Pragmatic Trials in Critical Care

Integrating comparative effectiveness trials into clinical care as part of a Learning Healthcare System

Network for Investigation of Delirium
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  • None
Traditional Model

Understand biology
Identify treatment targets

Identify treatments surrogates outcomes

Safety in Humans

Efficacy in Patients

Implementation Into Practice

Surfactant for ARDS
Monoclonal antibodies for sepsis
Prostaglandin for ARDS
Statins for ARDS
Fish oil for ARDS
B-agonists for ARDS
Ketoconazole for ARDS

Phase III Explanatory RCTs
Traditional Randomized Trials

Don’t look a gift horse in the mouth...

...don’t bite the hand that feeds you.
11,312 Patients screened

- 10,511 Excluded
  - 21% Had a pulmonary-artery catheter
  - 16% Had their physician refuse
  - 14% Had chronic lung disease
  - 11% Had high risk of death within 6 mo
  - 9% Required dialysis
  - 8% Exceeded time window
  - 8% Had chronic liver disease
  - 6% Had acute myocardial infarction
  - 6% Were unable to provide consent
  - 4% Declined to give consent
  - 4% Were not committed to full support
  - 3% Had neuromuscular disease

1,001 Underwent randomization

503 Assigned to conservative fluid management
498 Assigned to liberal fluid management

0 Lost to follow-up
1 Lost to follow-up (withdrew consent before study treatment was received) and excluded from analysis

503 Analyzed
497 Analyzed

<table>
<thead>
<tr>
<th>Patients</th>
<th>Albumin Group</th>
<th>Saline Group</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>726/3473</td>
<td>729/3460</td>
<td>0.99 (0.91–1.09)</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>81/596</td>
<td>59/590</td>
<td>1.36 (0.99–1.86)</td>
</tr>
<tr>
<td>No</td>
<td>641/2831</td>
<td>666/2830</td>
<td>0.96 (0.88–1.06)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>185/603</td>
<td>217/615</td>
<td>0.87 (0.74–1.02)</td>
</tr>
<tr>
<td>No</td>
<td>518/2734</td>
<td>492/2720</td>
<td>1.05 (0.94–1.17)</td>
</tr>
<tr>
<td>ARDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24/61</td>
<td>28/56</td>
<td>0.93 (0.61–1.41)</td>
</tr>
<tr>
<td>No</td>
<td>697/3365</td>
<td>697/3354</td>
<td>1.00 (0.91–1.09)</td>
</tr>
</tbody>
</table>
$16 million / 7 years
>$10,000 per patient
Diffuse slowly into care!
Traditional Randomized Trials

• Don’t apply to patients we care for
  – Too narrow
  – Too broad

• Too expensive & difficult

• Delayed diffusion into care

• Aren’t conducted by real clinicians in real settings
  – Over-estimate benefit
  – Under-estimate harm

Angus. JAMA. 2015;314:767-768.
T0 T1 T3 T4

Identify treatments
Identify surrogate outcomes
Understand biology
Identify treatment targets

Safety in Humans
Efficacy in Patients
Implementation Into Practice

Inform biology & surrogate outcomes

vasopressors
supplemental oxygen
human serum albumin
contrastvancomycin
LR saline
piperacillin

Identify Best Treatments

Pragmatic Comparative Effectiveness Trials
Pragmatic...

<table>
<thead>
<tr>
<th></th>
<th>Explanatory Trial</th>
<th>Pragmatic Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Question</strong></td>
<td>“Can the intervention work under ideal conditions?”</td>
<td>“Does the intervention work in practice?”</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Resource-intensive ideal setting</td>
<td>Real-world clinical setting</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Highly selected, homogenous</td>
<td>Heterogeneous, limited exclusions</td>
</tr>
<tr>
<td><strong>Providers</strong></td>
<td>Highly trained</td>
<td>Representative of usual practice</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Strictly standardized &amp; enforced</td>
<td>Flexibly applied</td>
</tr>
</tbody>
</table>
...Comparative Effectiveness...
(common ICU therapies for which the effect on patients is unknown)

