Clinically Important Outcomes in ICU research

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Disclosures

• None
Objectives

• Raise awareness that selection of “clinically important outcomes” in clinical trials is important
• Describe practices in ICU research outcome selection
• Discuss potential solutions to help in the optimal selection of outcomes in ICU research
Why discuss outcome selection?

• Ultimate goal of clinical trials
  – Identify interventions to benefit future patients

• This goal is reached through outcome measure

Rahimi K, BMJ. 2010 Nov 1;341:c5707
Why discuss outcome selection?

• Clinical trials are often considered as the “best evidence” for patient care
  – Provide precious data for the best patient care
  – Will often be the only available data for “a long time”
Why discuss outcome selection?

• Can misled clinical practice when done wrong...
• Lengthy
• Expensive
• Expose patients to potential risks

Rahimi K, BMJ. 2010 Nov 1;341:c5707
Do all outcomes are “meaningful”? 

VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME 

The Acute Respiratory Distress Syndrome Network®
Better survival although oxygenation worse initially
Oxygenation as an outcome?

Taylor R, JAMA. 2004 April 7;291:1603

Low-Dose Inhaled Nitric Oxide in Patients With Acute Lung Injury
A Randomized Controlled Trial
Oxygenation as an outcome?

No difference for any outcome
MORTALITY AND MORBIDITY IN PATIENTS RECEIVING ENCAINIDE, FLECAINIDE, OR PLACEBO

The Cardiac Arrhythmia Suppression Trial

Debra S. Echt, M.D., Philip R. Liebson, M.D., I. Brent Mitchell, M.D., Robert W. Peters, M.D., Dulce Obias-Manno, R.N., Allan H. Barker, M.D., Daniel Arensberg, M.D., Andrea Baker, R.N., Lawrence Friedman, M.D., H. Leon Greene, M.D., Melissa L. Huther, David W. Richardson, M.D., and the CAST Investigators*
CAST trial

• Prior evidence suggested that:
  – 1) Ventricular arrhythmia = reduced survival
  – 2) Flecainide, encainide, moricizine… suppressed ventricular arrhythmia (surrogate)
High rates of premature ventricular contractions (PVCs) are predictive of sudden death after myocardial infarction. Several drugs were developed (and approved) for suppression of PVCs, with the ultimate goal of reducing death after myocardial infarction. The CAST study was initiated in 1987 with flecainide, moricizine, and encainide, which had been shown to be highly effective at reducing PVCs. At initiation of the trial, there was debate over whether it was ethical to randomize patients to placebo when the drugs had been demonstrated to reduce PVCs. In all, 2309 patients were randomized.
CAST trial

Figure 1. Actuarial Probabilities of Freedom from Death or Cardiac Arrest Due to Arrhythmia in 1498 Patients Receiving Encainide or Flecainide or Corresponding Placebo.

The number of patients at risk of an event is shown along the bottom of the figure.
Outcome selection is important

- The problem with inappropriate outcome selection is not new... The list can be long...

<table>
<thead>
<tr>
<th>Table 3. OUTCOME MEASURES IN A HYPOTHETICAL REGISTRY OF PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>Survival</td>
</tr>
<tr>
<td>Quality of life</td>
</tr>
<tr>
<td>Physiologic measures</td>
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<tr>
<td>Process of care</td>
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<tr>
<td>Cost</td>
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</tbody>
</table>

American Thoracic Society Workshop

MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

Outcomes Research in Critical Care

Results of the American Thoracic Society Critical Care Assembly Workshop on Outcomes Research

GORDON D. RUBENFELD, DEREK C. ANGUS, MICHAEL R. PINSKY, J. RANDALL CURTIS, ALFRED F. CONNORS, Jr., GORDON R. BERNARD, and The Members of the Outcomes Research Workshop

Are we better now?
Selection of endpoints in clinical research

- To determine the proportion of trials incorporating a clinically important outcome as their primary endpoint:
  - Systematic review of a random sample
  - 3 disciplines (ICU, respirology, nephrology)
  - Exclusions: studies of healthy subjects, only ped, pilot studies, interim reports, phase 1 and 2 trials, non randomized
Selection of endpoints in clinical research

- Data collected (2008 – 2013):
  - Study description
  - Eligibility criteria, Type of intervention, Funding
  - Risk of bias
  - Sample size
  - Description of endpoints
  - Type of analysis
  - …
Definition used for “clinically important outcomes”

