Statistical challenges in endpoint definition and analysis in clinical trials for ICU sedation

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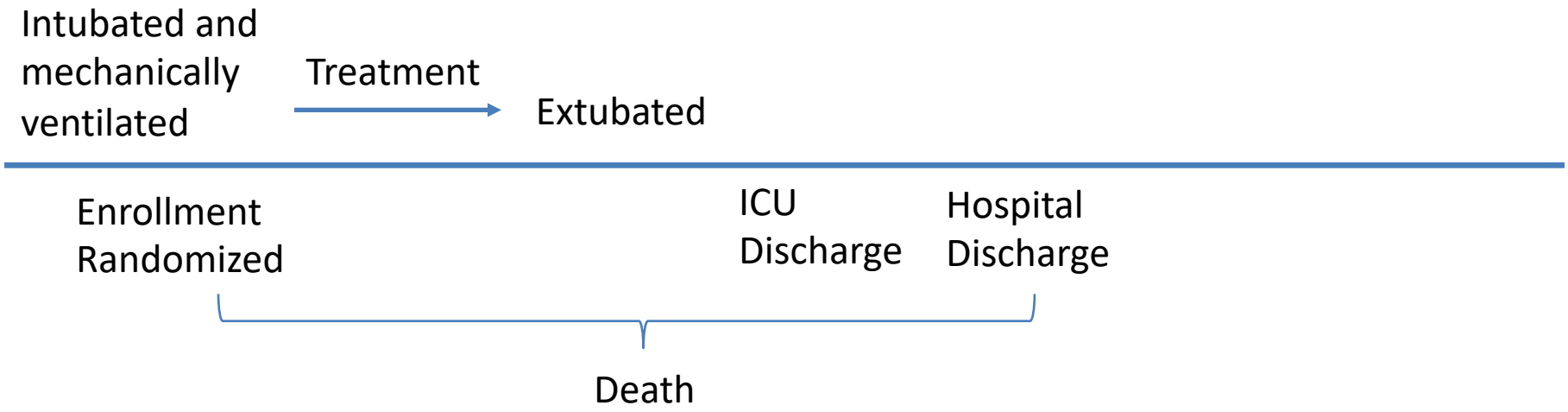
Sedation Trial Design

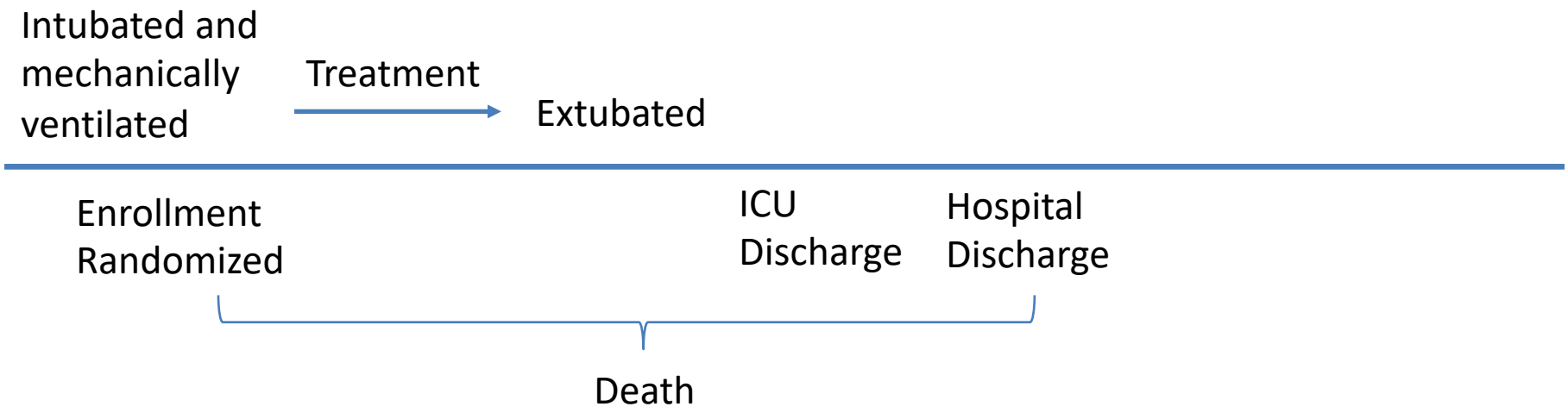


Sedation Trial Design

Completed and on-going trials:

