


Assessing the comparative effectiveness of advances in pre-hospital trauma care:

Lessons learned

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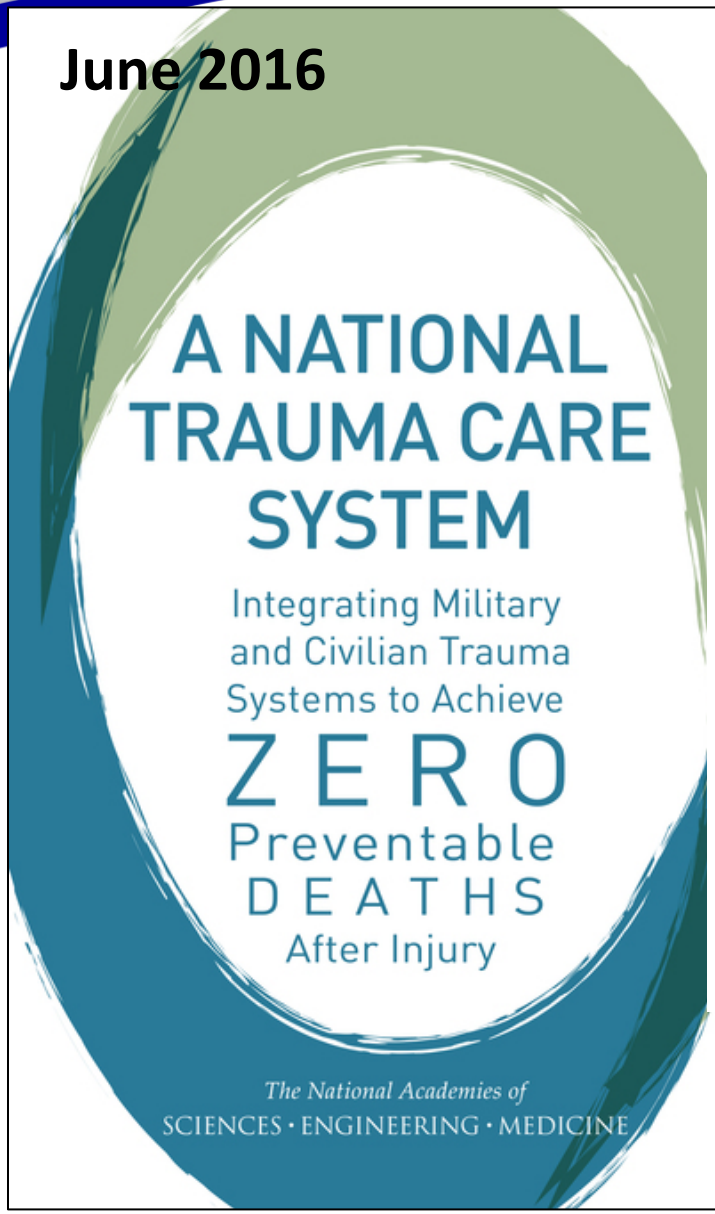
- There are no conflicts of interest to disclose.

June 2016



Wartime Lessons — Shaping a National Trauma Action Plan

Todd E. Rasmussen, M.D., and Arthur L. Kellermann, M.D., M.P.H.

Since the end of major combat operations in Iraq and Afghanistan, analysis of the lessons learned from those wars has focused largely on the wisdom of various foreign-policy decisions, the wars' financial and human costs, and their repercussions for U.S. national security. Although it's long been held that "the only victor in war is medicine," until recently there had been little consideration of the effect of war on military and civilian trauma care.

That changed with the June 2016 release of a report on the topic by the National Academies of Sciences, Engineering, and Medicine.[1] The academies examined how the U.S. military pursued its goal of reducing morbidity and mortality after injury and the implications that its work might have for improving care in civilian settings. The report provides a blueprint for change in national health policy and calls for a National Trauma Care System aimed at eliminating preventable deaths and disabilities caused by accidents, intentional acts of violence, and natural disasters.[1]

The wars in Iraq and Afghanistan presented U.S. military medicine with its toughest challenge since the Vietnam War. In the wars' early phases, the military had no overarching system to collect actionable data on the causes and timing of death, much less to monitor care delivery and outcomes. As injuries and deaths mounted, it became clear that a better approach was needed. In 2004, the Army, Navy, and Air Force agreed to create the Joint Trauma System (JTS), an enterprise modeled on high-performing civilian trauma systems. The initial goals of the JTS included the creation of a trauma registry, modeled on the American College of Surgeons National Trauma Data Bank, to compile treatment and outcomes data, including information on the timing and causes of death and disability; the establishment of procedures to improve performance and the quality of care; and the formation and dissemination of clinical practice guidelines.

Data from the trauma registry illuminated the most pressing challenges, such as bleeding control, and identified aspects of care that were suboptimal or were associated with poor outcomes. The JTS also provided a mechanism for informing the military's trauma research program, evaluating new products and interventions, and integrating techniques developed in the civilian sector, such as damage-control surgery. Because it's not feasible to conduct randomized, controlled trials to assess new innovations or practice methods in a war zone, the JTS relied on retrospective and

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Seven Deadly Sins in Trauma Outcomes Research: An Epidemiologic Post-Mortem for Major Causes of Bias

Deborah J. del Junco, PhD[1,2], Erin E. Fox, PhD[1,2], Elizabeth A. Camp, MSPH[1], Mohammad H. Rahbar, PhD[2,3], and John B. Holcomb, MD[1] on behalf of the PROMMTT Study Group

