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Pediatric Blood Resuscitation Trials

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MATIC 2

MASSIVE TRANSFUSION IN CHILDREN

Principal Investigators: Philip C. Spinella @ Pittsburgh, Christine Leeper, Stephen Wisniewski, Abdus Wahed, Angelo D'Alessandro

Funded by: BARDA

Current Status: EFIC activities and study start-up

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MATIC-2 Overview

- **Design:** Bayesian, randomized, multicenter, adaptive platform phase III trial
- **Subjects:** Injured children with hemorrhagic shock anticipated to require massive blood transfusion
- **Interventions:**
  - Low-titer O-positive whole blood LTOWB (LTOWB) or component therapy
  - Tranexamic Acid (TXA) or placebo
- **Primary endpoint:**
  - 24-hour all-cause mortality
- **Secondary endpoints:**
  - Cumulative survival: 6-hour, 72-hour and 28-day survival
  - 24-hour total blood product transfusion volumes

Trial Domains

- Domain 1: Blood products
  - LTOWB compared to CT
  - Non-inferior and/or superior for 24-hour mortality
  - Does not increase the risk of adverse events

- Domain 2: TXA
  - TXA compared to placebo
  - Superior for 24-hour mortality
  - Does not increase the risk of adverse events

Study Objectives

- The **primary objectives** are:
  1. To determine the effectiveness of LTOWB to reduce all-cause 24-hour mortality compared to CT in children with traumatic life-threatening hemorrhage
  2. To determine the effectiveness of TXA to reduce all-cause 24-hour mortality compared to placebo in children with traumatic life-threatening hemorrhage

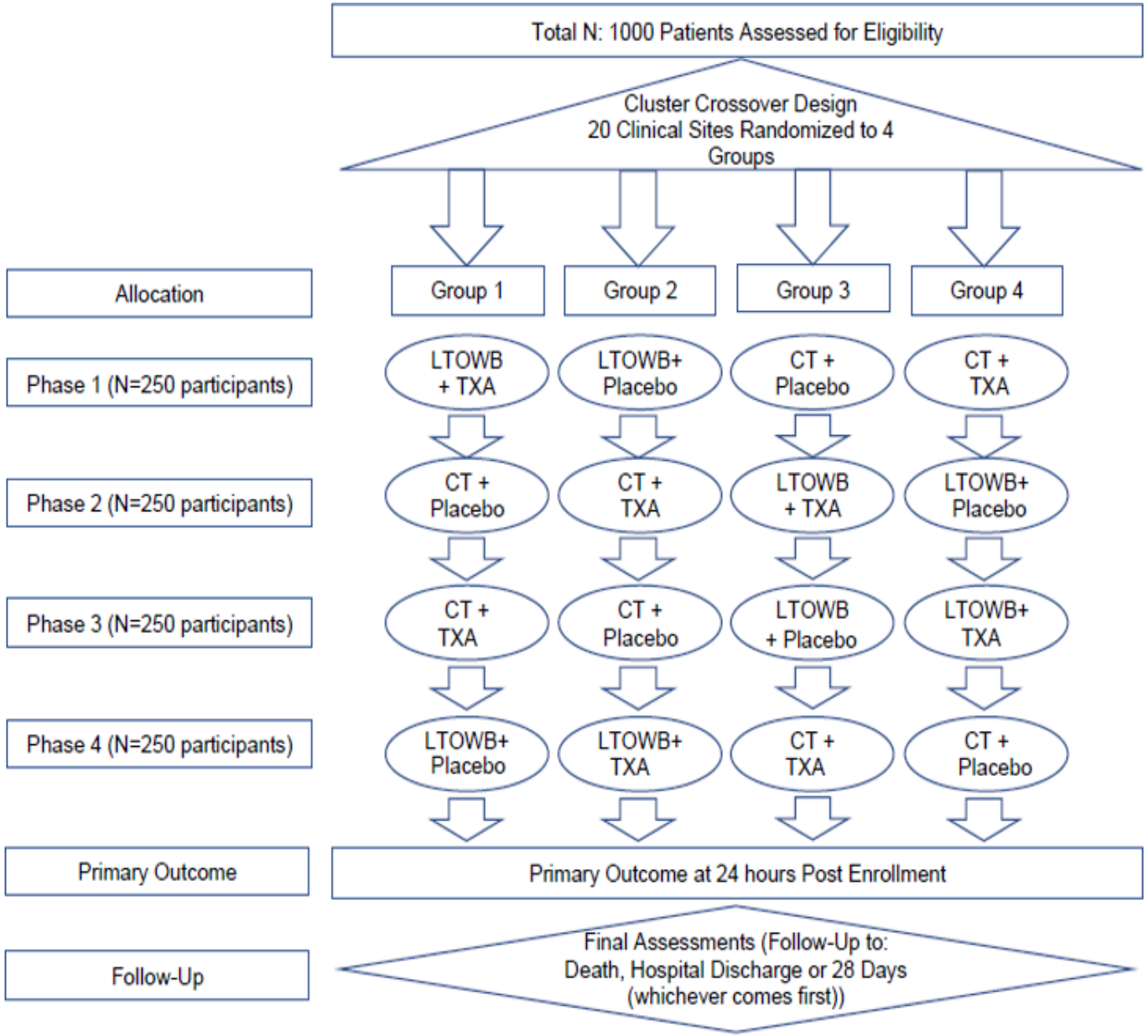
- The **safety objective** is to determine the effect of LTOWB and TXA on safety endpoints

