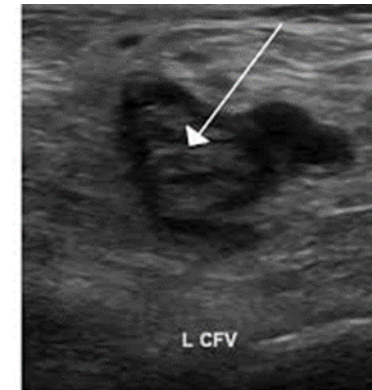
Number with DVT=32 (3.1% rate)

- 11 detected on surveillance (34.3%)

- 15 symptomatic (46.9%)

- 6 not listed

Average time to detection: 7.85 days



Pulmonary Embolism

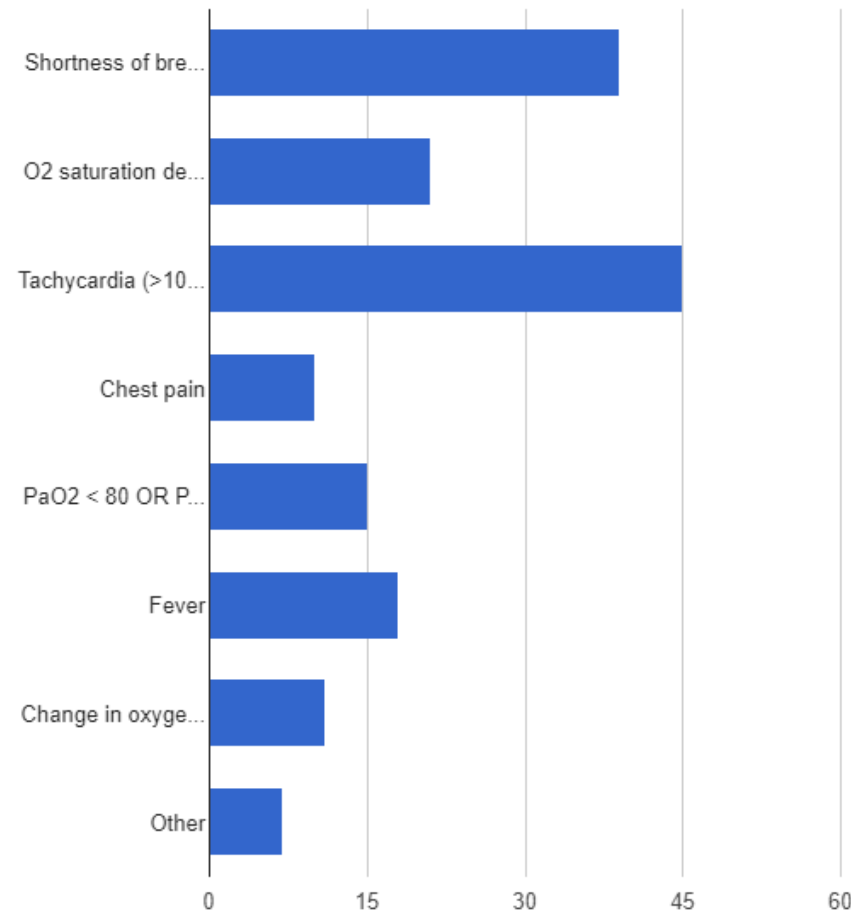
Number=20 (1.9% rate)

7-surveillance (35%)

9-symptoms (45%)