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1. Ignoring indication bias
2. Ignoring survival/immortal time bias
3. Ignoring time-varying treatment
4. Ignoring time-dependent confounding
5. Assuming uniform effects over time
6. Assuming missing values are missing at random
7. Selecting invalid covariates (collider bias)

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OPEN

Review Article

PREHOSPITAL BLOOD PRODUCT RESUSCITATION FOR TRAUMA: A SYSTEMATIC REVIEW

Iain M. Smith,*†‡ Robert H. James,§‖¶ Janine Dretzke,** and Mark J. Midwinter*†

- 37 unique studies identified, 1 prospective, 0 RCTs, 10 excluded for ambiguities
- Significant heterogeneity precluded a valid summary relative risk (RR) from meta-analysis
- 25/27 studies rated very low quality
- **No survival benefit identified**

Three Major Methodologic Flaws

noted in systematic review by Smith et al

1. **Study groups not equivalent, bias/confounding**
   a. Indications for PHT (bleeding severity)
   b. Interventions other than PHT (pre-post designs)
   c. Time (from injury to start of PHT, post-PHT survival time)
   d. Misclassification of PHT (transported from scene vs. transferred)

2. **Sample sizes too small, too few patients at high risk of hemorrhage-related mortality**

3. **Key data often missing**

Our MEDEVAC PHT Study

Methods

First to frame the issue in explicit terms of timing

- ✓ Minimized bias & confounding
- ✓ Included a large, representative sample of the highest-risk patients most likely to benefit
- ✓ Tracked down missing data

Identified 5 key lessons for future pre-hospital studies

Lesson 1: Select valid covariates (potential confounders) for matching or statistical adjustment

MEDEVAC PHT Retrospective Study Flow Diagram

502 potential study candidates met 3 criteria:

1) U.S. military casualty in Afghanistan April 1, 2012 - August 7, 2015
2) Evacuated alive from the point of injury by MEDEVAC helicopter
3) Documented one of the established indications for PHT:
   a) Multiple traumatic amputations, at least one above knee or elbow
   b) Pre-hospital heart rate >120 beats/minute or systolic blood pressure <90 mmHg

55 PHT recipients were stratified based on 5 factors:

1) Mechanism of injury (gunshot vs. explosion)
2) Positive indicator of hemorrhagic shock (Yes/No)
3) Traumatic limb amputations
   a) 0=none
   b) 1=1 below knee/elbow
   c) 2=2 or more below knee/elbow or 1 above knee/elbow but below hip
   d) 3=2 or more above knee/elbow
4) Maximum severity of head injury by Abbreviated Injury Severity (AIS) score (0-1 vs. 2 vs. ≥3)
5) Significant torso hemorrhage by AIS score (Yes/No)

447 non-recipients were group-matched to recipients

=

345 matching non-recipients

102 unmatched non-recipients.

Injury, Int. J. Care Injured 46 (2015) 775–780

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Collider bias in trauma comparative effectiveness research: The stratification blues for systematic reviews

Deborah J. del Junco [a,*], Eileen M. Bulger [b], Erin E. Fox [a], John B. Holcomb [a], Karen J. Brasel [c], David B. Hoyt [d], James J. Grady [e], Sarah Duran [a], Patricia Klotz [b], Michael A. Dubick [f], Charles E. Wade [a] On Behalf of the ROC Investigators

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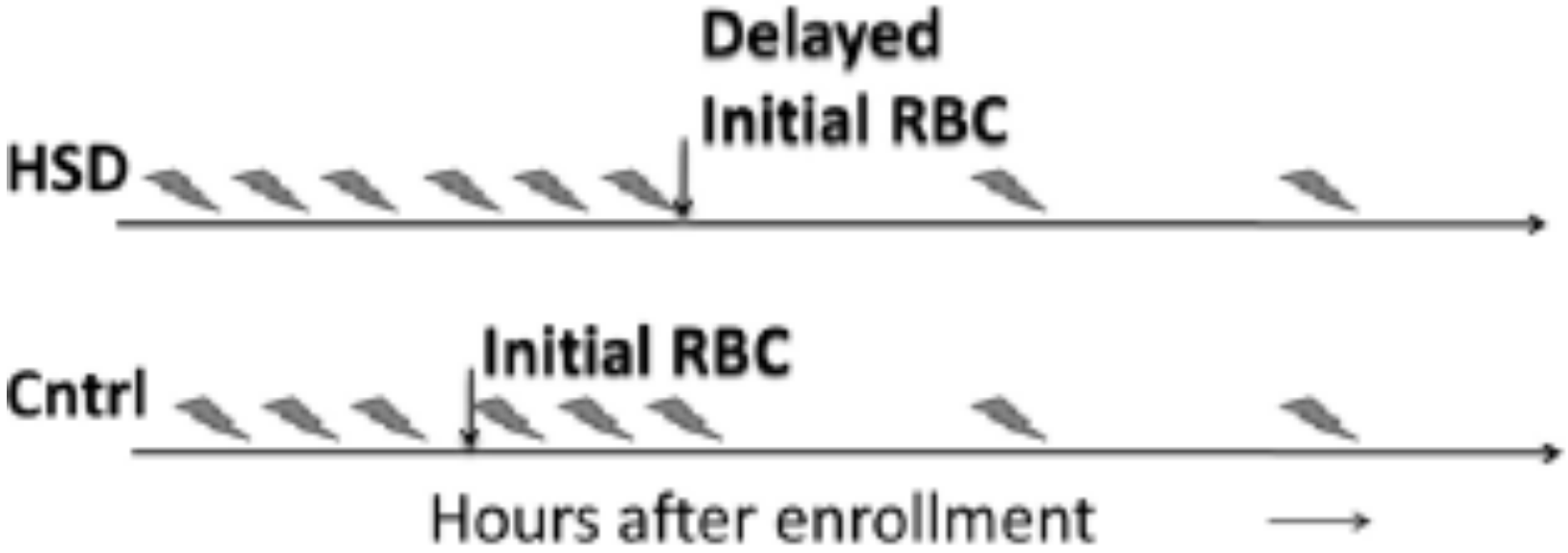
Pre-hospital hypertonic saline RCT stratified by the 24 hour sum of RBC transfusions (0, 1-9, 10 or more units) as a surrogate for bleeding severity



Options toward a Solution 1.