Primary and Secondary endpoints

- Proportion of time at sedation target/goal
- Duration of MV / ventilator-free days
- ICU/Hospital LOS
- Mortality
- **Delirium**



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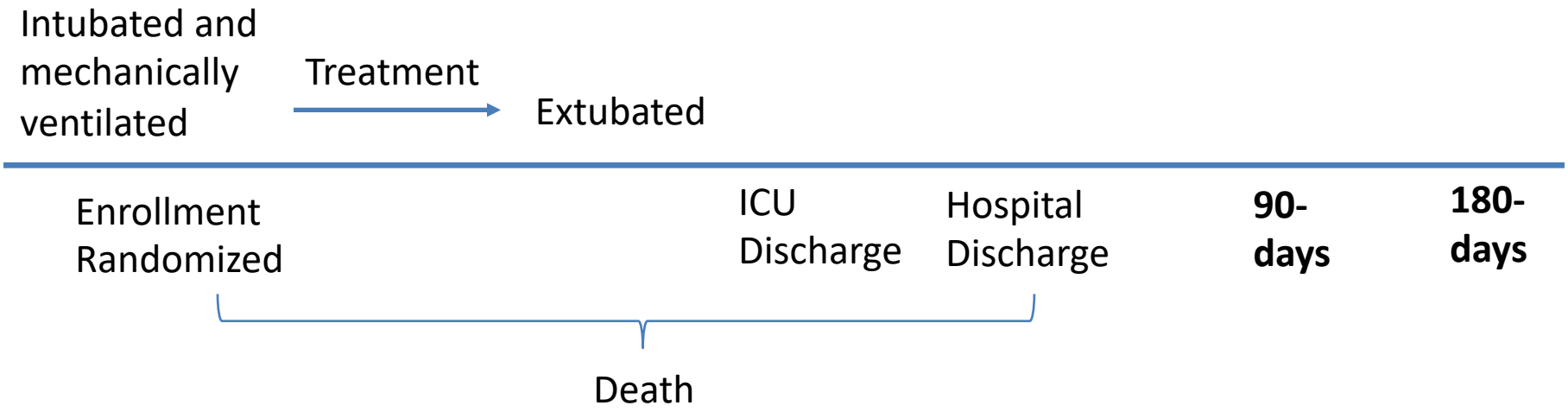
  - **Physical function**
  - **Mental health**
  - **Quality of life**