- Saline vs balanced crystalloids
- Albumin vs crystalloids in septic shock
- Higher vs lower SpO2 targets
- HFNC vs NIV vs COT in AHRF
- Mode of ventilation
- Restrictive vs liberal fluid management in sepsis
- Fluid responsiveness measures to guide fluid therapy
- Etomidate vs ketamine
- Rocuronium vs succinylcholine
- Sedative-first vs NMB-first
- NIV vs HFNC vs BMV
- Neuromuscular blocker vs none
- Bag-mask ventilation vs none during intubation
- “Apneic oxygenation” vs none
- Fluid bolus vs none
- Vasopressor vs none
- Bougie vs stylet
- Ramped vs sniffing position
Arbitrary Variation in Clinical Care

Patient with a common condition with at least two available therapies

Neither therapy known to be superior for the patient

 Evidence one therapy superior for the patient

Patient experiences benefits & risks of selected therapy, but knowledge is not gained and care for future patients is not improved

Therapy A

Therapy B

Benefits & Risks

Benefits & Risks

Arbitrary Variation in Clinical Care

Patient with a common condition with at least two available therapies

Neither therapy known to be superior for the patient

Evidence one therapy superior for the patient

Therapy A

Therapy B

Benefits & Risks

Benefits & Risks

Patient experiences benefits & risks of selected therapy, but knowledge is not gained and care for future patients is not improved
Structured Variation in a Clinical Trial

Patient with a common condition with at least two available therapies

Evidence one therapy superior for the patient

Neither therapy known to be superior for the patient

random

Therapy A
Therapy B

Benefits & Risks
Benefits & Risks

Patient experiences benefits & risks of selected therapy, knowledge is gained and care for future patients is improved
Clinical Care

Research

New Drugs & Devices
Existing Therapies

Results
- Too Narrow
- Too Broad
- Too Expensive
- Too Long
- Overestimate benefit
- Underestimate Harm
Common treatments for common conditions

Patients
Community Members
Community Engagement Experts
Ethicists
Researchers
Clinicians
Hospital Leaders
Quality and Safety
Implementation Scientists
Bioinformaticians
Biostatisticians
Students

Results
- Generalizable
- Representative
- Personalized
Balanced crystalloids vs saline

15,000-patient trial conducted without study personnel for $25,000
<table>
<thead>
<tr>
<th>Balanced Crystalloids</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Lactated Ringer's" /></td>
<td><img src="image" alt="0.9% Sodium Chloride" /></td>
</tr>
<tr>
<td><img src="image" alt="Plasma-Lyte A®" /></td>
<td><img src="image" alt="0.9% saline" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Na⁺</th>
<th>Cl⁻</th>
<th>K⁺</th>
<th>Ca²⁺</th>
<th>Mg²⁺</th>
<th>Organic anion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% saline</td>
<td>154</td>
<td>154</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactated Ringer’s</td>
<td>130</td>
<td>109</td>
<td>4.0</td>
<td>2.7</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Plasma-Lyte A®</td>
<td>140</td>
<td>98</td>
<td>5.0</td>
<td></td>
<td>3.0</td>
<td>+</td>
</tr>
</tbody>
</table>
Pragmatic Trial Design

- Isotonic Solutions and Major Adverse Renal Events Trial (SMART)
- Cluster-randomized, multiple-crossover trial
- Adults admitted to five ICUs at Vanderbilt

|-------|--------|--------|--------|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|

Coordination of pre-ICU crystalloid with ED and OR
Step 1
This patient has been assigned to receive LR or PLA for all isotonic fluid orders, unless a contraindication is present.

If a contraindication to LR and PLA is present, please select from the list below to order off-study IV fluid. Otherwise, please select option 1 to order LR or 2 to order PLA.