4-not listed

Average day to detect: 6



With gratitude to ALL for Patience and Persistence

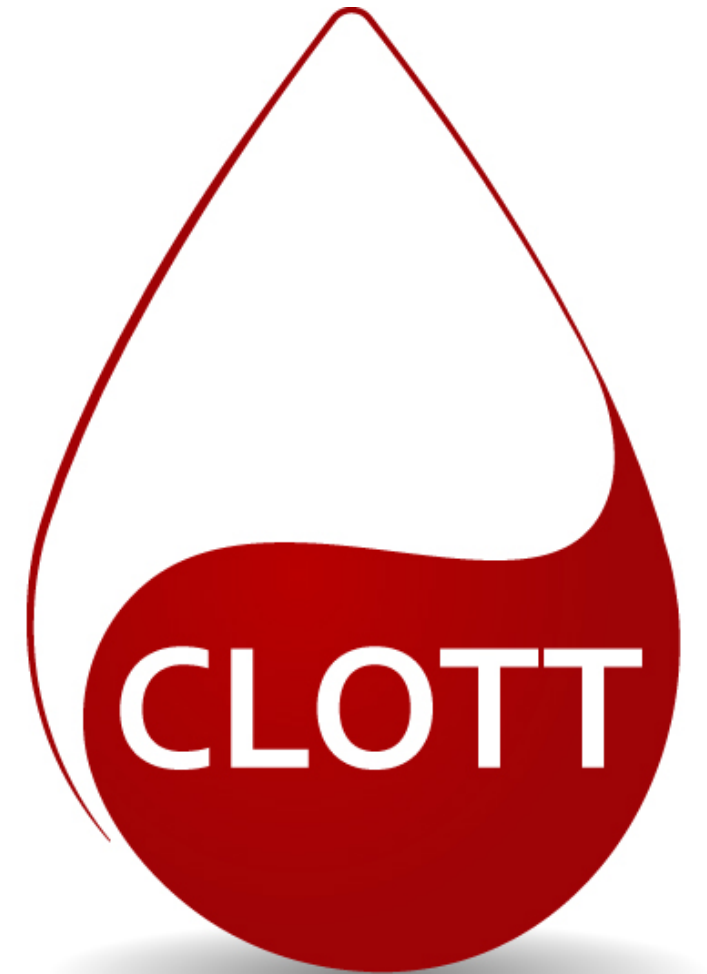


Assessing Platelet Aggregation in Post-Traumatic VTE

Phase 2 Addition, CLOTT Study Group

Lucy Zumwinkle Kornblith, MD
Assistant Professor of Surgery, In Residence
University of California San Francisco
Zuckerberg San Francisco General Hospital