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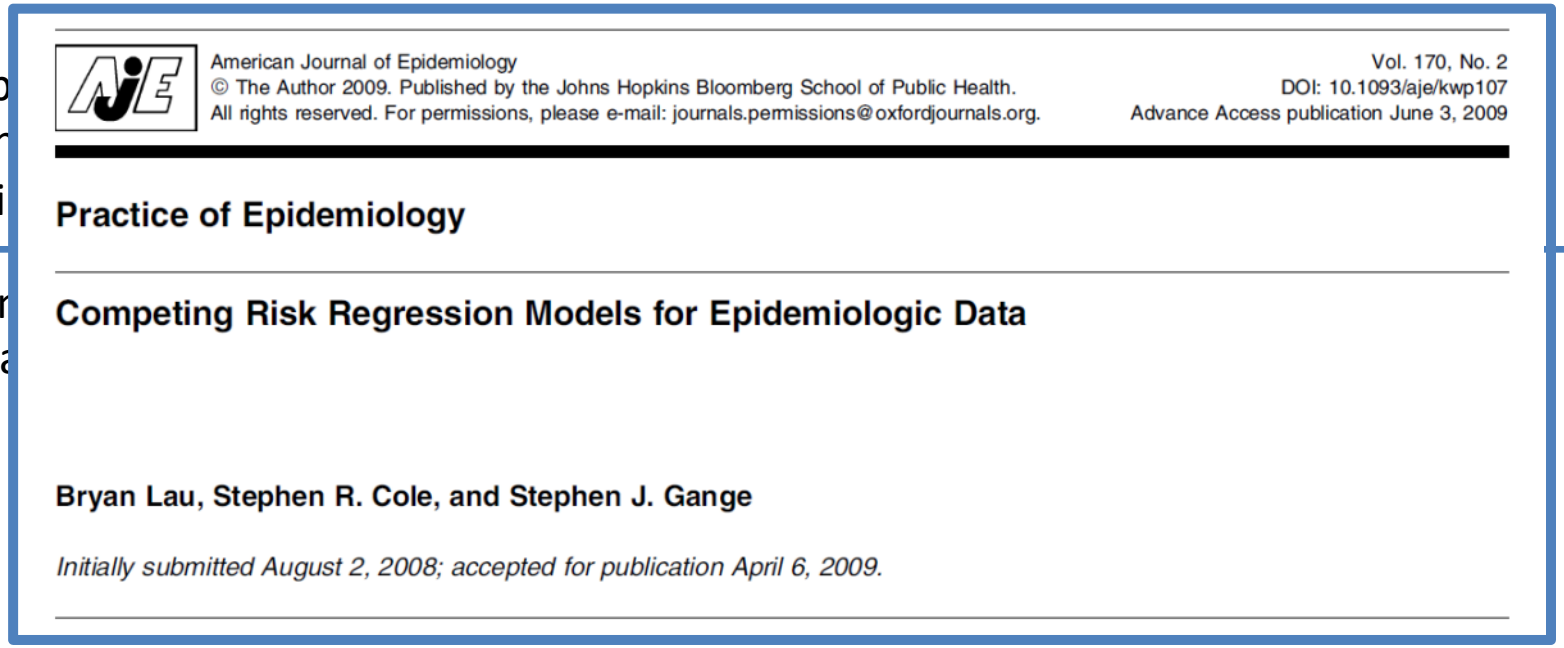

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Advance Access publication June 3, 2009

Practice of Epidemiology

Competing Risk Regression Models for Epidemiologic Data

Bryan Lau, Stephen R. Cole, and Stephen J. Gange

Initially submitted August 2, 2008; accepted for publication April 6, 2009.

Delirium as an endpoint

Rosuvastatin versus placebo for delirium in intensive care and subsequent cognitive impairment in patients with sepsis-associated acute respiratory distress syndrome: an ancillary study to a randomised controlled trial

Dale M Needham, Elizabeth Colantuoni, Victor D Dinglas, Catherine L Hough, Amy W Wozniak, James C Jackson, Peter E Morris, Pedro A Mendez-Tellez, E Wesley Ely, Ramona O Hopkins

Statistical methods for evaluating delirium in the ICU

Published Online June 2, 2016 http://dx.doi.org/10.1016/S2213-2600(16)30138-2

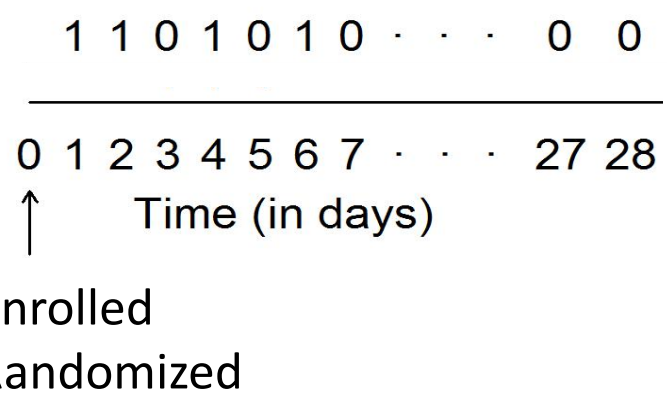
Recently, several studies have evaluated the effectiveness of statins and other interventions in reducing delirium in critically ill patients.[1-4] Studying the effectiveness of interventions on delirium in the intensive care unit (ICU) setting is challenging for counting the days free of delirium up to day 28, with days after ICU discharge typically counted as delirium-free. We recommend against the use of this endpoint in favour of a joint modelling approach proposed[7] in 2007 and implemented in the *R* statistical package