Select an option:

1. Order Lactated Ringer’s bolus
2. Order Plasma-lyte bolus
3. Hyperkalemia
4. Brain injury
5. Specific attending request
15,904 patients admitted to 5 ICUs

5 ICUs randomized to crystalloid sequence

Assigned sequence:
- odd-numbered months = balanced crystalloid
- even-numbered months = saline

Assigned sequence:
- odd-numbered months = saline
- even-numbered months = balanced crystalloid

Medical ICU
- 5,383 patients
- 22 months

Trauma ICU
- 3,413 patients
- 14 months

Surgical ICU
- 1,311 patients
- 12 months

Neurological ICU
- 2,822 patients
- 18 months

Cardiovascular ICU
- 2,975 patients
- 16 months

15,802 included in the primary analysis
- 7,860 in the saline group
- 7,942 in the balanced group
<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Balanced (n = 7942)</th>
<th>Saline (n = 7860)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – years</td>
<td>58 [44 – 69]</td>
<td>58 [44 – 69]</td>
</tr>
<tr>
<td>Men</td>
<td>4540 (57.2)</td>
<td>4557 (58.0)</td>
</tr>
<tr>
<td>Admitted from ED</td>
<td>3975 (50.1)</td>
<td>3997 (50.9)</td>
</tr>
<tr>
<td>Study ICU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>2735 (34.4)</td>
<td>2646 (33.7)</td>
</tr>
<tr>
<td>Trauma</td>
<td>1640 (20.6)</td>
<td>1688 (21.5)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1470 (18.5)</td>
<td>1501 (19.1)</td>
</tr>
<tr>
<td>Neurological</td>
<td>1440 (18.1)</td>
<td>1377 (17.5)</td>
</tr>
<tr>
<td>Surgical</td>
<td>657 (8.3)</td>
<td>648 (8.2)</td>
</tr>
<tr>
<td>Sepsis or septic shock</td>
<td>1167 (14.7)</td>
<td>1169 (14.9)</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>2094 (26.4)</td>
<td>2058 (26.2)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>2723 (34.3)</td>
<td>2731 (34.7)</td>
</tr>
<tr>
<td>Baseline creatinine – mg/dL</td>
<td>0.89 [0.74 – 1.10]</td>
<td>0.89 [0.74 – 1.10]</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>681 (8.6)</td>
<td>643 (8.2)</td>
</tr>
</tbody>
</table>

Data given as no. (%) or median [IQR]
Patients received largely the assigned fluid.
Balanced crystalloids prevented Major Adverse Kidney Events

14.3% vs. 15.4%
P = 0.04

Percent of Patients

Balanced Crystalloids

Saline

15.4%

14.3%

Persistent Renal Dysfunction

RRT

Death

P = 0.04
Design Efficiencies

1. Cluster-level designs
2. Leveraging the electronic health record
Cluster-randomized trial

**Intra-cluster correlation:** Patients are more similar to other patients in their cluster

Cluster sample size = RCT sample size $\times 1+(m-1)\rho$

Patient-level RCT $\rightarrow$ 1,000 patients
Clusters of 4 patients $\rightarrow$ 1,150 patients
Clusters of 200 patients $\rightarrow$ 9,950 patients

YOU WANT A LOT OF LITTLE CLUSTERS!
3. Cluster-crossover Trial

Challenges

• Intra-cluster correlation
• Intra-period correlation
• Temporal changes
• Carry-over (washout)
  • Patient-level
  • Provider-level

YOU WANT A LOT OF CROSS-OVERS!
Stepped-wedge trial

YOU WANT A LOT OF STEPS!
Leveraging the EHR for RCTs
How do we integrate pragmatic comparative effectiveness trials into critical care to create a Learning Healthcare System?

1. Challenge the idea that arbitrary variation in clinical care is safer than structured variation in a clinical trial

2. Develop new approaches for involving patients and community members in research when prospective informed consent is impracticable due to urgency or scale

3. Innovate approaches to embedding each step of a clinical trial within clinical care (e.g., EHR for eligibility, enrollment, randomization, delivery of the intervention, data collection)

4. Develop and apply novel clinical trial designs better suited for pragmatic comparative effectiveness research

5. Aim to understand the effects of common interventions for all patients who would be exposed to an intervention in practice & develop tools to estimate effects of interventions for individual patients rather than average effects
Thank you.
During usual care in the Vanderbilt MICU, around $60-75\%$ of IV crystalloid was saline.
During the SMART trial, around 50% of IV crystalloid was saline.
During usual care after the SMART trial, 75% of IV crystalloid was saline.
After implementation, <5% of IV crystalloid in MICU is saline.