September 28, 2018



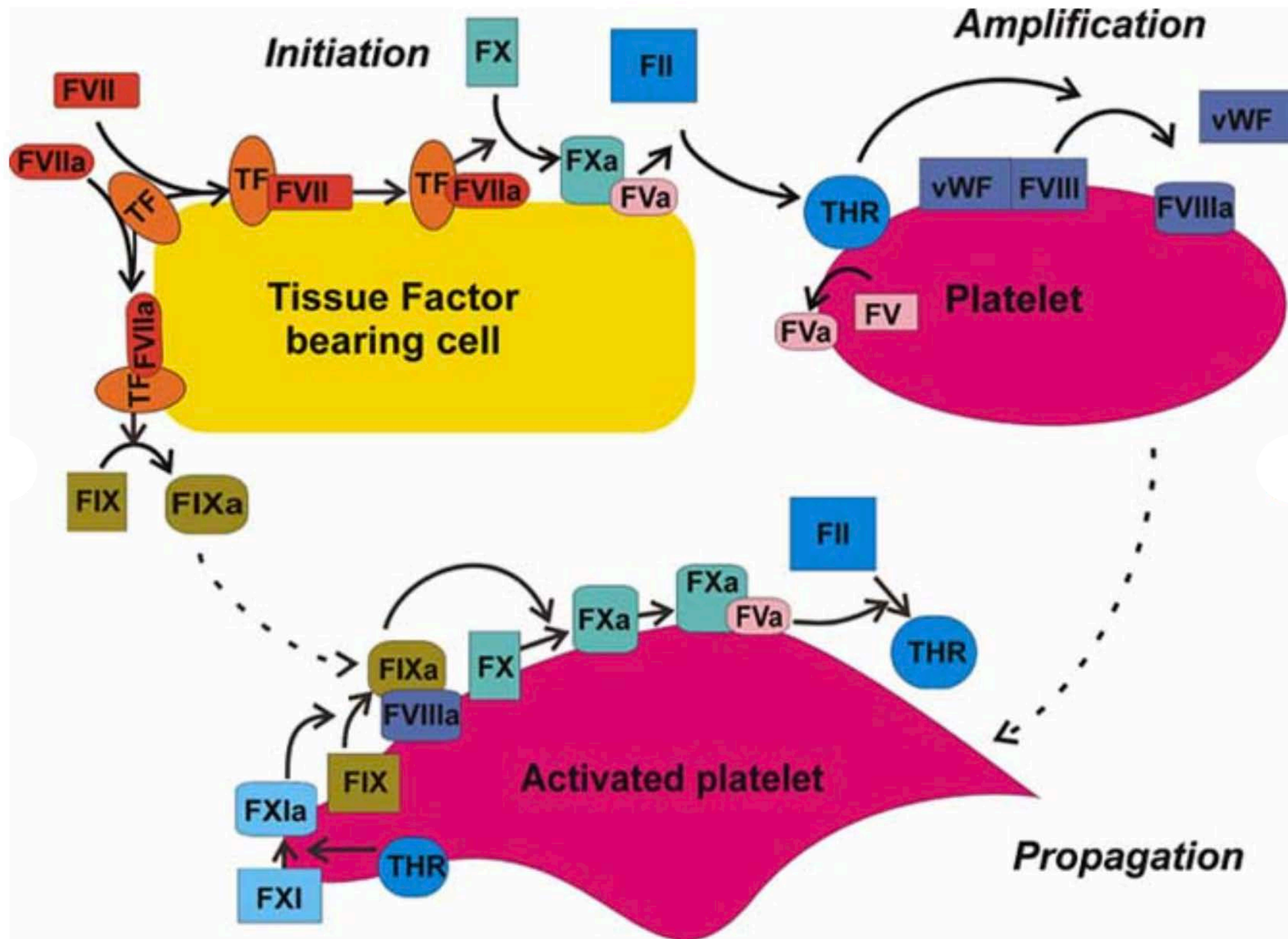
**CONSORTIUM OF LEADERS
IN THE STUDY OF
TRAUMATIC
THROMBOEMBOLISM**

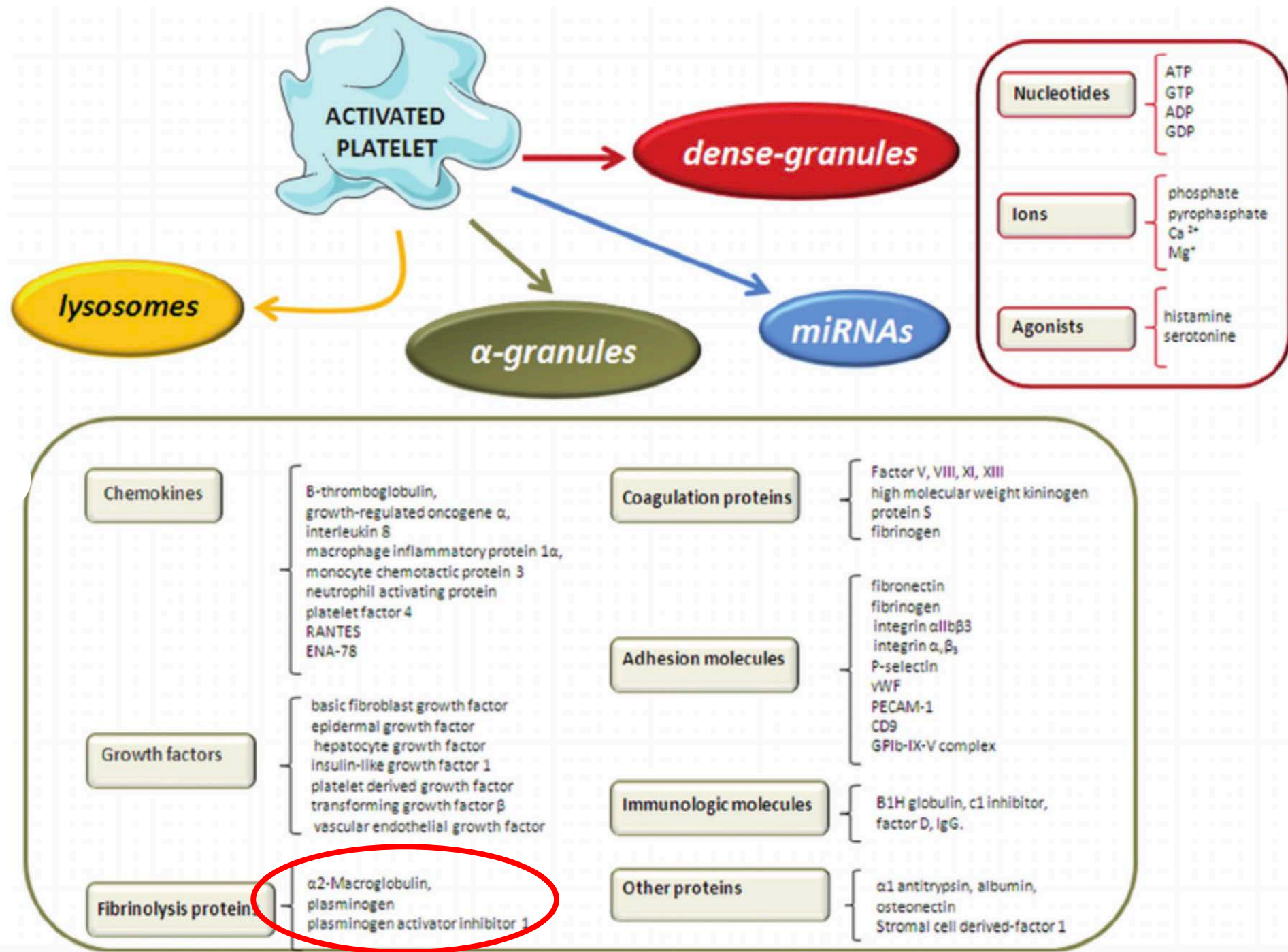
No disclosures

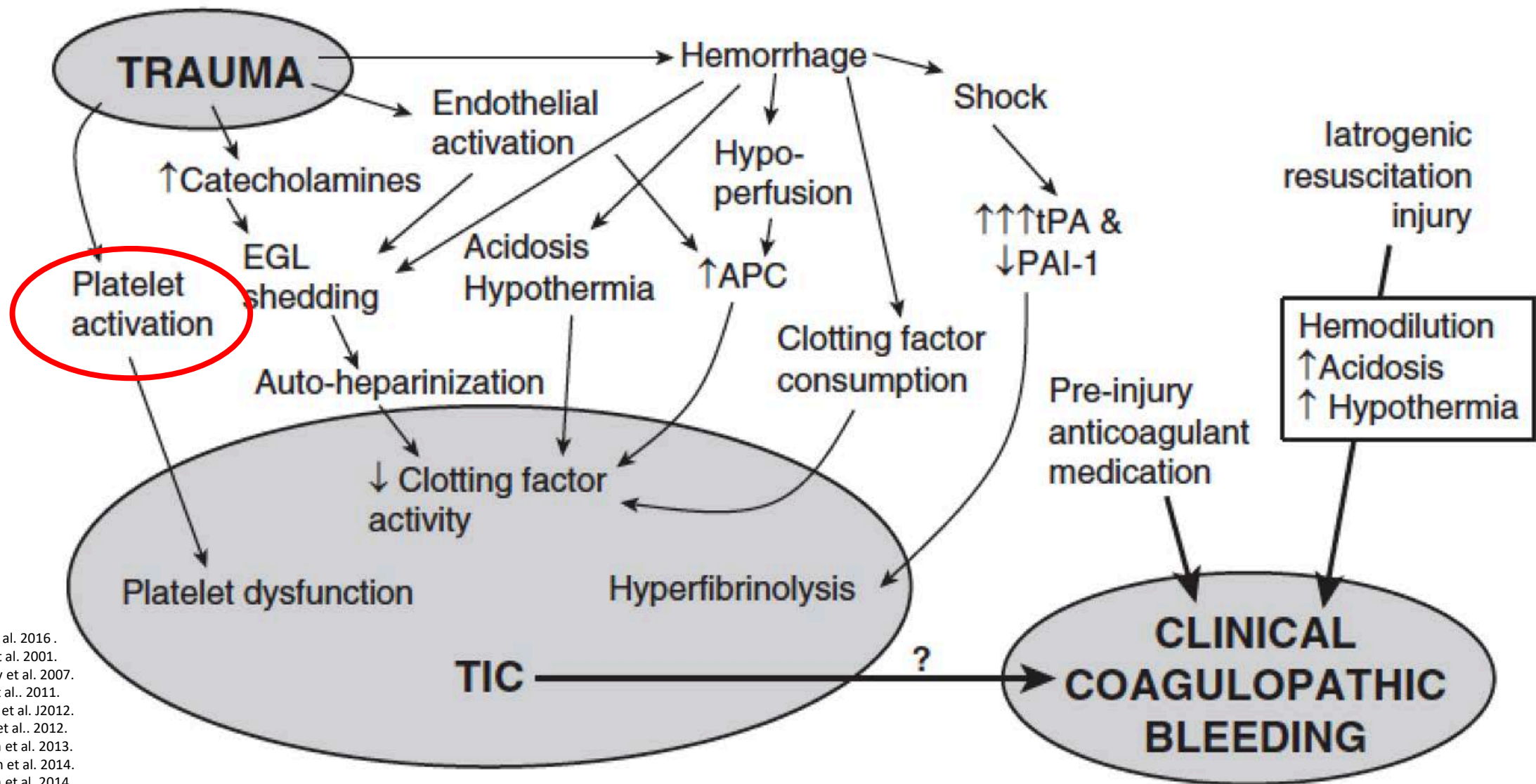
Funding:

NIH K23GM130892-01

Post-Injury Platelet Biology: Mechanisms and Outcomes







Chang et al. 2016.
 Jacoby et al. 2001.
 Nakludov et al. 2007.
 Brown et al., 2011.
 Maegele et al. J2012.
 Kutcher et al., 2012.
 Kornblith et al. 2013.
 Chapman et al. 2014.
 Kornblith et al. 2014.
 Diamond et al. 2016.
 Wilson et al. 2016.
 Brill et al. 2016.