1a.
Intervention:
Prehospital HSD/control

Valid covariate:
Pre-intervention
injury and bleeding
severity status

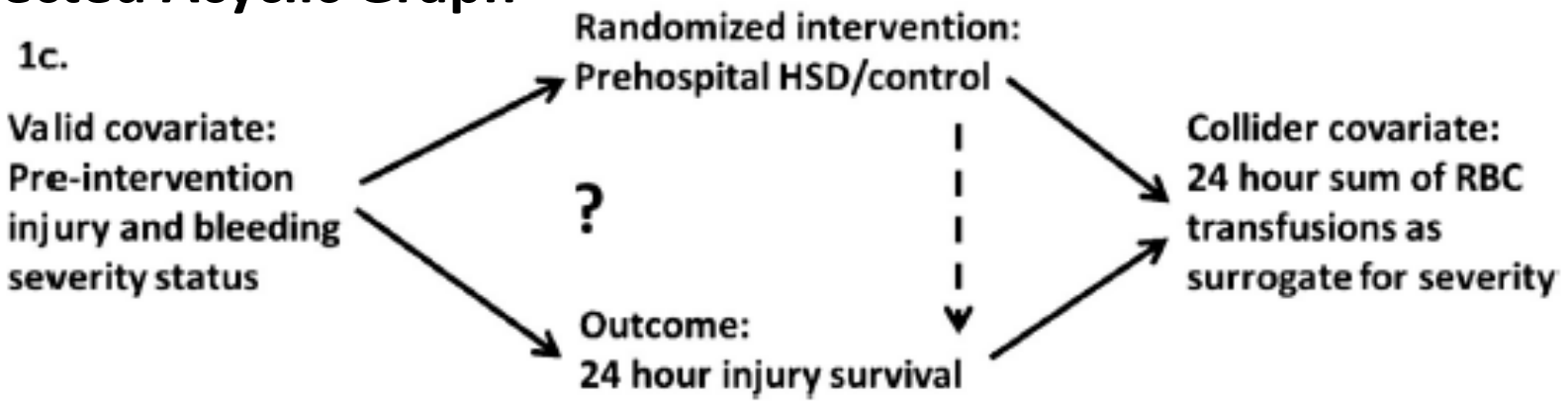
Outcome:
24 hour injury survival

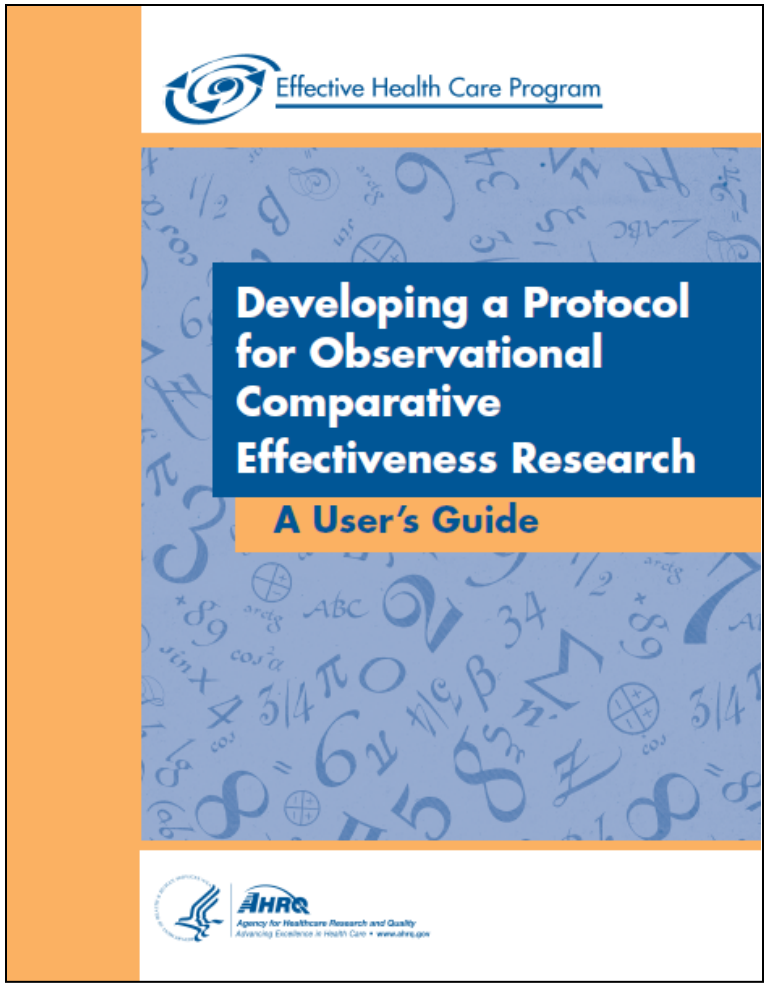
1b.
Intervention:
Prehospital HSD/control

Collider covariate:
24 hour sum of RBC
transfusions as
surrogate for severity

Outcome:
24 hour injury survival

Directed Acyclic Graph





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AHRQ Publication No. 12(13)-EHC099
January 2013