Elizabeth Colantuoni, Victor D Dinglas, E Wesley Ely, Ramona O Hopkins, Dale M Needham

Lancet Respiratory Medicine, 2016

Challenges in defining delirium endpoint

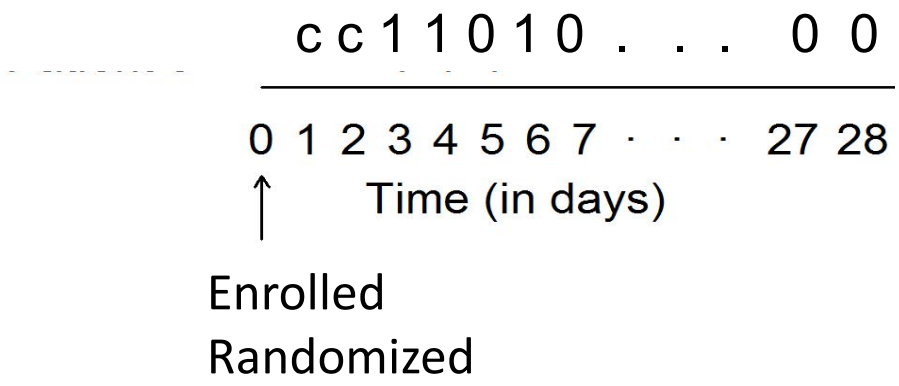
1. Delirium state can change over hours or days



NOTE: Sedation status would also demonstrate this feature, with potentially greater variation and rapid changes over time.

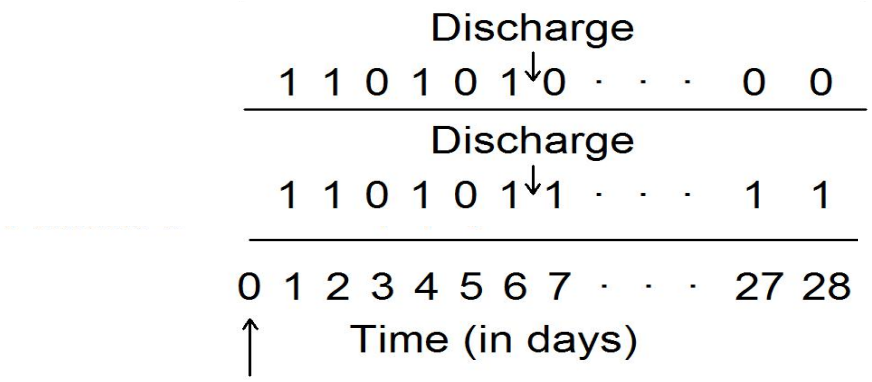
Challenges in defining delirium endpoint

2. Delirium occurs along a continuum and cannot be assessed when the patient is severely impaired (e.g. comatose)



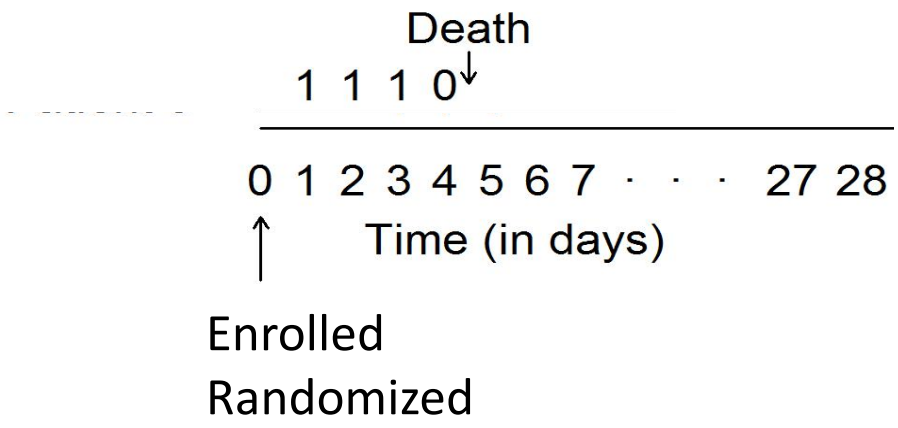
Challenges in defining delirium endpoint

