



International Collaborative PREDICT Studies over the Horizon

Franz Babl, Royal Children's Hospital and PREDICT

Outline



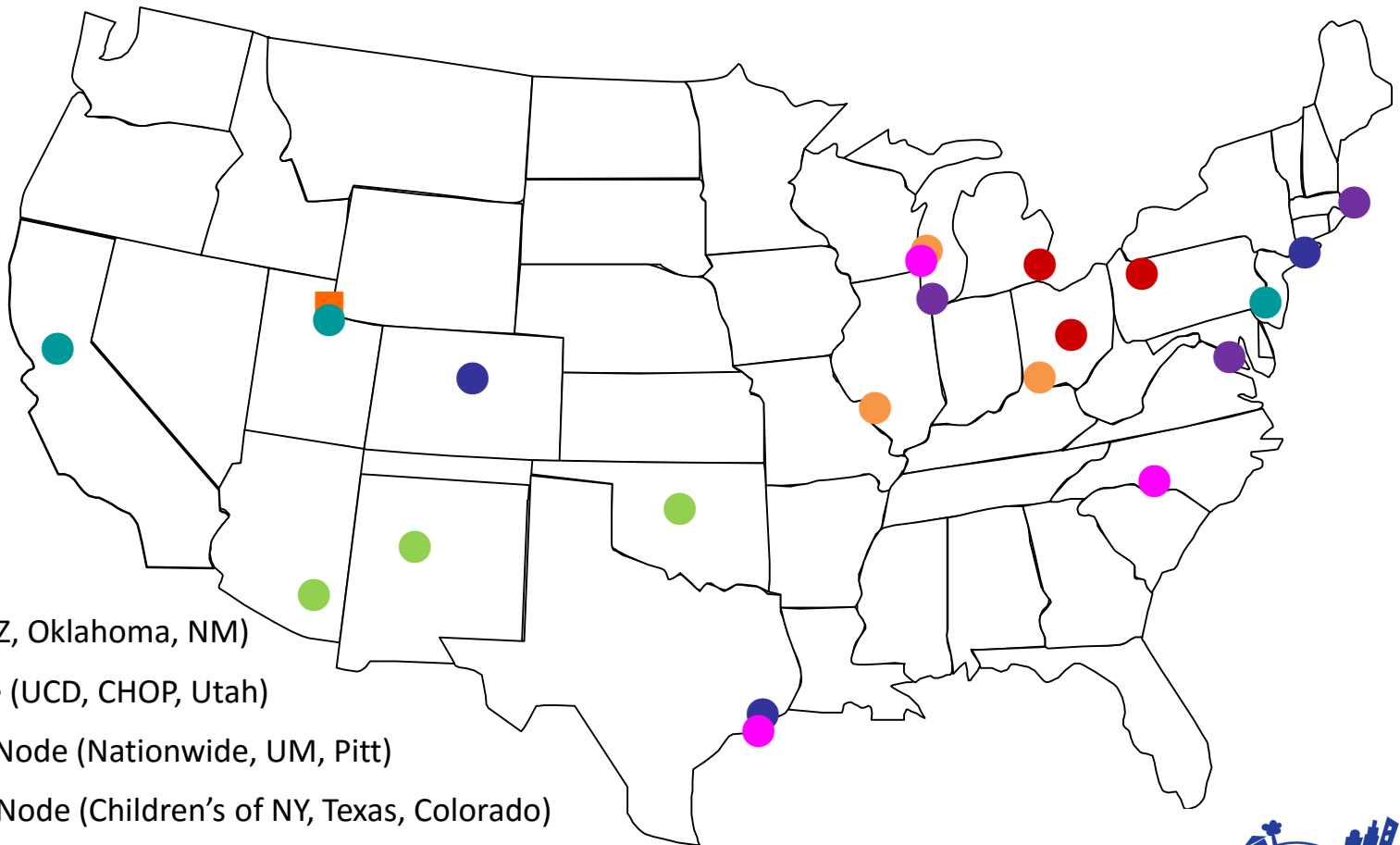
- Collaboration with PECARN network
- Study on Tranexamic acid in trauma
- Study on Balanced Fluids in Sepsis

PECARN Network

- Major US research network
- Established early 2000s; funded via federal grant
- Structured via hub and spoke model
 - 7 research nodes, 18 sites, 1 data centre

The Pediatric Emergency Care Applied Research Network

Seven Nodes and a Data Coordinating Center (DCC)



- = DCC (Utah)
- = SW Node (AZ, Oklahoma, NM)
- = PRIME Node (UCD, CHOP, Utah)
- = GLEMSCRN Node (Nationwide, UM, Pitt)
- = PEM-NEWS Node (Children's of NY, Texas, Colorado)
- = WBCARN Node (Children's National, Chicago, Boston)
- = HOMERUN Node (Cincinnati, Wash U, Wisc)
- = CHaMP Node (Milwaukee, Charlotte, Houston)

