Randomized Trials in the ICU

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Outline

• Trial designs
• Control groups
• Outcomes/Endpoints
• Attributable mortality
• Cluster randomized designs

Trial Designs

• Depends on patient population, disease, treatment, prophylaxis, availability of other accepted treatments and safety.

• Randomized cross-over – highly efficient, but…

• Retrospective cohort – rare diseases, assoc studies, waiver of consent. Benefit from dose-effect and propensity analysis.

• Before/After

• RCT – gold std but expensive and time-consuming
Control Groups

- Case matched
- Placebo controlled.
- Active comparator (Helsinki).
- Add-on trial design (most common RCT).
- Rescues in control or intervention arms.
Controls: Usual Care ("wild-type")

• Sounds good, but…
• Not good if:
  – wide variation in practice
  – not supported by evidence
  – large overlap between range of usual practices and the intervention arm.
  – usual care is not stable
  – Hawthorne effect
Outcomes

• Associated vs. attributable (statistical power)
• Physiological outcomes
• Biomarkers (clinically relevant?)
• Morbidity examples
  – Ventilator time
  – Ventilator free days
  – Organ failure free days
  – Time to shock reversal
Attributable Mortality and Power

Power .80
N=20 per arm

Placebo: 50% Mortality
Treatment: 10% Mortality
ARR: 40%; RRR: 40 / 50 = 80%

% Mortality
Initial Trophic vs Full Enteral Feeding in Patients With Acute Lung Injury
The EDEN Randomized Trial

The amount of enteral nutrition patients with acute lung injury need is unknown.

To determine if initial lower-volume trophic enteral feeding would increase ventilator-free days and decrease gastrointestinal intolerances compared with...
From: Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012

Absolute decrease of 1.3% per year!

Mortality %

35%  Less is More?

• Fewer drugs (esp. steroids, sedatives, starch)
• Less enteral and esp. parenteral feeding
• Less maintenance fluid
• Lower tidal volume
• Even less bed rest

18%

Date of download: 10/18/2015
Survival is Higher In Experienced Hospitals

Walkey et al. AJRCCM 2014 189:548-555
Randomized Evaluation to Improve Health Care Delivery

• Science (Feb 13, 2015)
  – “Randomized evaluations of fundamental issues in health care policy and delivery should be—and can be—closer to the norm than the exception.”
  – “When feasible, randomized designs have an unparalleled ability to provide credible evidence on an intervention’s impact.”
  – Funding available for this work:
    • PCORI - $3.5 billion
    • CMS Innovation Awards - $1 billion
WASHINGTON — The gold standard of scientific research, routinely used in the development of new drugs, has been neglected in studies meant to improve the American health care system, researchers reported on Thursday in the journal Science.

The method, known as random assignment, compares outcomes for people randomly chosen to receive a treatment with the results for those...
Cluster Randomized Trials

• Unit of study is hospital, ward, cohort.
• Concerns for Hawthorne or “bleed-over” effect.
• Multiple units and cross-over designs are more powerful.
• Usually more pragmatic
• Often more meaningful to conducting sites b/c results are so directly applicable (or not).
• Best for minimal risk studies
Isotonic Solutions and Major Adverse Renal Events Trial (SMART)

Hypothesis: Use of “physiologically-balanced” isotonic crystalloids compared to 0.9% saline in ICU patients will decrease the incidence of death, dialysis, and persistent renal dysfunction.
Challenge:

- Enroll >5,000 ICU patients
- Control delivery of a time-sensitive intervention
- Collect patient-level fluid, lab, and outcome data

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<th>Traditional Approach:</th>
<th>Alternative Approach:</th>
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<td>- Half a decade</td>
<td>- Novel study structure</td>
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<td>- Hundreds of personnel</td>
<td>- Informatics-enhanced:</td>
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<td>- Dozens of centers</td>
<td>- Intervention</td>
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<td>- Millions of dollars</td>
<td>- Data collection</td>
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Study Structure

- **Cluster-randomized**
  - Each ICU randomized to a Fluid Group ("NS" vs. "balanced")

- **Multiple-crossover**
  - 1 month blocks, 11 crossovers (one year) → 8,000 patients

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Delivery of the Intervention
Delivery of the Intervention

Step 3

Behind-the-scenes

Isotonic Fluid Advisor

1. Triggering Fluid Orders

Group A
- LR BOLUS
- LR: LACTATED RINGERS
- LR FOR RAPID INFUSION (SICU)
- DSSR
- PLASMA-LYTE A BOLUS
- PLASMA-LYTE A
- DSSR + KCL 10 MEQ/L
- DSSR + KCL 20 MEQ/L

Group B
- NS BOLUS
- NS: SODIUM CHLORIDE 0.9%
- NS + KCL 10MEQ/L
- NS + KCL 20MEQ/L
- NS + KCL 40MEQ/L
- NS FOR RAPID INFUSION (SICU)
- DSNS
- DSNS BOLUS
- DSNS + KCL 10 mEq/L
- DSNS + KCL 20 mEq/L
- DSNS + KCL 30 mEq/L
- DSNS + KCL 40 mEq/L