3. Delirium evaluation is often stopped when patients are transferred from one unit to another (e.g. ICU -> hospital ward) but delirium may persist



Challenges in defining delirium endpoint

4. Death can be common



Delirium-free days to X-days

- Based on ventilator-free days to X-days
  - Composite endpoint:
    - 0 if patient dies prior to day X
    - Days free from ventilator among survivors to X-days
  - Compare composite endpoint across treatment groups
    - Rank-based test, e.g. Wilcoxon Rank-Sum test
    - Pre-specified quantiles, e.g. median

Ventilator-Free Day Outcomes Can Be Misleading

Laetitia Bodet-Contentin, MD, PhD[1,2]; Denis Frasca, MD, PhD[1,3,4]; Elsa Tavernier, PhD[1,5]; Fanny Feuillet, PhD[1,6]; Yohann Foucher, PhD[1,6]; Bruno Giraudeau, PhD[1,5]

Crit Care Med. 2018 Mar;46(3):425-429. doi: 10.1097/CCM.0000000000002890.

Delirium-free days to X-days

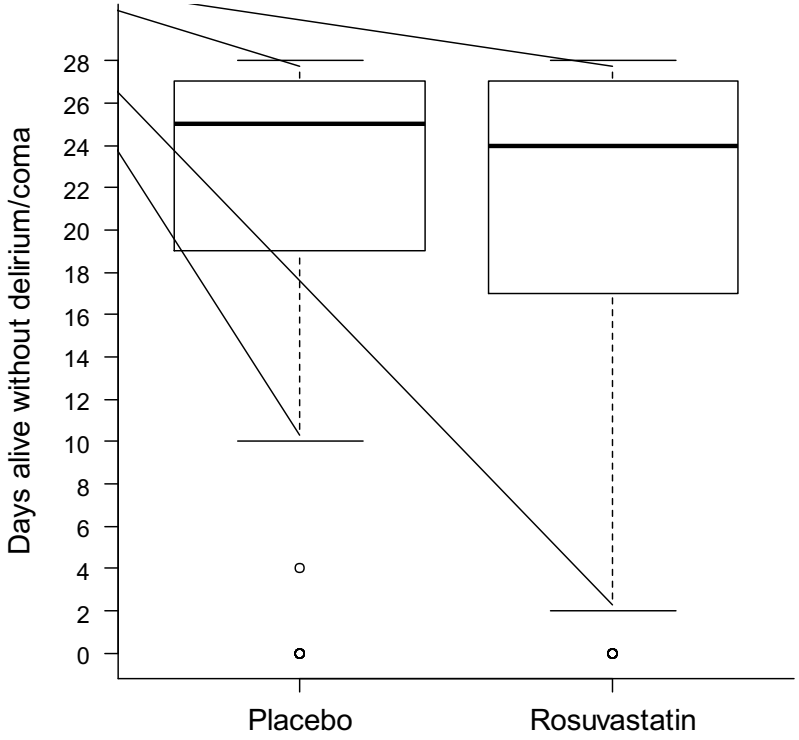
- In sedation trials,
  - Variation in X: 7 (Mayo Clinic), 12 (MENDS), 28 (many)
  - Coma:
    - ABC-trial: days CAM-ICU +, when not comatose
    - Delirium and coma free days
  - Death:
    - Set to 0 (many)
    - Count days free of delirium prior to death (SPICE III)
  - Delirium within X-days but no longer in ICU:
    - Assume no delirium