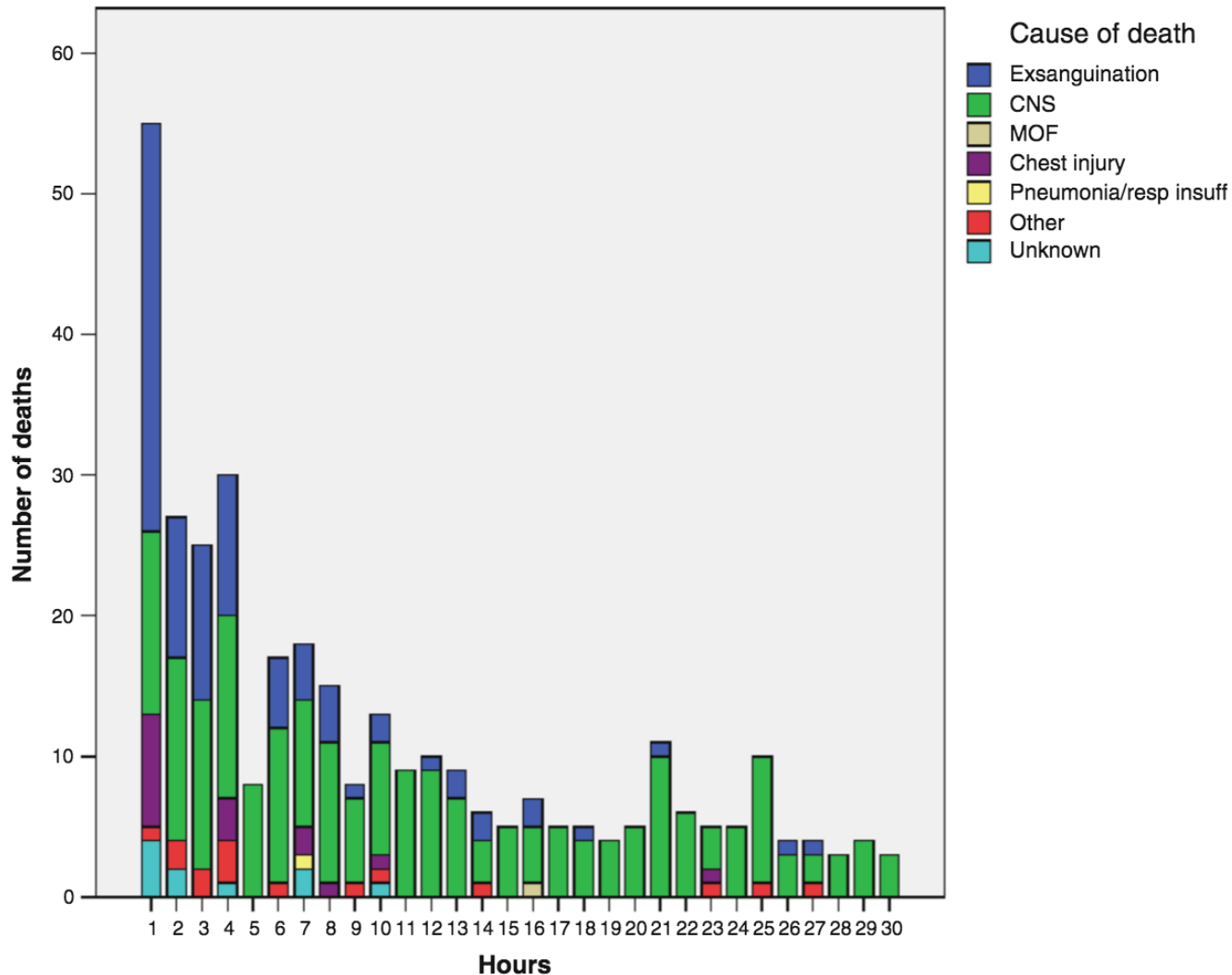
PECARN Network

- Very successful
 - Major, definitive projects on head injury rules, status epilepticus, abdominal trauma, fluids in DKA, others
 - 132 publications



Tranexamic Acid in Children with Traumatic Injuries

TBI and Torso Haemorrhage Leading Causes of Death in <24 h

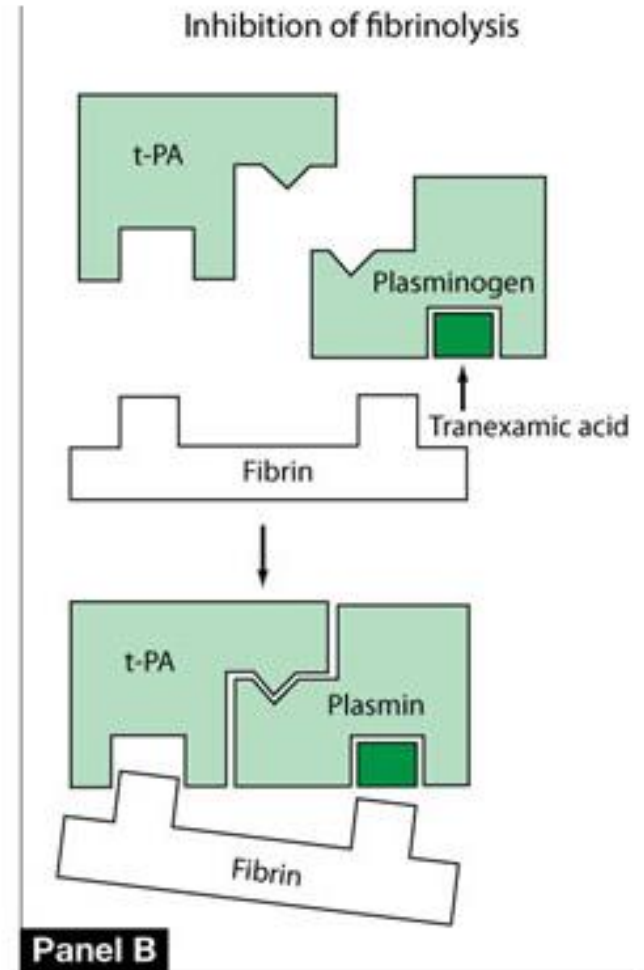
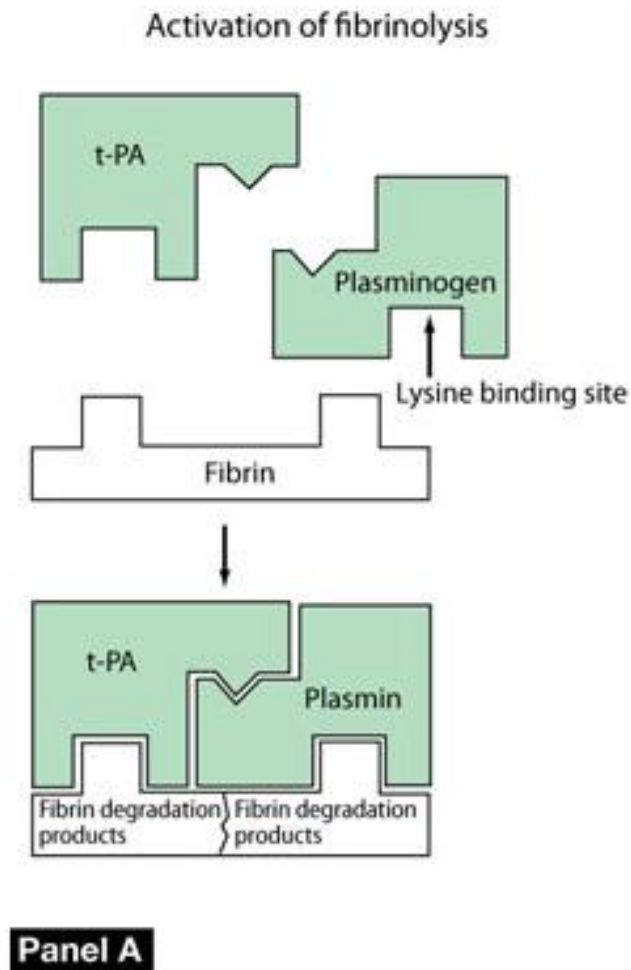


Tranexamic Acid (TXA)

- Antifibrinolytic agent
- Most frequently used for pediatric and adult surgery
- Inexpensive
- Safe

Tranexamic Acid (TXA)