2. Assignment of fluid groups

Isotonic Fluid Advisor

3. Select an option below:
- Choosing an “order” option will order the study fluid
- Choosing a “Bypass” option will order the originally selected fluid
- Bypassing due to specific attending request will cause a form to pop up with a field to enter the attending’s name

4. Exit the Isotonic Fluid Advisor to the ordered fluid

1. No
   - Pilot Period
     - Within study period?
       - Yes
         - Patient 2 18 yrs?
           - Yes
             - Trigger Isotonic Fluid Advisor Logic
           - No
             - Patient in study ICU?
               - Yes
                 - Isotonic Fluid Advisor to original fluid selected by provider
               - No
                 - Patient in MICU?
                   - Yes
                     - Patient enrolled in Salt Study
                   - No
                     - No
                       - Was correct fluid chosen per study allocation?
                         - Yes
                           - See fluid allocation schedule
                         - No
                           - No
                             - Patient enrolled in Salt Study
4. Exit the Isotonic Fluid Advisor to the ordered fluid

Assigned fluid = Group A (PLA or LR)

Assigned fluid = Group B (NS)
VUMC is comparing the use of NS with LR/Plasmalyte in ICU patients. Your patient has been assigned to NS unless a contraindication is present.

If a contraindication is present, please select from the list below to order off-study IV fluid. Otherwise select Option 1.

Contraindications for Balanced Fluid the can trigger bypass:
- hyperkalemia
- brain injury
- specific attending request

Select an option below:
1. Order normal saline bolus
2. Bypass due to specific attending request
3. Exit Without Ordering
Isotonic Solution Administration: Logistical Testing (‘SALT’ Pilot)

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- MICU only
- Tested:
  - Pharmacy system to stock study fluid
  - CPOE application to direct providers
  - Physician and nurse compliance
  - Electronic data collection
Results...
## Delivery of the Intervention

### SALT Study Dashboard

<table>
<thead>
<tr>
<th>Month of Order Date</th>
<th>Group</th>
<th>PCU</th>
<th>Initial Fluid Correct</th>
<th>Override: Att Request</th>
<th>Override: Brain Injury</th>
<th>Override: Hyperkalemia</th>
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<td><strong>Grand Total</strong></td>
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Clinical Outcomes

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<tr>
<th>Outcome</th>
<th>Saline (n = 451)</th>
<th>Balanced (n = 521)</th>
<th>P value</th>
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<td>In-hospital mortality</td>
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<td>Hospital length of stay (days)</td>
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MAKE30: 31.9%

Died: 15.1%

New RRT: 5.0%

*Cr>200%: 22.5%
Conclusion – Pilot successful!

Next stop: Neurocare unit Oct 1st

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Next stop: Neurocare unit Oct 1st
Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit

The SPLIT Randomized Clinical Trial

Paul Young, FCICM; Michael Bailey, PhD; Richard Beasley, DSc; Seton Henderson, FCICM; Diane Mackle, MN; Colin McArthur, FCICM; Shay McGuinness, FANZCA; Jan Mehrtens, RN; John Myburgh, PhD; Alex Psirides, FCICM; Sumeet Reddy, MBChB; Rinaldo Bellomo, FCICM; for the SPLIT Investigators and the ANZICS CTG

Figure 2. Cumulative Incidence of Patients Requiring Renal Replacement Therapy Until Day 90 After Enrollment in the SPLIT Trial

Mortality
8.6% Saline (n=1110)
7.6% Balanced (n=1152)
P = n.s.
Chlorhexidine – Example

- Randomized-cluster cross-over design.
- 9,340 patients randomized to:
  - Chlorhexidine
  - Control group
- 5 Vanderbilt ICUs randomized for 1 year.
- Used only the Vanderbilt Electronic Medical Record for data collection.
CONCLUSION AND RELEVANCE  In this pragmatic trial, daily bathing with chlorhexidine did not reduce the incidence of health care–associated infections including CLABSIs, CAUTIs, VAP, or C difficile. These findings do not support daily bathing of critically ill patients with chlorhexidine.
Attributes of the Chlorhexidine Cluster Randomized Trial

• Feasible and Pragmatic
• Low cost
• Participant screening minimal
• Waived informed consent
• Rapid (less than one year, n=9,340)
• Results immediately applicable
Senior Investigators
Todd Rice
Art Wheeler
Gordon Bernard

Collaborators
Mike Noto
Dave Janz

ICU medical directors
Avi Kumar
Andrew Shaw
Oscar Guillamondegui
Addison K. May
John A. Barwise

Nephrology
Eddie Siew
Alp Ikizler
Jamie Dwyer

Pharmacy
Fred Hargrove
Seth Strawbridge
David Mulherin
Mark Sullivan
Joanna Stollings

Bioinformatics
Jesse Erhenfeld
Jonathan Wanderer
Michael Plante

Biostatistics
Dan Byrne
Hank Delmonico
Thank You!