191 Pages

http://www.effectivehealthcare.ahrq.gov/ehc/products/440/1166/User-Guide-to-Observational-CER-1-10-13.pdf

Lesson 2: Identify all highest-risk, PHT-eligible patients (especially pre-hospital deaths) and adjust for left truncation (immortal time/survival bias) given patients had to survive long enough to receive PHT

Injury mortality rates precipitously decline reflecting the sequence of competing risks: early death from bleeding, later head injury, and finally, complications

Time interval after ED admission	Deaths	Hours at Risk	Mortality Rate
Within 6 hours	88	3,590	0.0245
From >6 hours to 24 hours	34	14,039	0.0024
From >24 hours to 30 days	84	491,618	0.0002

PROMMTT study after removal of deaths within 30 minutes of ED arrival

The Journal of TRAUMA® Injury, Infection, and Critical Care

The Missing Dead: The Problem of Case Ascertainment in the Assessment of Trauma Center Performance

David Gomez, MD, Wei Xiong, MSc, Barbara Haas, MD, Sandra Goble, MS, Najma Ahmed, MD, PhD, FACS, and Avery B. Nathens, MD, PhD, FACS

Background: If there are systematic differences in the types of patients captured in registries, then differences in outcomes in centers might be related not to differences in the practice of care, but differences in registry inclusion criteria. We set out to evaluate the effect of variable case ascertainment of dead on arrivals on external benchmarking of risk-adjusted mortality using a form of sensitivity analysis.

Methods: We used data from the National Trauma Data Bank to look for indirect evidence of systematic differences in case ascertainment. We evaluated whether there was any relationship between fewer than expected early (≤24 hours) deaths and overall risk-adjusted mortality. Fewer than expected early deaths were estimated through the W statistic and through an adjusted ratio of early to late (E/L) deaths. E/L ratios were assessed due to the potential correlation between performance and absolute number of early deaths as assessed by the W statistic.

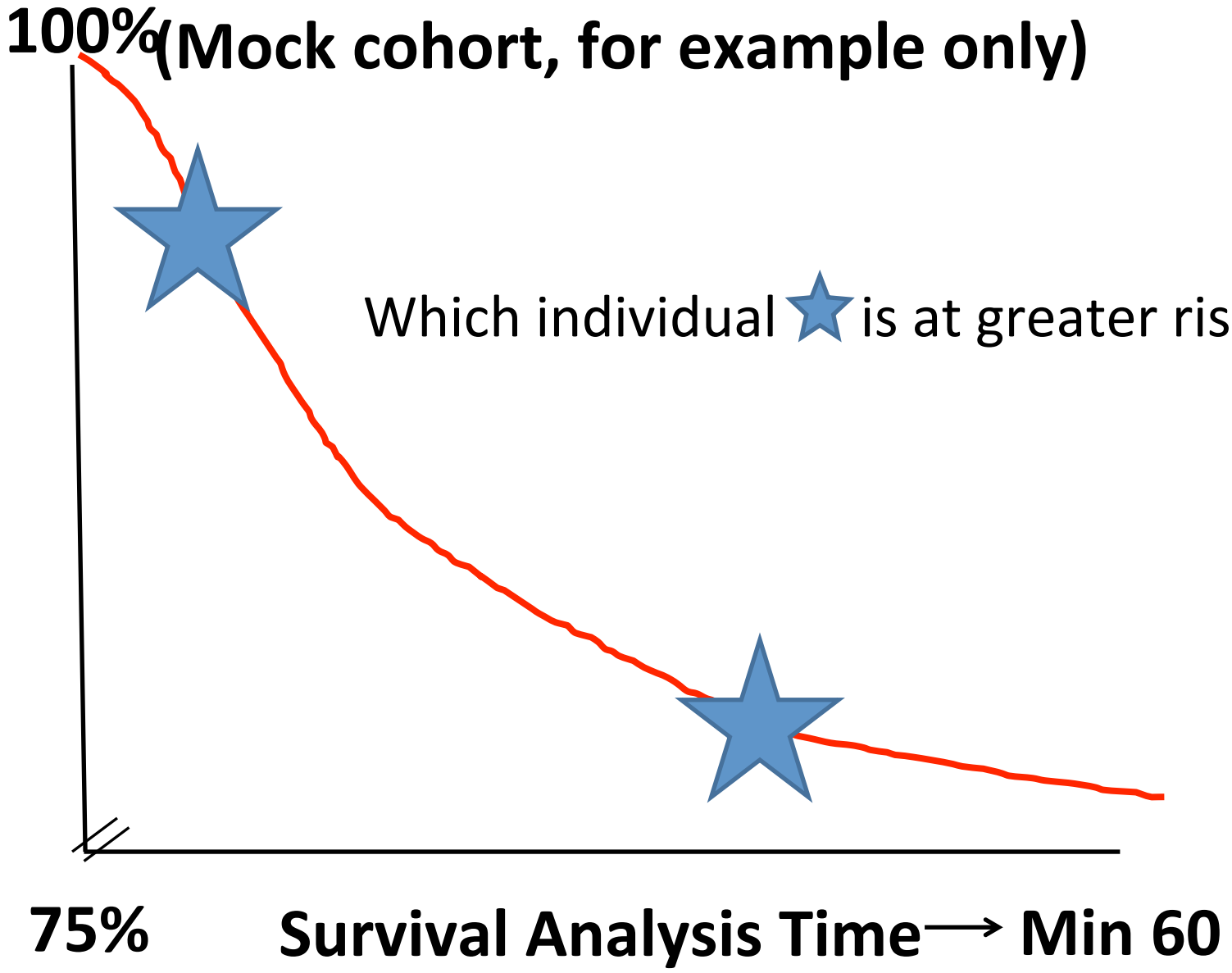
Results: We estimate that as many as 47% of all deaths might be missing due to problems with case ascertainment. Centers with unexpectedly few early deaths (W statistic) were consistently high performing centers with a lower than expected overall mortality. More importantly, there was no relationship between the E/L death ratio and overall risk-adjusted mortality.