- Lysine
analogue



Coagulation and Fibrinolysis

Tissue Injury

Coagulation Factors

Fibrinogen

Fibrin

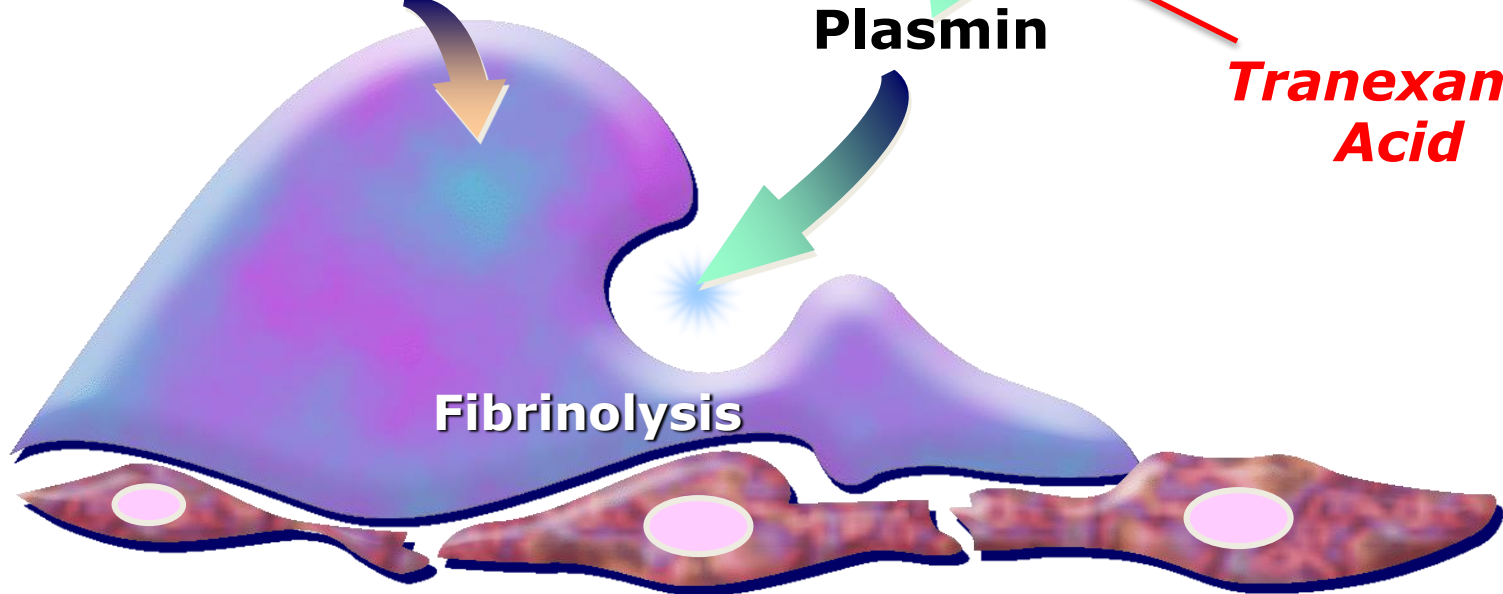
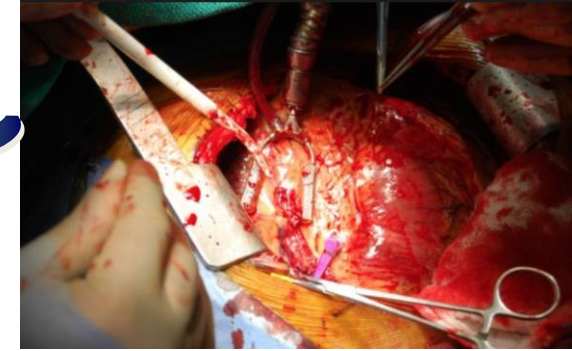
Fibrinolysis

↑↑↑ **t-PA**

Plasminogen

Plasmin

Tranexamic Acid



Efficacy of tranexamic acid in paediatric cardiac surgery: a systematic review and meta-analysis[†]

David Faraoni^{a,*}, Ariane Willems^b, Christian Melot^c, Stefan De Hert^d and Philippe Van der Linden^a

BMJ

BMJ 2012;344:e3054 doi: 10.1136/bmj.e3054 (Published 21 May 2012)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery

Effect of tranexamic acid on surgical bleeding:
systematic review and cumulative meta-analysis

Effect of early tranexamic acid administration on mortality,
hysterectomy, and other morbidities in women with
post-partum haemorrhage (WOMAN): an international,
randomised, double-blind, placebo-controlled trial

WOMAN Trial Collaborators*

TXA: Clinical Use

- Robust *surgical* data that TXA is effective in decreasing blood loss and transfusion requirement (adults and children)
- Robust *safety* data (adults and children)

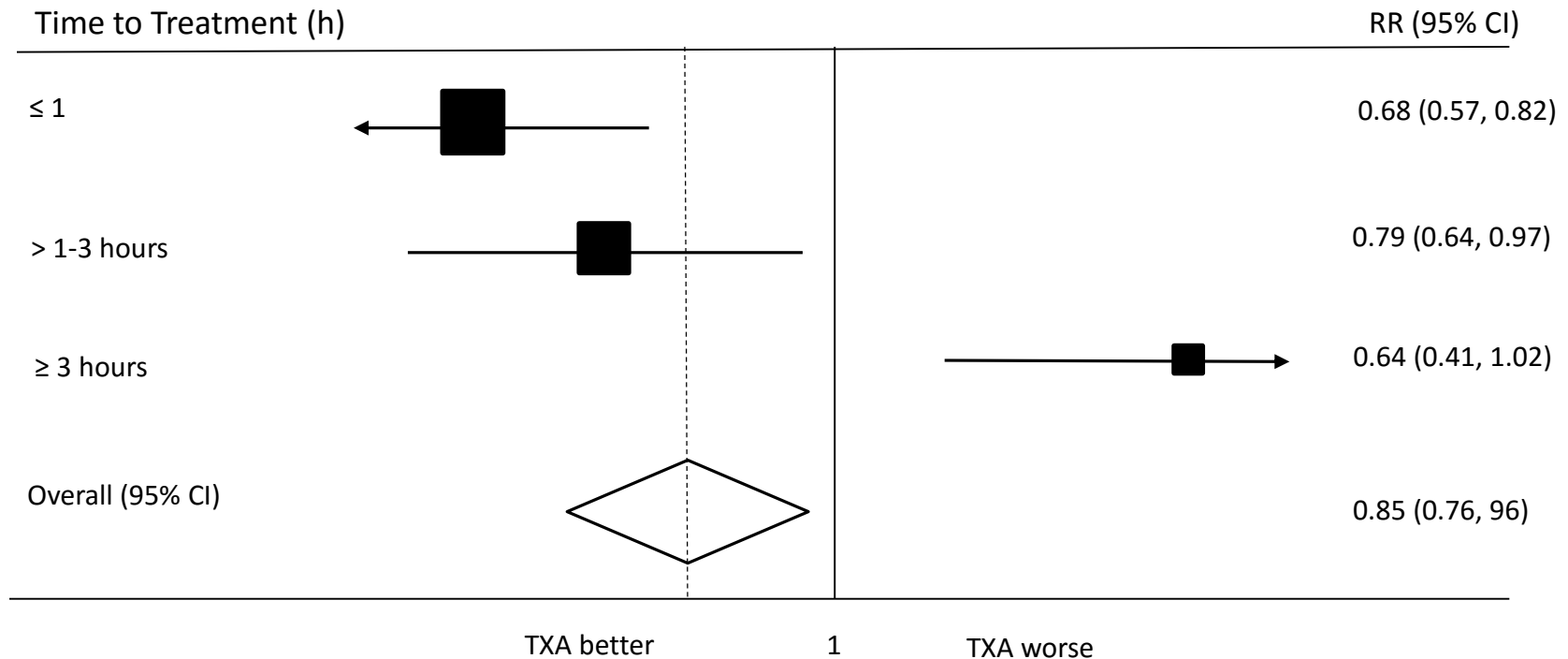
Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial

*CRASH-2 trial collaborators**

- 20,000+ adults with significant hemorrhage
- Randomized to TXA or placebo
- All-cause mortality: TXA 1463 [14.5%] vs. Placebo 1613 [16.0%], NNT = 67
- No increase in adverse events

The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial

*The CRASH-2 collaborators**



VIEWPOINT

Tranexamic acid in pediatric trauma: why not?