Mechanistic and Pharmacokinetics Objectives

- The **mechanistic objectives** are to:
  - Define trauma induced coagulopathy (TIC) according to measures of shock, hemostasis, and endothelial and immune function
  - Determine if measures of shock, endothelial, immune and hemostatic function upon admission predicts which hemostatic resuscitation therapies improves outcomes without increasing adverse events
  - Determine the mechanisms of how hemostatic resuscitation therapies or combinations of therapies improve TIC endotypes and outcomes
- The **pharmacokinetic objectives** are to evaluate the pharmacokinetics and pharmacodynamics properties of TXA in a population of children with LTH

Study Design

- Number of sites: 20-24
- Target enrollment: 1,000 children
- Cluster randomization
  - Blood and TXA/placebo are assigned by site (not by patient) for a given time period
  - Crossover occurs every 250 subjects (~1 year)



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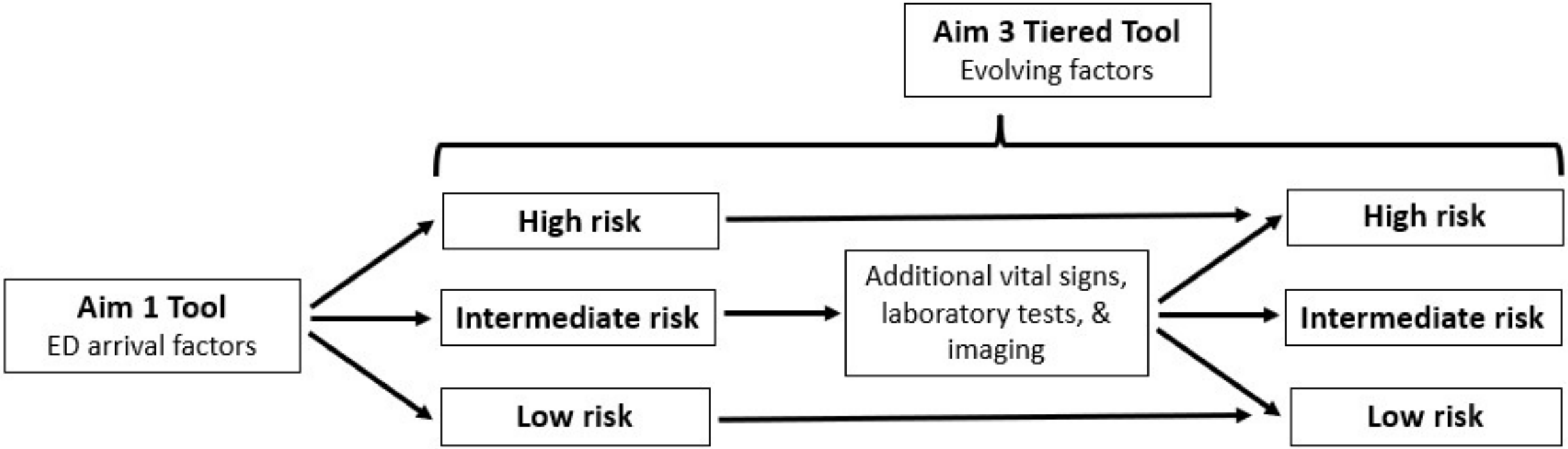
PEDIATRIC TRANSFUSION PROBABILITY AFTER INJURY TOOL (TRAIN)

TRAIN Aims

- *Develop a tool to help guide treatment of hemorrhagic shock that has high performance* and *performs better than physician judgment*

1. Derive and validate a prediction tool for actionable hemorrhagic shock occurring within 6 hours of arrival in a multicenter cohort of injured children using initial ED observations.
2. Compare the performance of the derived tool with clinical judgment for identifying actionable hemorrhagic shock in this cohort.
3. Evaluate the impact of additional vital sign values and laboratory/imaging studies on predicting actionable hemorrhagic shock among children at intermediate risk using the derived tool.



Outcome:

- Actionable hemorrhagic shock within 6 hours, defined by:
  - Needed transfusion
  - Hemorrhage control procedure
  - Death from hemorrhage

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TRAIN Study Design

- **Study Design**
  - Prospective observational cohort
- **Study Population:**
  - Children <18 years old evaluated for blunt or penetrating trauma as "trauma activations" at 12 emergency departments (10 PECARN sites)
- **Data Collection:**
  - Initial patient factors (vital signs, injury mechanism, prehospital interventions)
  - Medical record review
  - Trauma team leader surveys

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TIC-TOC

Traumatic Injury Clinical Trial Evaluating Tranexamic Acid in Children

PIs: Daniel Nishijima, MD, MAS @ UC Davis, Nathan Kuppermann, MD, MPH

Funding: NINDS

Status: Revised, resubmission; R34 completed

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TIC-TOC SPECIFIC AIMS

- **Specific Aim 1:** To evaluate the efficacy of *different doses* of TXA in improving post-injury overall health (PedsQL) in severely injured children with hemorrhagic TBI.
- **Specific Aim 2:** To evaluate the efficacy of TXA on PedsQL across different levels of fibrinolysis.

TIC-TOC Study Design

- **Subjects**: Children (<18 years old) with head trauma (Glasgow Coma Scale (GCS) score of 13 or less) with intracranial hemorrhage on CT scan (patient enrolled after CT scan)
- **Design:** Randomized Controlled Trial
- **Interventions:**
  - TXA 15 mg/kg bolus and 2 mg/kg/hr infusion
  - TXA 30 mg/kg bolus and 4 mg/kg/hr infusion
  - Placebo
- **Outcome:**
  - *Pediatric Quality of Life (PedsQL) Inventory, a global functional outcome measure, one week, one month, three months, and six months after injury.*
  - *Intracranial hemorrhage progression at 24 hours ($\pm$6 hours):*
  - *Safety outcomes: thrombosis, seizures*

TIC-TOC Study Flow