Conclusions: Variable case ascertainment of dead on arrivals does not affect the ability to assess performance. Given that our approach has several assumptions, it is critically important that external validation of trauma registries be performed. If centers are to be judged through the quality of their data, then it is incumbent to first assure that data quality meets expectations.

Key Words: Trauma quality improvement, External benchmarking, Risk adjustment, Dead on arrival.

J Trauma. 2009;66:1218–1225.

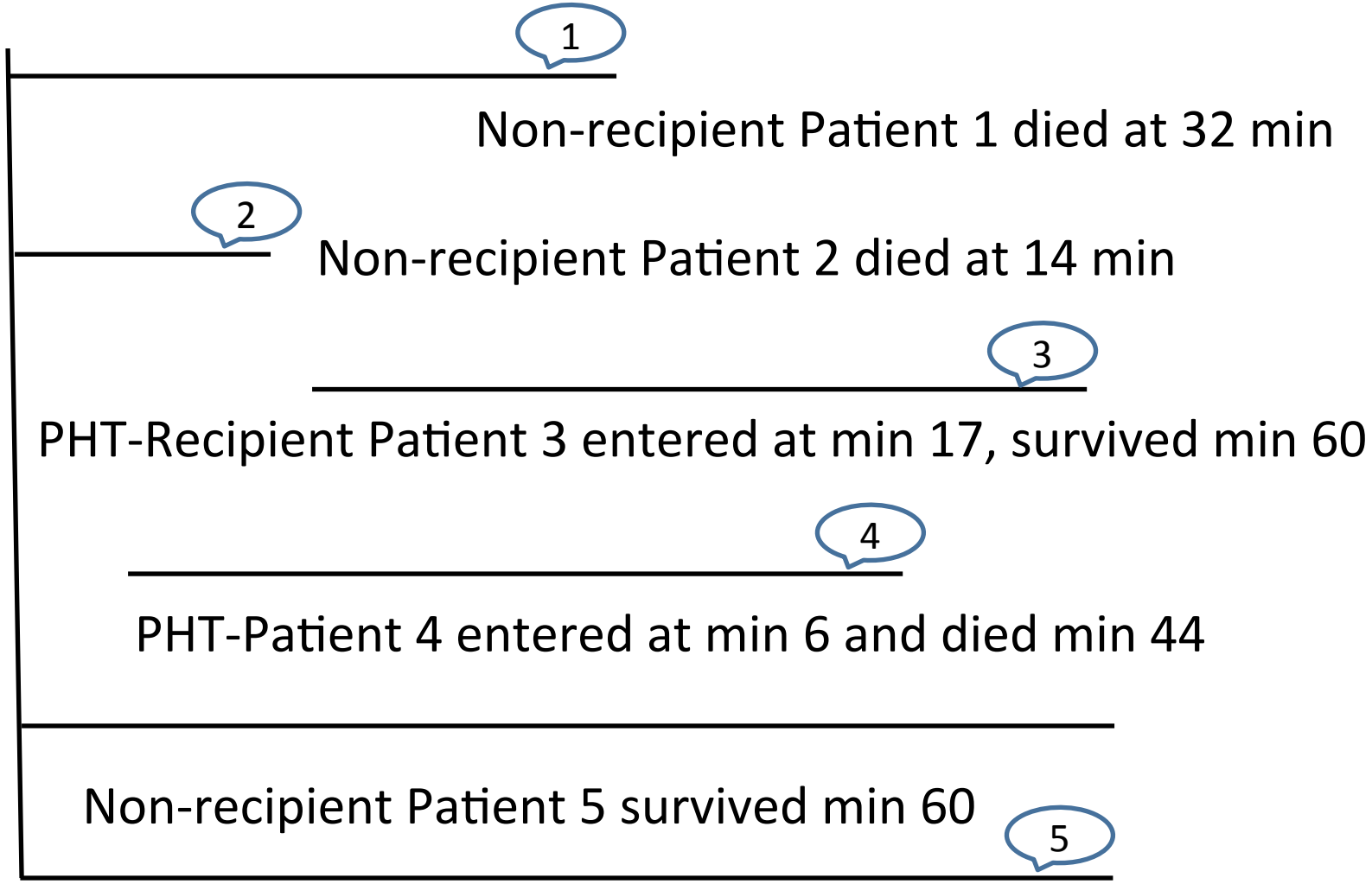
Pattern of Early Survival in Trauma After Injury



Options toward a Solution 2.