Suzanne Beno^{1*}, Alun D Ackery², Jeannie Callum³ and Sandro Rizoli²

The PREDICT DELPHI STUDY:

Establishing the Research Priorities of Paediatric Emergency Medicine Physicians in Australia and New Zealand

- | | |
|-------------|---|
| 9
(5.02) | In paediatric patients who sustain blunt trauma with haemodynamic instability, does early tranexamic acid 15mg/kg compared to placebo improve mortality and reduce morbidity? |
|-------------|---|



PERUKI

What are the Research Priorities of Paediatric Emergency Medicine (PEM) Clinicians in the United Kingdom & Ireland? - an International Survey

¹S Hartshorn, ²C Bevan, ³F Cleugh, ⁴M Lyttle, ³I Maconochie, ^{5,6}R O'Sullivan



PERUKI

- | | |
|---|---|
| 5 | In paediatric major trauma patients with major haemorrhage does IV tranexamic acid compared to no treatment reduce mortality and morbidity? |
|---|---|

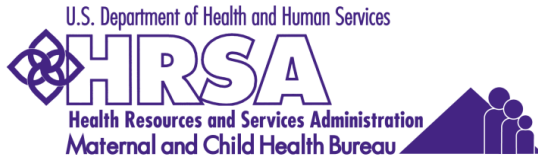
TiC-ToC

Traumatic Injury Clinical Trial Evaluating Tranexamic Acid in Children

Daniel Nishijima, MD, MAS

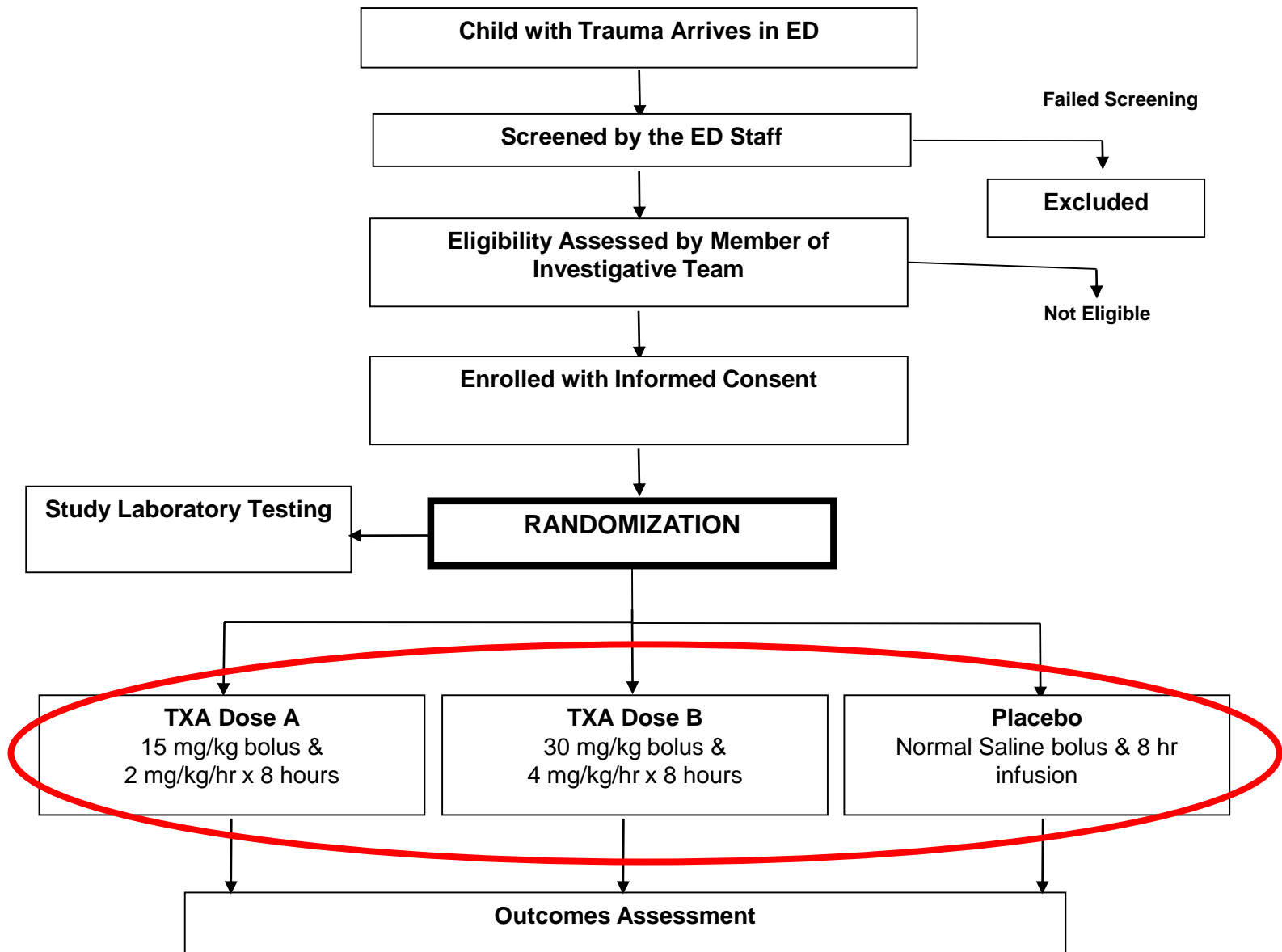
Nathan Kuppermann, MD, MPH

*Department of Emergency Medicine
UC Davis Health*



Pilot Study for RCT on Tranexamic Acid

- Assess feasibility of TXA RCT
- Three arm RCT: 2 TXA doses and placebo
- N=40 at 4 PECARN sites
- Funded by National Institutes of Health (NIH)
- Currently paused due to change from prospective informed consent to exception from informed consent



Inclusion Criteria

Blunt Torso Trauma:

- Clinician suspicion of hemorrhagic blunt torso injury *and at least one of the following*
- Hypotension/tachycardia despite fluids OR
- Haemothorax on chest tube placement or imaging; OR
- Clinical suspicion of hemorrhagic blunt torso injury and intraperitoneal fluid on FAST OR CT
- Pelvic fracture with contrast extravasation or hematoma on abdominal/pelvic CT scan.