Alternative approach

- Directly model the delirium and discharge/death process using joint model / shared frailty model
  - Model 1: survival model for daily delirium
  - Model 2: survival model for ICU-discharge/death
  - Random effect (i.e. frailty)
    - Appears in Model 1 linking daily delirium outcome to patient
    - Appears as main term in Model 2 linking daily hazard of delirium with hazard of ICU-discharge/death for each patient
  - Coma days: not at risk
- Treatment effect: main term of treatment in Model 1
  - On any non-comatose day in the ICU, the relative hazard of delirium comparing the treatment to control

SAILS trial: Results

Primary endpoint	Placebo	Rosuvastatin	P-value
Ever Delirious	74%	75%	0.94
Days alive wo delirium/coma	25 (19, 27)	24 (17, 27)	0.39



Joint model:
HR: 1.14 (0.92, 1.41) p = 0.22

On any non-comatose day in the ICU, the hazard of delirium is 14% greater for patients receiving rosuvastatin compared to placebo.

Summary

- Many challenges
  - Composite endpoint approach: Consistent definition accounting for death, coma and delirium after ICU discharge
  - Joint model: Directly models the delirium process but currently allows for a single model for the competing risk
  - Alternatives?
  - Missing data

NIA funded R01

NIA funded R01 exploring these challenges within preventative and therapeutic RCTs for delirium

- R01AG061384: 2/19 – 12/22
- **Aim 1**: Systematic review of delirium endpoint definition and analysis plus extensive simulation studies designed to evaluate advantages/disadvantages of current approaches
- **Aim 2:** To create and disseminate novel extensions of existing joint models statistical methods to separately account for both the competing risk of death and of discharge in evaluating delirium interventions.
- **Aim 3:** Extensive simulation studies to compare current approaches (Aim 1) to novel approaches (Aim 2), and make relevant methodological recommendations.

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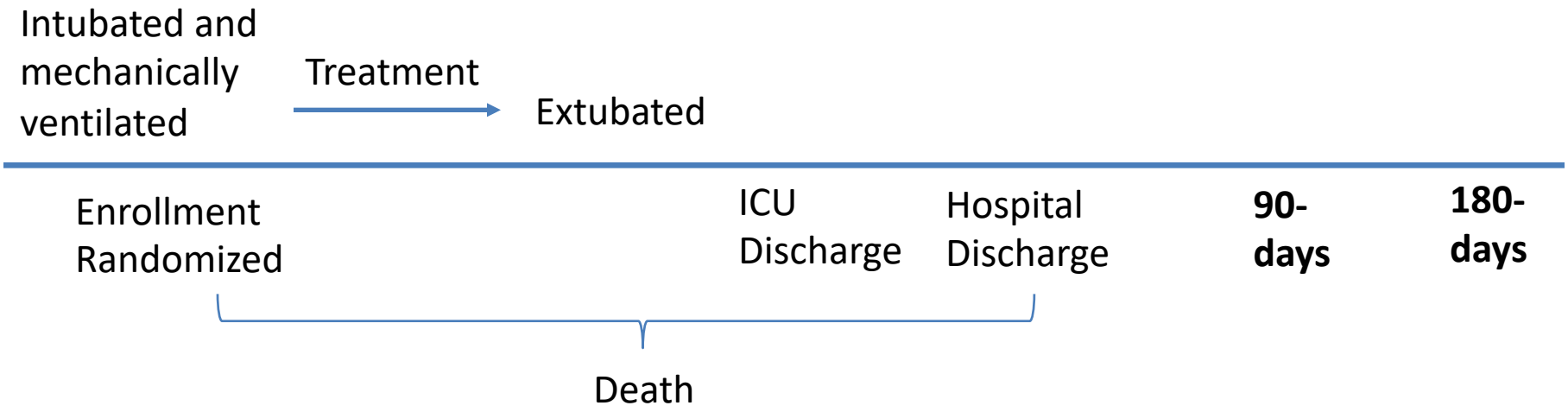

Statistical methods to compare functional outcomes in randomized controlled trials with high mortality

Elizabeth Colantuoni,[1,2] Daniel O Scharfstein,[1,2] Chenguang Wang,[3] Mohamed D Hashem,[1,4] Andrew Leroux,[2] Dale M Needham,[1,4,5] Timothy D Girard[6]