Conduct survival analysis using Cox proportional hazards modeling to adjust for covariates (potential confounders) and specify "delayed entry" to appropriately adjust for left truncation (survival long enough to receive PHT)

Delayed Entry in Survival Analysis

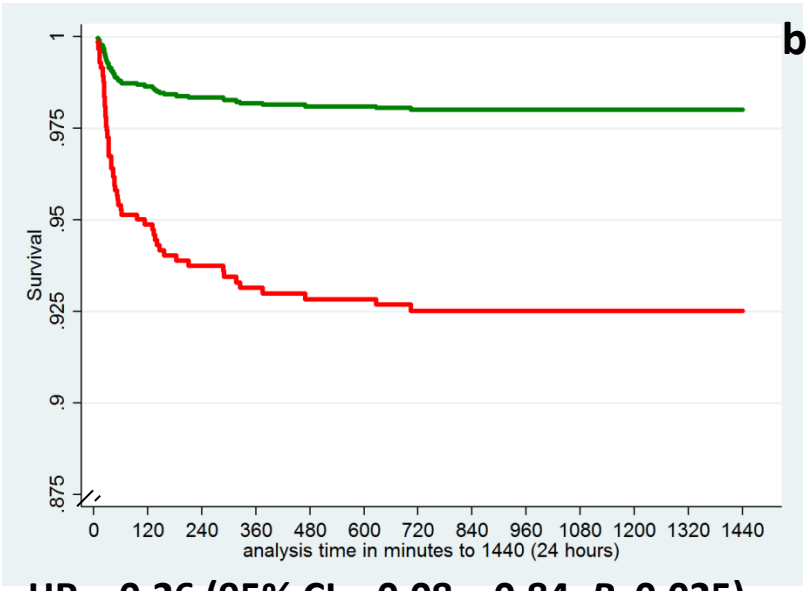


Prior to EDEVAC ??

Adjusted Cox Proportional Hazards Models

a.

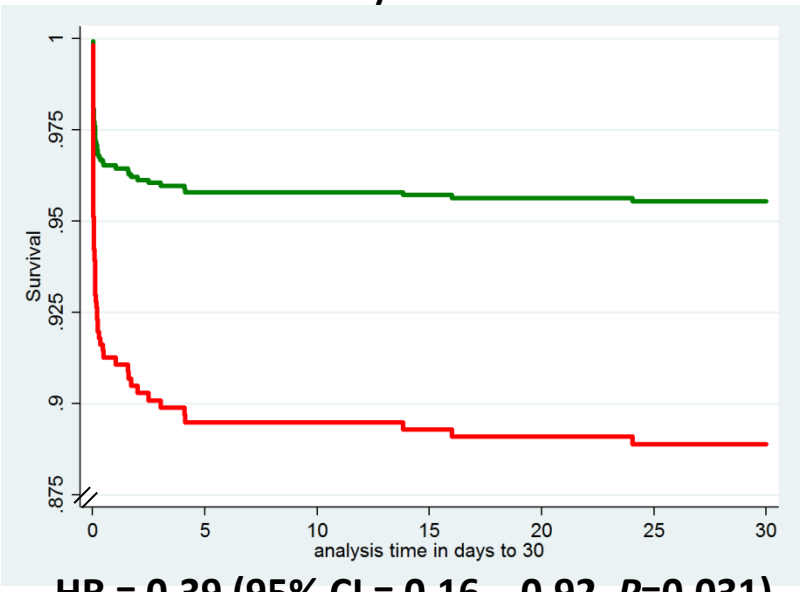
24 hour survival



HR = 0.26 (95% CI = 0.08 – 0.84, *P*=0.025)

b.

30 day survival



HR = 0.39 (95% CI = 0.16 – 0.92, *P*=0.031)

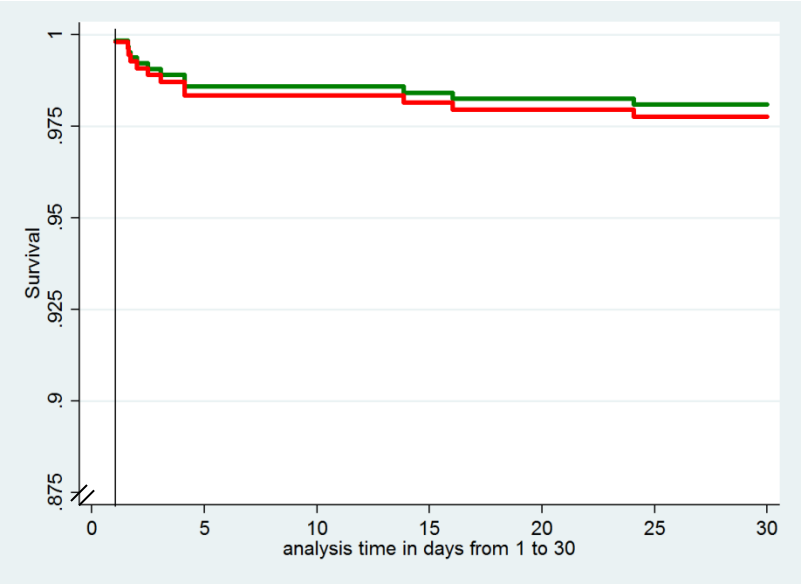
PHT recipients

Non-recipients

HR = 0.84 (95% CI = 0.18 – 4.00, *P*=0.831)

c.