Penetrating trauma to the chest, abdomen, neck, pelvis, or thigh with :

- Hypotension or tachycardia or radiographic evidence of internal hemorrhage

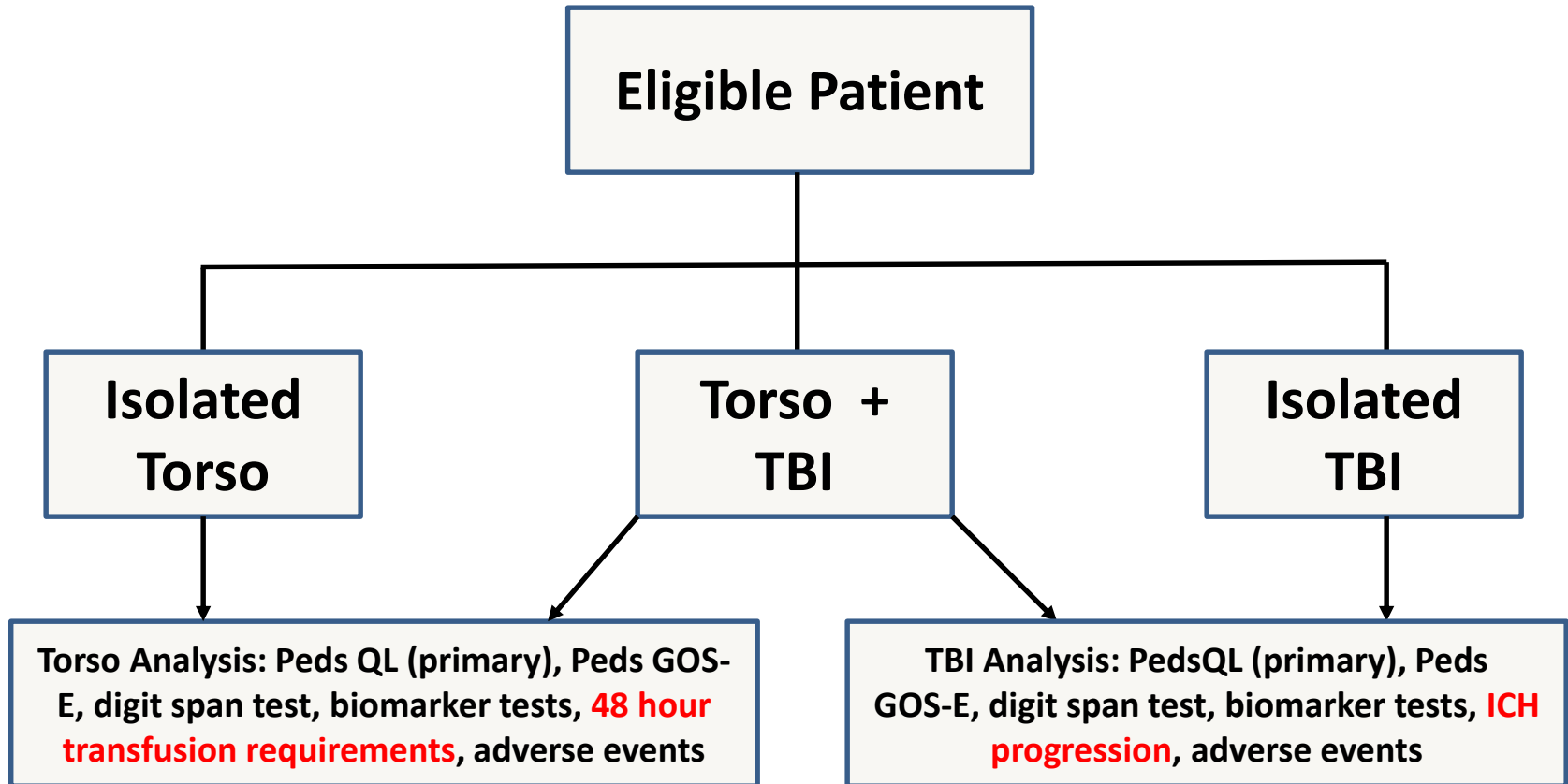
Head Trauma:

- GCS score 3 to 13 with associated intracranial hemorrhage on cranial CT scan

Exclusion Criteria

- Unable to administer study drug <3 hrs of traumatic event
- GCS score of 3 with bilateral unresponsive pupils
- Known bleeding/clotting disorders
- Known seizure disorders