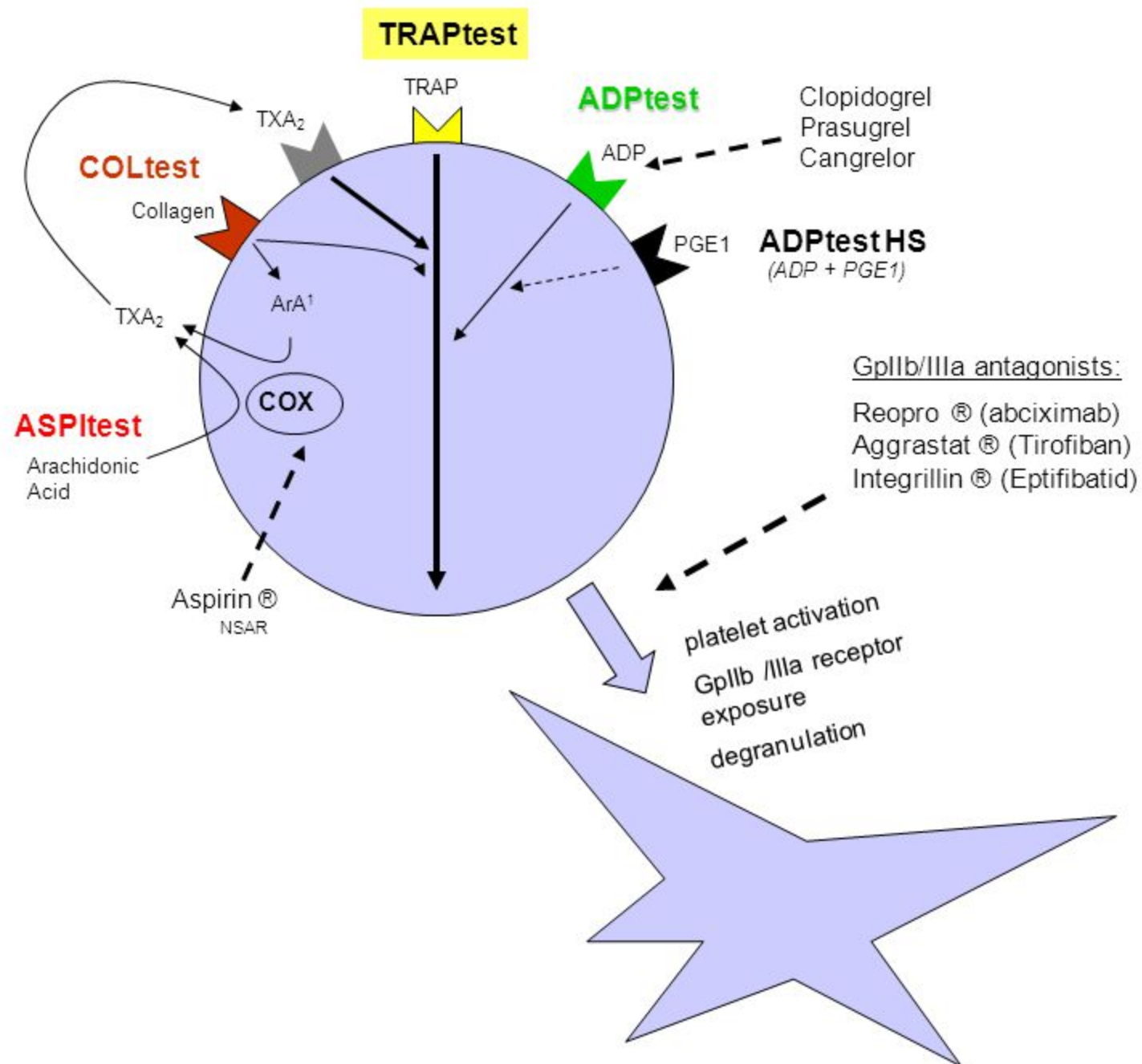
Table 1. Evaluating platelet function in the research setting