[1]Outcomes After Critical Illness and Surgery (OACIS) Group, Johns Hopkins University, Baltimore, MD, USA
[2]Department of Biostatistics, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA
[3]Division of Biostatistics and Bioinformatics, Johns Hopkins University School of Medicine,

Mortality is a common primary endpoint in randomized controlled trials of patients with a high severity of illness, such as critically ill patients. However, researchers are increasingly evaluating functional outcomes, such as quality of life. Importantly, in such controlled trials evaluating treatments for seriously ill patients, such as those with critical illness receiving care on an intensive care unit (ICU). In such trials mortality is a common primary outcome measure. However, given the high value that patients place on outcomes other than mortality, including cognition, physical function, and quality of life, such functional outcomes are increasingly being evaluated as coprimary or key secondary outcomes in such

Cite this as: *BMJ* 2018;360:j5748
http://dx.doi.org/10.1136/bmj.j5748

Treatment effect definition:
Functional outcome, No mortality

- Assume no patient mortality
- Goal: Compare 90-day cognitive function across treatment groups

Cognitive Function		Causal Effect
Intervention	Control	
Y(1)	Y(0)	Y(1) – Y(0)

- Marginal or Average Treatment Effect: E[Y(1) – Y(0)]

Treatment effect definition:
Functional outcome, “truncated due to death”

	Survival Experience to 90-days		**90-day Cognitive Function**	
	Intervention	Control	Intervention	Control
Time of death (days)	T(1)	T(0)		
Survive to 90-days	S(1)	S(0)		

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Always survivors	S(1) = 1	S(0) = 1		
Mortality Benefiters	S(1) = 1	S(0) = 0		
Always Diers	S(1) = 0	S(0) = 0		
Specials	S(1) = 0	S(1) = 1		

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Survivor Average Causal Effect, SACE: E [Y(1) – Y(0) | *Always survivors*]

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Survivors Only: $E [Y(1) \mid S(1) = 1] - E [Y(0) \mid S(0) = 1]$

Conditional Methods

Survivor Average Causal Effect, SACE: $E [Y(1) – Y(0) \mid$ *Always survivors* $]$

- Advantage:
  - Direct effect of intervention on functional outcome
- Disadvantage:
  - Requires untestable assumptions to compute
  - Does not include all randomized patients

Survivors Only: $E [Y(1) \mid S(1) = 1] – E [Y(0) \mid S(0) = 1]$

- Advantage:
  - Simple to implement
- Disadvantage:
  - May be misleading
  - Does not include all randomized patients

Composite Endpoint Approaches

- Requires that we can rank the patients
- Example, Lachin (1999)
  - Earlier death is worse than later death
  - Among survivors, poor functional outcome worse than good functional outcome

- Define $W(1) = T(1)$ if $S(1) = 0$
  $= Y(1) + c$ if $S(1) = 1$

- Does not make sense to define $E[W(1) – W(0)]$
- Compare the distribution of $W(1)$ and $W(0)$, e.g. rank sum test
- Compute quantiles for the distribution of $W(1)$, e.g. median

Composite Endpoint Approaches

Percentile	Intervention	Control
25th	Experienced death by 60 days	Experienced death by 12 days
50th	Survive to 90 days with cognitive function ≤30	Experienced death by 50 days
75th	Survive to 90 days with cognitive function ≤ 45	Survive to 90 days with cognitive function ≤40
90th	Survive to 90 days with cognitive function ≤ 49	Survive to 90 days with cognitive function ≤ 47

Recommendations

No clear winner, choice depends on belief in assumptions:

- When it is biologically unlikely that the intervention impacts mortality → Survivors only analysis
- When mortality is the primary endpoint,
  - It is hypothesized that there will be a difference in mortality across intervention groups
  - Analyses of functional outcomes should consider alternative methods (e.g. composite endpoint approach).

Other Observations

- Limited use of group-sequential designs
  - NONSEDA trial, single interim analysis after 350 patients
  - Rate of recruitment, duration of follow-up
- Baseline covariate adjustment
- Adaptive enrichment designs
- Other novel designs