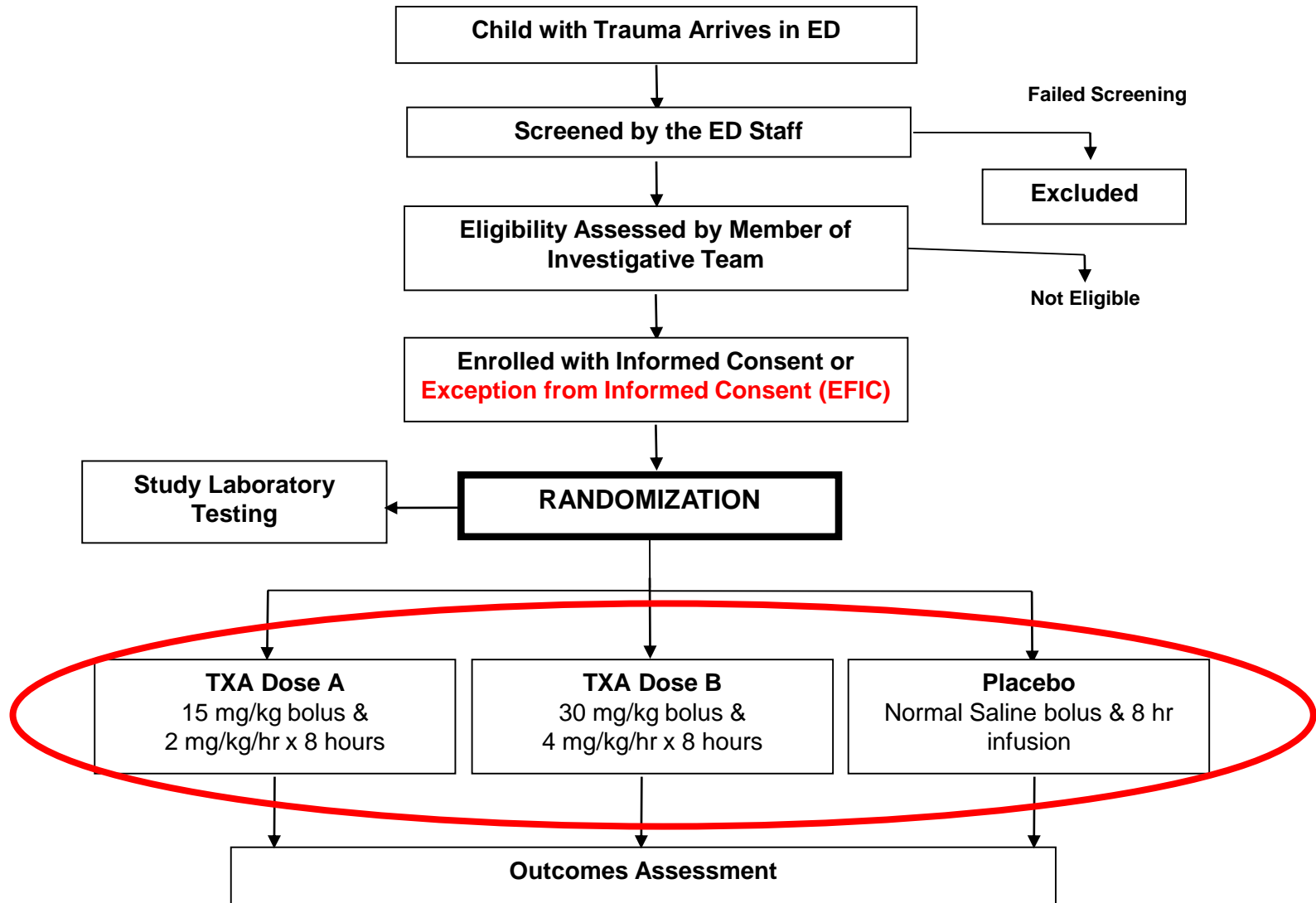
Outcomes



Biomarkers: Thromboelastography; TXA levels

Multicenter, randomized, placebo controlled, phase II/III, adaptive trial

- Phase II: best TXA dose, Phase III TXA: vs placebo
- 40+ clinical sites
 - Potential networks: PECARN, PERN, national CTSA consortium, international sites
 - 5 years
- Evaluate both torso and head injuries
 - 1000 (head), 1000 (torso)
 - Children < 18 years
 - Primary outcome: PedsQL



RCT on Tranexamic Acid

- Exact number of sites in US and PREDICT pending
- PECARN: NIH funding submission in 2019
- PREDICT: MRFF/NHMRC submission in 2019 or 2020 for Australian and New Zealand sites



Balanced Fluids in Sepsis

Sepsis in Children

- US: 1 million hospitalized with sepsis per year
 - 75,000 children
 - 5000 child deaths per year
- Mortality septic shock in children in ED 2-6%
- Fluid resuscitation is cornerstone
 - Unclear optimal amounts
 - Unclear optimal fluids:
0.9% normal saline vs balanced (lactated Ringer's, Plasmalyte)

Fluids in Sepsis

0.9% Na Cl (NS): Na 154 mmol/l, Cl 154 mmol/l

Lactated Ringers: Na 130, Cl 109, lactate 28, K 4, Ca 1.5

Hartmann's: Na 131, Cl 111, lactate 29, K 5, Ca 2

Plasmalyte: Na 140, Cl 98, K 5, Mg 1.5, Acetate 27, Gluconate 23

Fluids in Sepsis

■ Concerns 0.9% normal saline

ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H.,
Jonathan P. Wanderer, M.D., Jesse M. Ehrenfeld, M.D., M.P.H.,
Li Wang, M.S., Daniel W. Byrne, M.S., Joanna L. Stollings, Pharm.D.,
Avinash B. Kumar, M.D., Christopher G. Hughes, M.D.,
Antonio Hernandez, M.D., Oscar D. Guillamondegui, M.D., M.P.H.,
Addison K. May, M.D., Liza Weavind, M.B., B.Ch., Jonathan D. Casey, M.D.,
Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D.,
and Todd W. Rice, M.D., for the SMART Investigators
and the Pragmatic Critical Care Research Group*

N ENGL J MED 378;9 NEJM.ORG MARCH 1, 2018

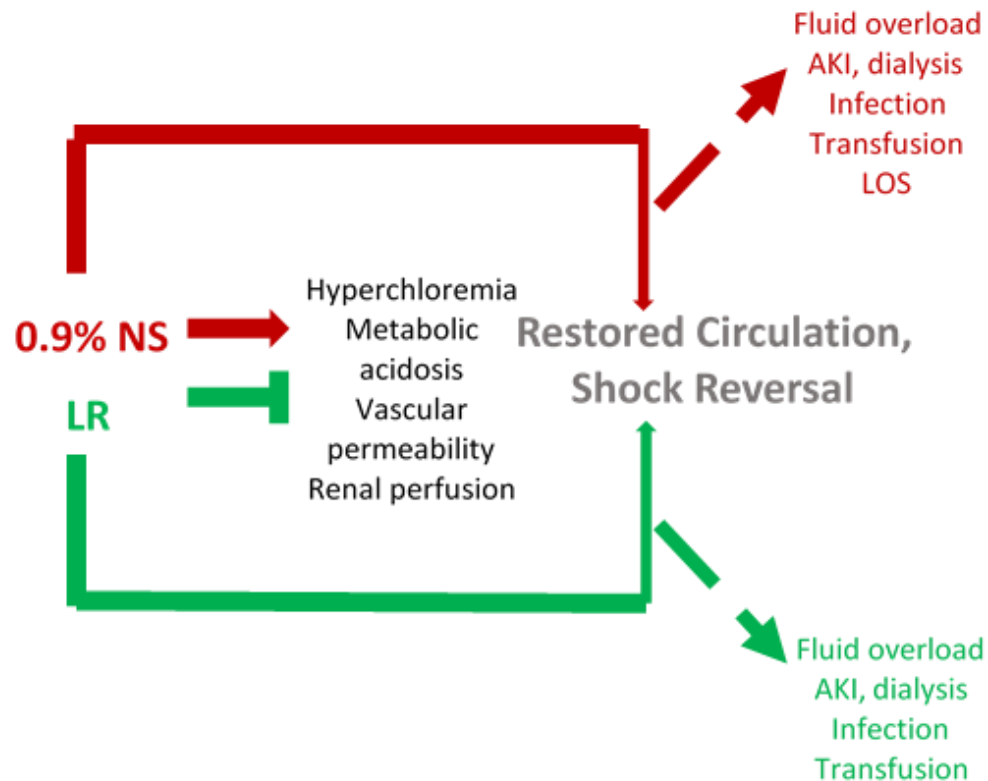


Resuscitation With Balanced Fluids Is Associated With Improved Survival in Pediatric Severe Sepsis*

Emrath, Elizabeth T. MD¹; Fortenberry, James D. MD, MCCM^{1,2}; Travers, Curtis MPH³; McCracken, Courtney E. PhD³;
Hebbar, Kiran B. MD, FCCM^{1,2}

Fluids in Sepsis

- Concerns 0.9% normal saline



PROMPT BOLUS

PRagMatic Pediatric Trial of Balanced vs nOrmaL Saline FLUID in Sepsis

Fran Balamuth, MD

Scott Weiss, MD

Nathan Kuppermann, MD, MPH

Children's Hospital of Philadelphia

*Department of Emergency Medicine
UC Davis Health*

PROMPT BOLUS

- Pragmatic, open label RCT comparing 0.9% normal saline vs balanced solution (lactated Ringer's) in sepsis
- Pragmatic – embedded in everyday clinical practice
- Inclusion:
 - Age > 6 mo to < 18 years
 - Clinical concern sepsis:
 - Positive sepsis alert OR physician decision to treat for septic shock
 - 20ml/kg bolus + more fluid necessary for poor perfusion