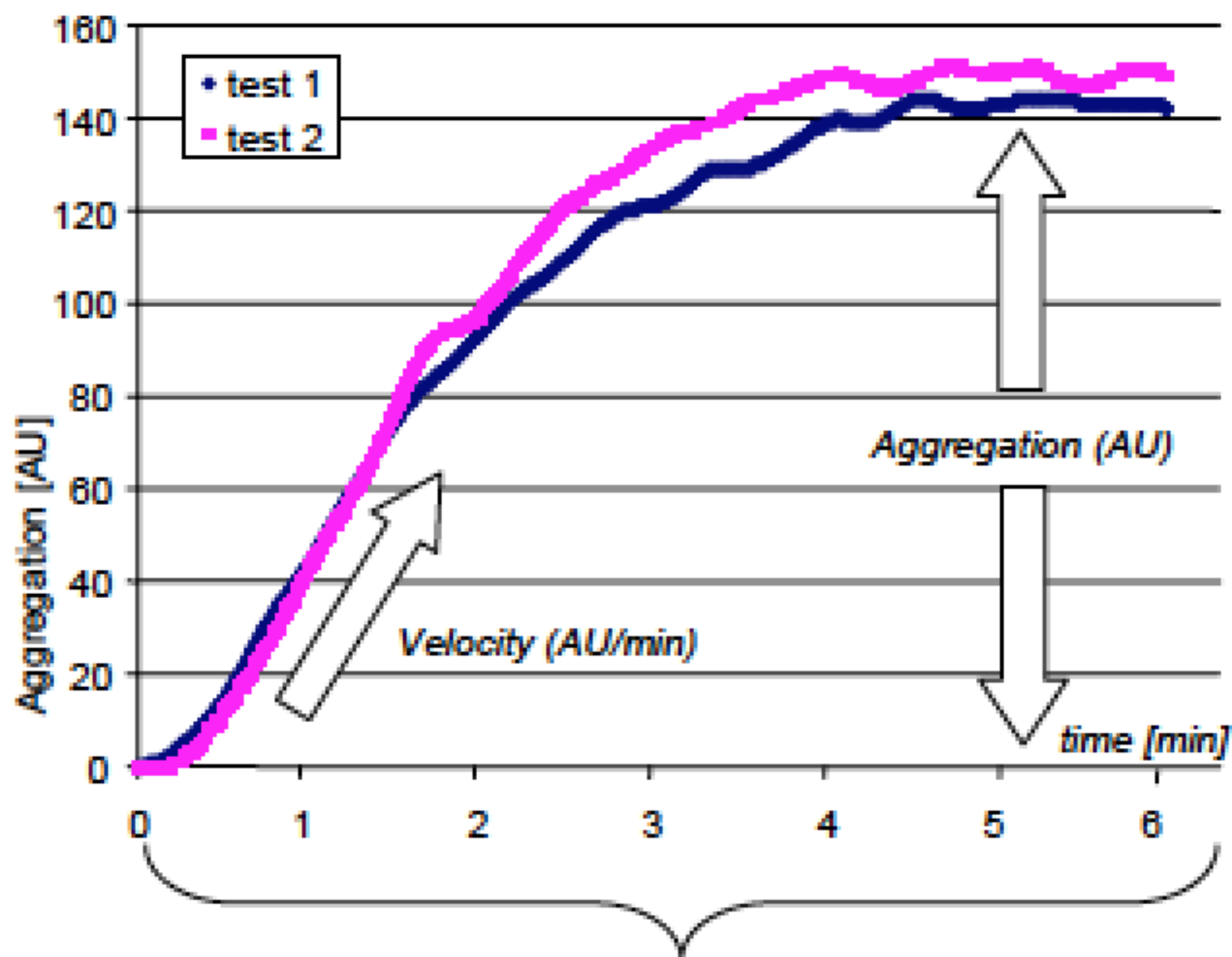
Where?	How?	When?
Animal models	Physical examination	Laboratory animals with defects in platelet function do not necessarily show evidence of spontaneous bleeding under the conditions of life in an animal facility, but bleeding may be detected through stool examinations or necropsy.
	Platelet count	Evaluating whether (in transgenic mouse models) gene manipulation has affected platelet formation or survival.
	Bleeding time	A variety of methods exist for performing bleeding times in animals. The most common used method in mice is the tail bleeding time.
	Vascular injury models	Platelet responses to injury in arteries of different sizes. In mice, most commonly used with carotid, mesentery and cremaster arteries and arterioles. Injuries include FeCl ₃ , rose Bengal, laser, mechanical and electrical.
<i>Ex vivo</i>	Light and fluorescence microscopy (peripheral blood smear)	Assessing platelet size and appearance. Localizing and documenting the presence of internal structures (immunofluorescence)
	Electron microscopy (scanning and transmission)	Assessing platelet morphology and structure. Immunogold labeling allows localization of proteins to structures in the platelet.
	Light transmission aggregometry (platelet rich plasma) and impedance aggregometry (whole blood)	Evaluating platelet responses to agonists (e.g. ADP, epinephrine, collagen, TRAP and arachidonate) and platelet activation in the absence of an agonist. Detecting hereditary and acquired defects of aggregate formation (e.g. Glanzmann's thrombasthenia).
	Dense granule secretion (lumi aggregometry and ¹⁴ C-serotonin)	Detecting hereditary and acquired abnormalities of secretion that affect dense granules.
	ATP:ADP ratio	Storage pool disorders that affect dense granule storage of adenine nucleotides.
	Flow cytometry	Among other uses, can detect surface expression of common platelet proteins, evaluate fibrinogen receptor function, assess secretory mechanisms and assess the impact of P2Y ₁₂ ADP receptor antagonists by measuring VASP phosphorylation.
	Flow chambers (full size and microfluidic)	Commonly used to evaluate platelet activation and "thrombus" formation on a surface coated with collagen, VWF or fibrinogen under flow.
	High throughput devices for performing fluorescence spectroscopy and flow cytometry in a microtiter plate format	Such devices offer the potential to study multiple aspects of platelet function using relatively small amounts of blood. Examples include detecting changes in cytosolic Ca ⁺⁺ or activation of $\alpha_{IIb}\beta_3$ in response to a panel of agonists introduced at a range of concentrations.