Conditional 30-day survival among 24-hour survivors



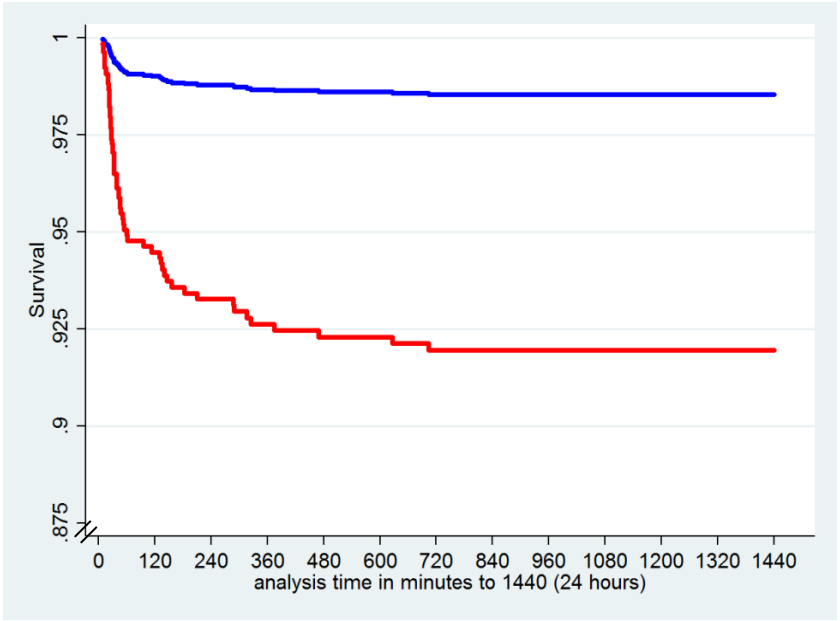
Lesson 3: Some in-hospital transfusions may be initiated sooner after injury than some pre-hospital transfusions.

Need to accurately define the intervention – its start-time (relative to injury occurrence) may be more important than the location or provider-type

Early Transfusion, Pre- or In-Hospital

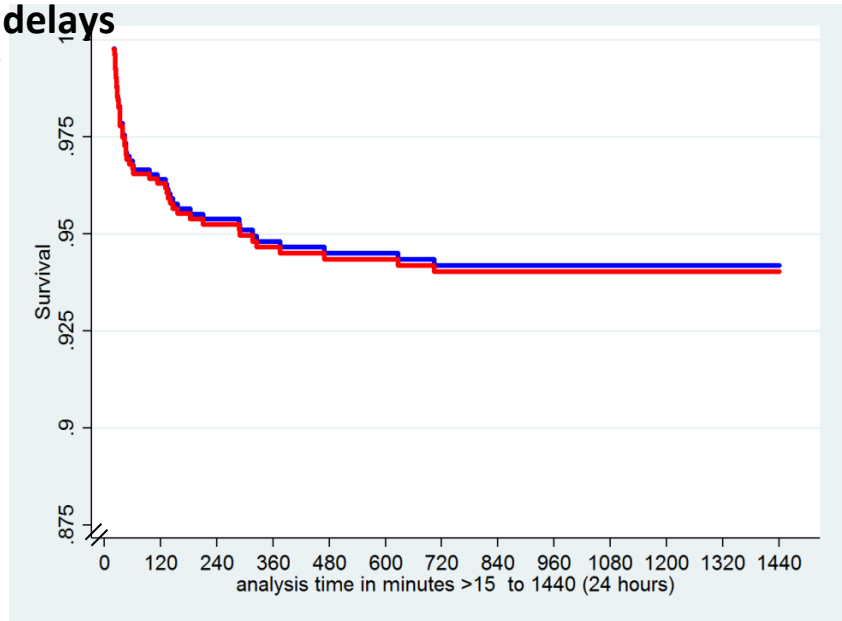
Adjusted Cox Proportional Hazards Models for 24 hour Survival

a. **Transfusion within 15 minutes vs. longer delays after MEDEVAC rescue from point of**



HR = 0.17 (95% CI = 0.04 – 0.73, *P*=0.017)

b. **Conditional survival among 16-minute survivors: Transfusion within 16-20 minutes vs. longer delays**



HR = 0.94 (95% CI = 0.41 – 2.17, *P*=0.887)