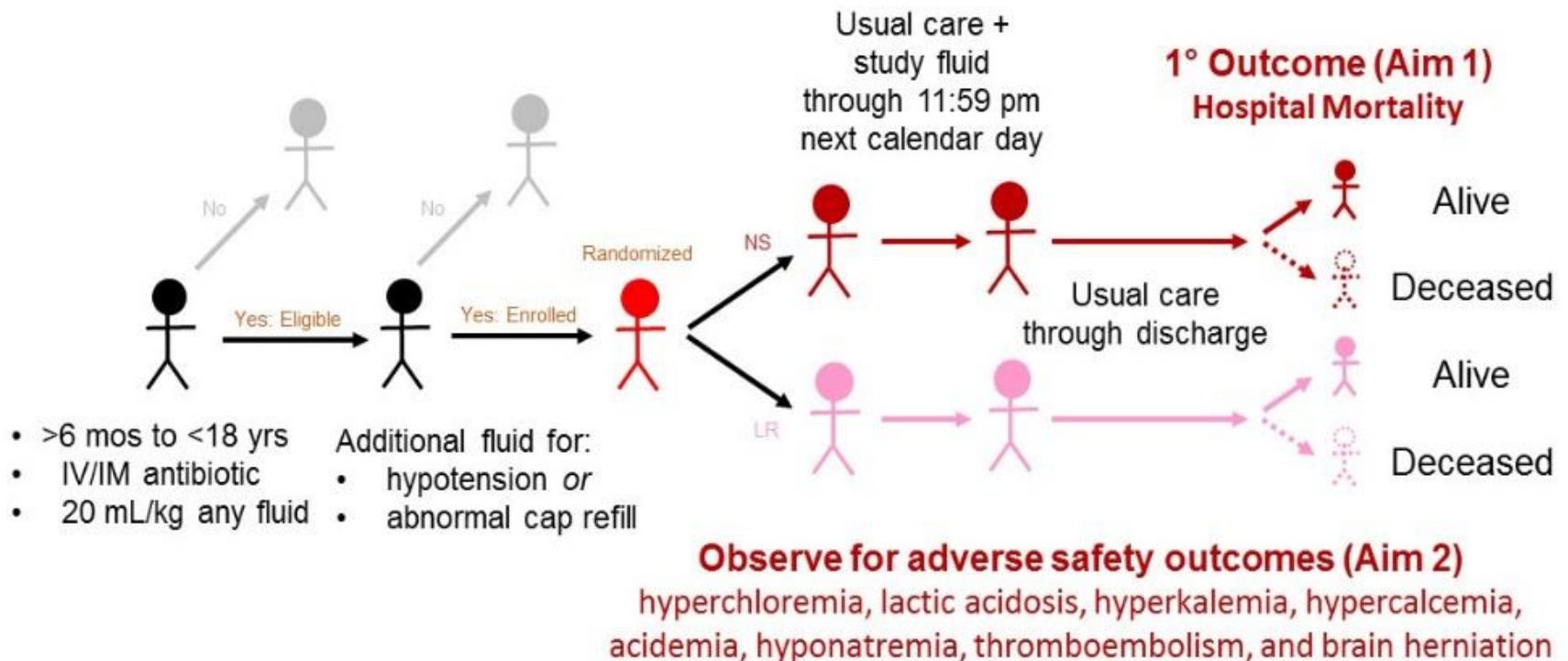
PROMPT BOLUS

- Primary outcome: death
- Sample size: 8,900 patients

Mortality in LR group	6%	5%	4%	3%	2%	1%	0%
Mortality in NS group							
7%	11134	2582	1057				
6%		9521	2174	874			
5%			7873	1758	687		
4%				6187	1332	495	
3%					4465	897	299
2%						2706	452

PROMPT BOLUS

- Study Flow: all fluids up to 48 h NS vs LR (bolus and maintenance)



PROMPT BOLUS

- 5 month pilot completed at Children's Hospital of Philadelphia
- Feasibility
 - Enrolment ~100/yr eligible; 85% eligible enrolled
 - Adherence to protocol ok
 - Caregivers ok with exception to informed consent (only 2% withdrawal)
 - Sample size

PROMPT BOLUS

- Exact number of sites in US and PREDICT pending
- PECARN: NIH funding submission in 2019
- PREDICT: MRFF/NHMRC submission in 2019 for Australian and New Zealand sites

Any questions ?

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Fibrinogen Early in Children with Severe Trauma Study (FEISTY)

- Investigate early fibrinogen replacement in traumatic haemorrhage utilising either fibrinogen or cryoprecipitate
- Compare time to administration of either
- Open label RCT in ED, ICU or OR
- Primary outcome: Time to administration of fibrinogen
- Secondary: multiple
- Feasibility outcomes
- Procedure:
 - Randomise >>
 - ROTEM fibrinogen requirement >>
 - Intervention (fibrinogen) vs control (cryo)