ATP indicated adenosine triphosphate; PAR-1, protease-activated receptor-1; TRAP, thrombin receptor activation peptide (an agonist for platelet PAR-1); VASP, vasodilator-stimulated protein.

→ activation
---→ inhibition

¹ release of
arachidonic
acid





Area under the curve = AUC (AU*min or U)
10 AU*min = 1 U

Multi-Center Investigation of Pulmonary Embolism to be Funded by Defense Research Program

Jun 30, 2017

Under the auspices of the Coalition for National Trauma Research (of which, NTI is a member), the CLOTT group (Coalition of Leaders in Thromboembolism) received a grant from the Defense Medical Research and Development Program to conduct a new study: "The Pathogenesis of Post-Traumatic Pulmonary Embolism: A Prospective Multi-Center Investigation by the CLOTT Study Group."

The CLOTT group has published papers documenting variances in practice and the impact of surveillance bias on the incidence of Deep Vein Thrombosis (DVT), as well as developed a venous thromboembolism (VTE)-specific data collection tool now uploaded to REDCap.

This study will focus on the significance of incidentally discovered pulmonary thrombi after injury as well as the role of fibrinogen breakdown in the development of post-traumatic Pulmonary Embolism.

and platelets

Archives

[August 2018](#)

[July 2018](#)

[May 2018](#)

[April 2018](#)

[March 2018](#)

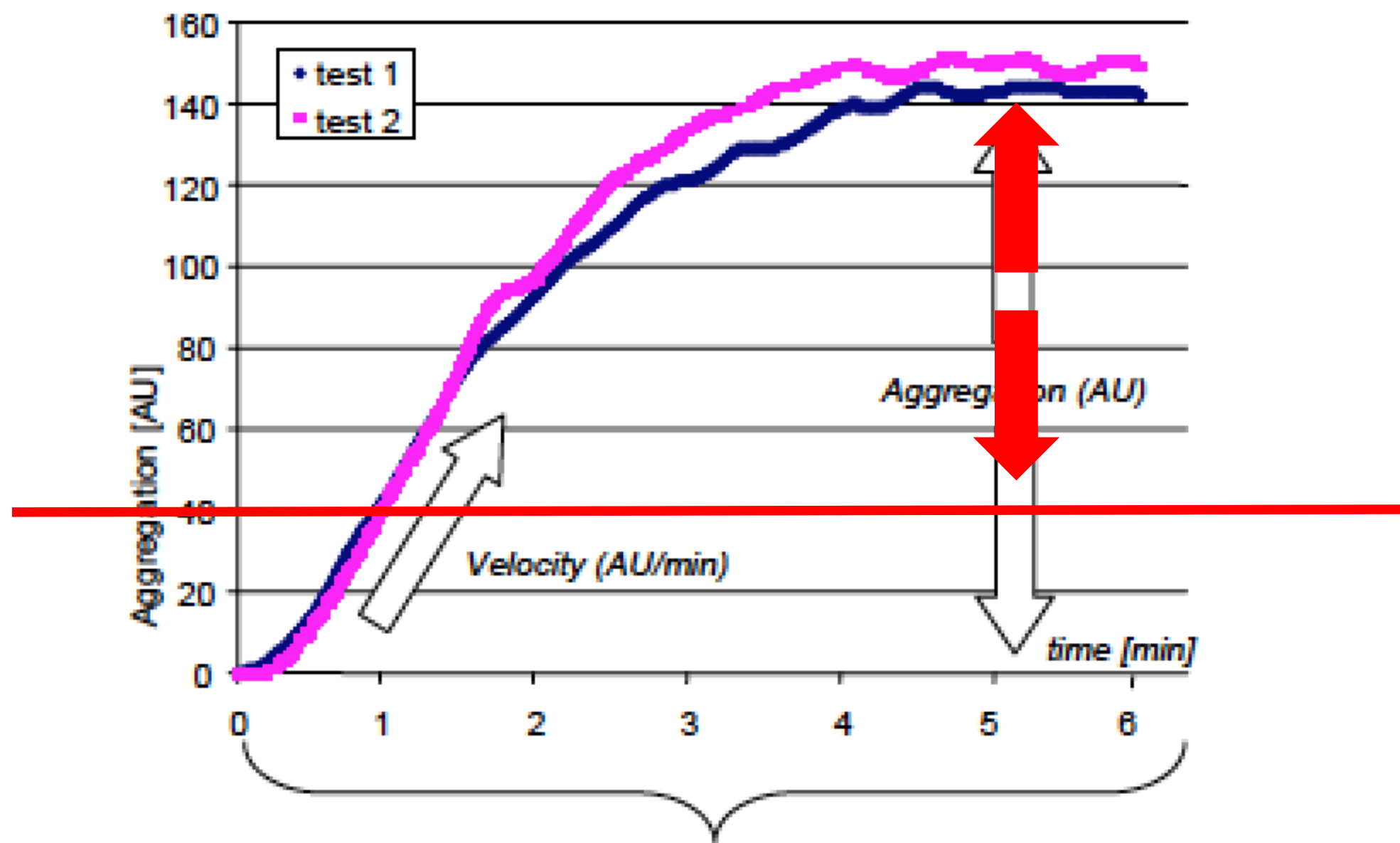
[February 2018](#)