Earlier transfusion

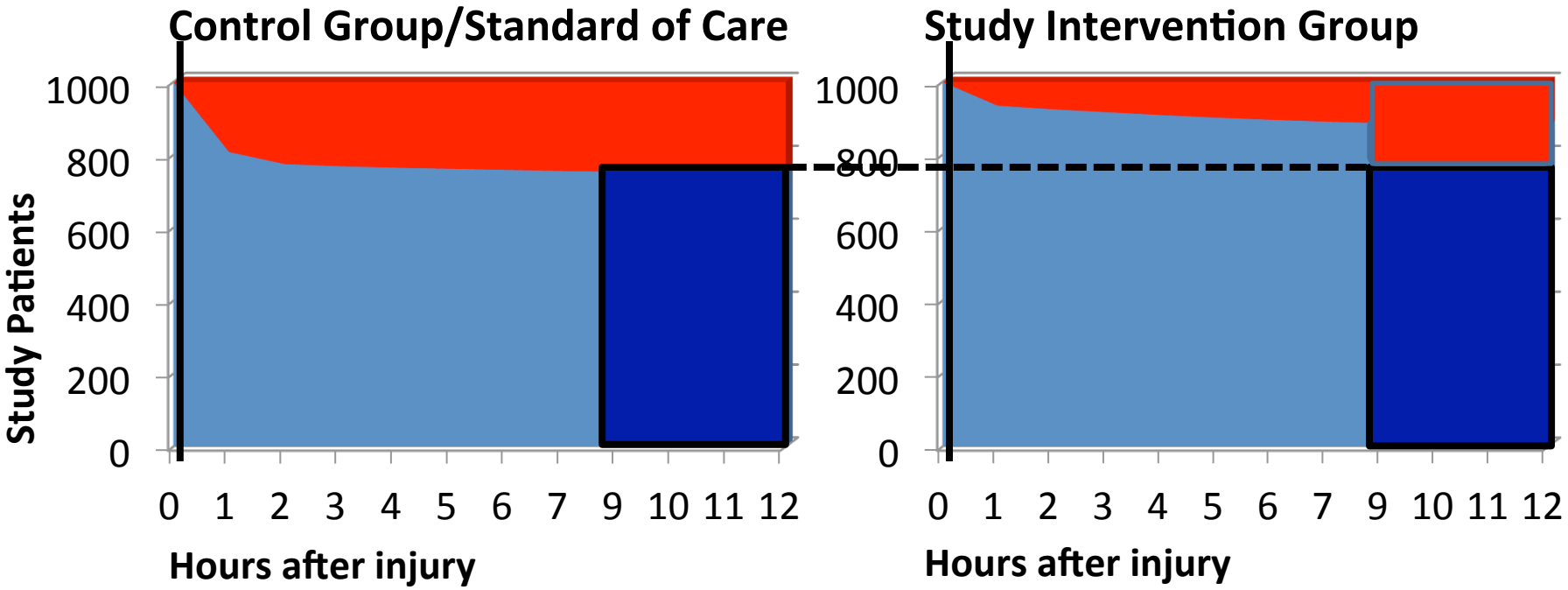
Delayed transfusion

Options toward a Solution 3.

Redefine the intervention in explicit terms of timing and perform appropriately adjusted survival analyses to determine whether there is a critical time window for initiation or administration.

Lesson 4: Early death precludes longer-term outcomes. If the intervention affects early death, the assessment of longer-term outcomes must be adjusted for the competing risk of early death.

Key Requisite: Study Groups are at Equal Risk of Death at Start of Treatment



As time progresses, only survivors can experience subsequent events

Options toward a Solution 4.

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On Estimation of the Survivor Average Causal Effect in Observational Studies when Important Confounders are Missing Due to Death

Brian L. Egleston[1], **Daniel O. Scharfstein**[2], and **Ellen MacKenzie**[3]

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2*Department of Biostatistics, Johns Hopkins School of Public Health*

3*Department of Health Policy and Management, Johns Hopkins School of Public Health*

Suppose we want to test the hypothesis that PHT reduces total 24 hour blood product consumption? Need SACE for any hope of an interpretable result.

Lesson 5: Cautiously interpret findings in light of other evidence available and evaluate robustness to alternative assumptions and analysis strategies

History of the *P* value as an index of significant between-group difference

- **~ 1770:** Pierre-Simon Laplace first calculated it to compare male vs. female births
- **1839:** The American Statistical Association founded
- **~ 1900:** Karl Pearson formally introduced it for χ^2
- **1925:** Ronald Fisher popularized its use in his book, "Statistical Methods for Research Workers"

246, 177, 116, 91 years later…

Taylor & Francis Group

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The ASA's Statement on p-Values: Context, Process, and Purpose

Ronald L. Wasserstein & Nicole A. Lazar

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To link to this article: http://dx.doi.org/10.1080/00031305.2016.1154108

Key Take-home Points from the ASA's 2016 Statement on P value:

1. Does **not** measure the size of an effect or the importance of a result.
2. Does **not** measure the probability that the hypothesis is true or that the data were produced by random chance alone.
3. Does **not** provide a good measure of evidence regarding a model or hypothesis.
4. Should **not** form the basis of scientific conclusions or policy decisions.

So, what does the *P* value actually mean?

Assuming the null hypothesis is true (i.e., between-group difference=0), the sample was drawn randomly, and the observed data are unbiased, it measures only the probability that the results could have been produced by random chance alone.

Options toward a Solution 5.

Eur J Epidemiol (2016) 31:337–350
DOI 10.1007/s10654-016-0149-3

ESSAY

Statistical tests, *P* values, confidence intervals, and power: a guide to misinterpretations

Sander Greenland[1] · Stephen J. Senn[2] · Kenneth J. Rothman[3] · John B. Carlin[4] · Charles Poole[5] · Steven N. Goodman[6] · Douglas G. Altman[7]

"describe in detail the full sequence of events that led to the statistics presented, including 1) the motivation for the study, 2) its design, 3) the original analysis plan, 4) criteria used to include and exclude subjects and data, and 5) a thorough description of all the analyses that were conducted."

Test for alternative assumptions using sensitivity analysis!

Recent Prospective PHT Studies/Trials

1. **PAMPer RCT –** plasma vs. standard of care – **multi-site**
   a. ClinicalTrials.gov NCT01818427, 03/2013 – 03/2017
   b. Currently enrolling
2. **COMBAT RCT –** fresh frozen plasma vs. crystalloid – **single site**
   a. ClinicalTrials.gov NCT01838863, 04/2013 – 04/2017
   b. Terminated due to futility
3. **PROHS observational study** – RBCs/plasma vs. crystalloid – **multi-site**
   a. ClinicalTrials.gov NCT02272465, 10/2014 – 11/2016
   b. Inconclusive results due to between-group imbalance
4. **PUPTH RCT** – thawed plasma vs. normal saline – **single site**
   a. ClinicalTrials.gov NCT02303964, 10/2014 - 2/2016
   b. Withdrawn due to low enrollment
5. **RePHILL RCT –** RBCs/lyophilized plasma vs. normal saline – **multi-site**
   a. EU Clinical Trials EudraCT2015-001401, 13 12/2015 – 06/2017
   b. Currently enrolling
6. **PREHO-PLYO RCT –** lyophilized plasma vs. normal saline – **multi-site**
   a. ClinicalTrials.gov NCT02736812, 03/2016 – 04/2017 (EU)
   b. Currently enrolling

Challenges for Recent PHT Studies/Trials

- Enroll sufficient numbers of high-risk patients
- Deliver PHT soon enough after injury occurrence to prevent hemorrhagic mortality
- Completely ascertain mortality (pre-hospital, in-hospital and 30-day) and other outcomes

Questions:

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