Coagulation and Fibrinolysis

Tissue Injury

Coagulation Factors

Fibrinogen

Fibrin

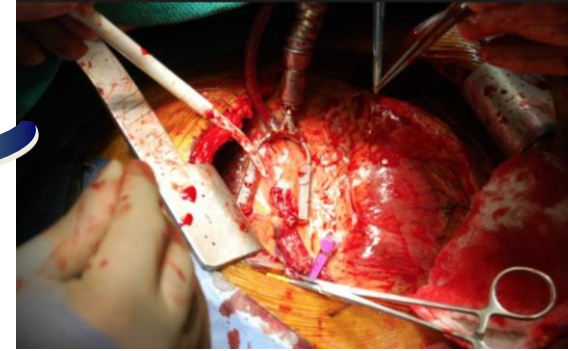
Fibrinolysis

↑↑↑ **t-PA**

Plasminogen

Plasmin

Premature fibrinolysis and
clot breakdown



Phase 2, pilot and feasibility trial



Trauma
surgeons

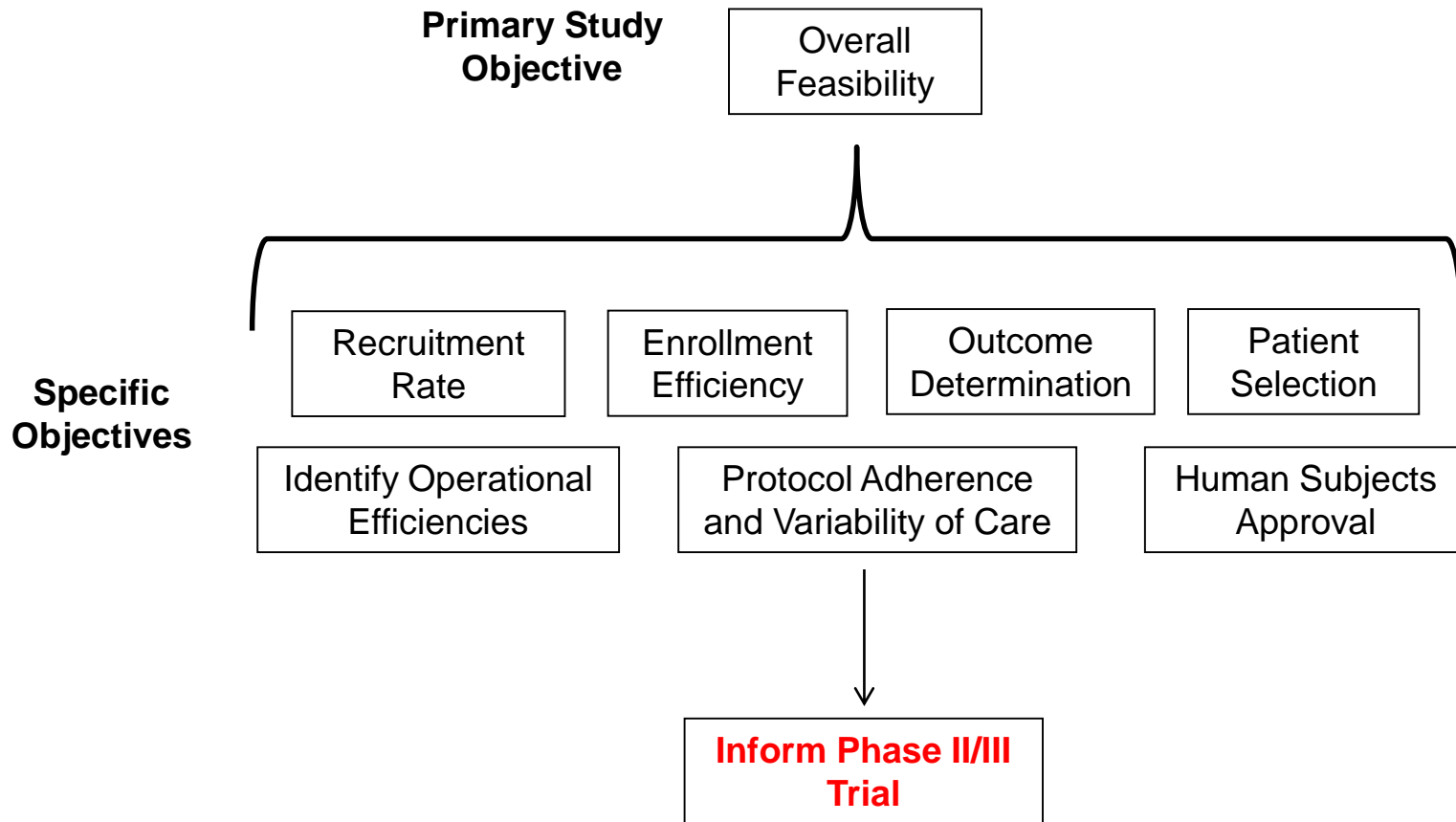
Emergency
medicine

Neuro-
surgeons

Transfusion
Medicine

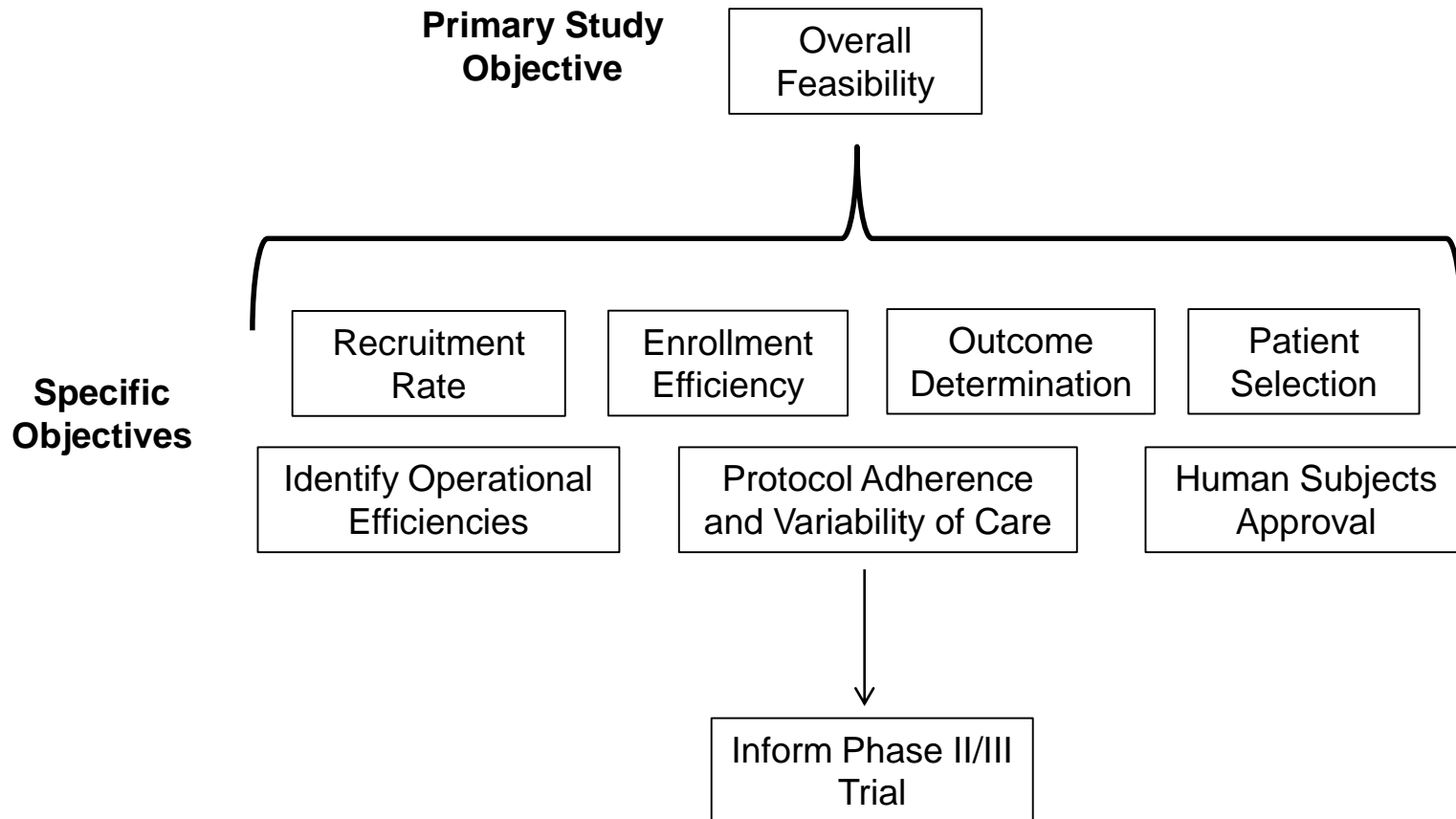
Critical
Care

R34HL135214



Current Pilot Study n=40

Not powered to evaluate efficacy or safety



Coagulation and Fibrinolysis

Tissue Injury

Coagulation Factors

Fibrinogen

Fibrin

t-PA

Plasminogen

Plasmin

Fibrinolysis