[December 2017](#)

[November 2017](#)

[October 2017](#)

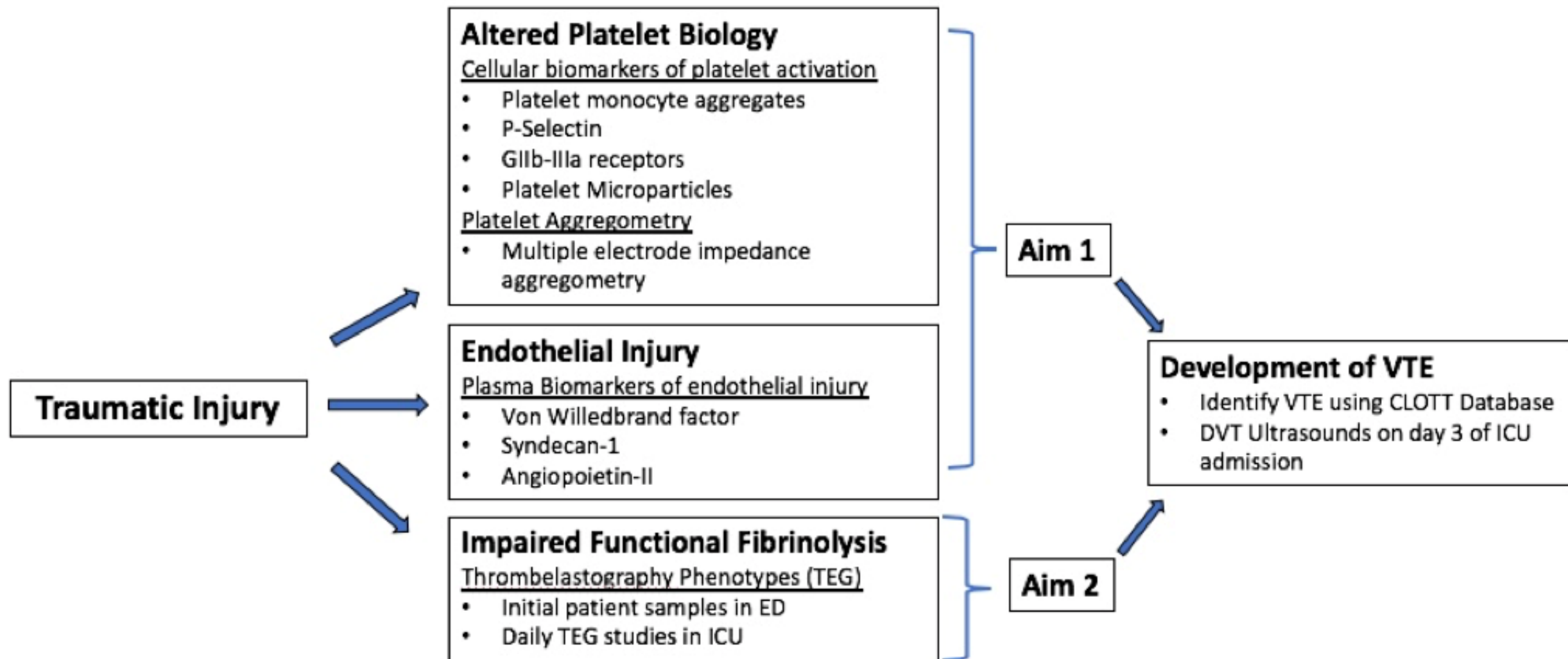
[September 2017](#)



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Table 1. Evaluating platelet function in the research setting

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Thank you:
Lucy.Kornblith@UCSF.edu