- Mortality
- Quality of life (any type of measure of)
- Functional status (any type of measure of)
- Serious morbidity (see next slide)
Definition used for “clinically important outcomes”

- **Serious morbidity:**
  - myocardial infarction
  - deep vein thrombosis/pulmonary embolism
  - stroke
  - major infection
  - cardiac failure, dysfunction, damage or injury
  - liver failure, dysfunction, damage or injury
  - renal failure, dysfunction, damage or injury
  - respiratory failure, dysfunction, damage or injury

- Multiple Organ Dysfunction Syndrome (MODS)
- Sequential Organ Failure Assessment (SOFA)
- Risk Injury Failure Loss End stage renal disease (RIFLE) criteria
- Acute Physiology and Chronic Health Evaluation (APACHE) I, II or III
- Glasgow Coma Scale
- Child-Pugh scoring system for cirrhotic patients
- Simplified Acute Physiology Score (SAPS) II
Analysis

- Stratification by journal impact
- Exploratory analysis of trend over time
- Timing of assessment of primary clinically important outcomes
Records identified through database searching (n = 21,258)
- Critical care (n = 2,958)
- Nephrology (n = 7,296)
- Pulmonary Medicine (n = 11,004)

Records randomly excluded (n = 17,900)

Records screened (n = 3,358)
- Critical care (n = 739)
- Nephrology (n = 2,018)
- Pulmonary Medicine (n = 601)

Records excluded (n = 2,269)

Full-text articles assessed for eligibility (n = 1,089)
- Critical care (n = 339)
- Nephrology (n = 372)
- Pulmonary Medicine (n = 378)

Full-text articles excluded, with reasons (n = 368)
- 15 no randomization
- 21 more than one trial reported
- 21 ineligible discipline
- 38 pilot study
- 46 subgroup analyses
- 15 post-hoc analyses
- 22 phase II trials
- 9 preliminary reports
- 33 healthy populations
- 46 follow-up studies
- 43 found eligible after target number of articles was reached
- 25 irrelevant
- 34 duplicates

Studies included for review (n = 721)
- Critical care (n = 242)
- Nephrology (n = 239)
- Pulmonary Medicine (n = 240)
## Description of studies

<table>
<thead>
<tr>
<th></th>
<th>Critical Care n = 242</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Journal category</strong></td>
<td></td>
</tr>
<tr>
<td>&quot;Top 5&quot;</td>
<td>81 (34)</td>
</tr>
<tr>
<td>&quot;Top 5&quot; specialty</td>
<td>83 (34)</td>
</tr>
<tr>
<td>Other</td>
<td>78 (32)</td>
</tr>
<tr>
<td><strong>Study Location</strong></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>50 (21)</td>
</tr>
<tr>
<td>Canada</td>
<td>19 (8)</td>
</tr>
<tr>
<td>Europe</td>
<td>134 (55)</td>
</tr>
<tr>
<td>Australia/NZ</td>
<td>16 (7)</td>
</tr>
<tr>
<td>Asia</td>
<td>29 (12)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (5)</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>111 (46)</td>
</tr>
<tr>
<td>Device</td>
<td>73 (30)</td>
</tr>
<tr>
<td>Drug + Device</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>57 (24)</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td></td>
</tr>
<tr>
<td>Single Centre</td>
<td>105 (43)</td>
</tr>
<tr>
<td>Multi-Centre</td>
<td>98 (41)</td>
</tr>
<tr>
<td>Unclear</td>
<td>39 (16)</td>
</tr>
<tr>
<td><strong>Funding</strong></td>
<td></td>
</tr>
<tr>
<td>Industry</td>
<td>40 (17)</td>
</tr>
<tr>
<td>Government</td>
<td>34 (14)</td>
</tr>
<tr>
<td>Non-governmental organization</td>
<td>34 (14)</td>
</tr>
<tr>
<td>Multiple funding sources</td>
<td>50 (21)</td>
</tr>
<tr>
<td>Unclear</td>
<td>84 (35)</td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
<td></td>
</tr>
<tr>
<td>Total number of patients</td>
<td>151,576</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>105 (46, 304)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>626 (4,807)</td>
</tr>
</tbody>
</table>
Outcomes reported

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total n = 721</th>
<th>Critical Care n = 242</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Clinically Important Outcome</td>
<td>551 (76)</td>
<td>172 (71)</td>
</tr>
<tr>
<td>Any Clinically Important Outcome as primary</td>
<td>349 (48)</td>
<td>116 (48)</td>
</tr>
<tr>
<td>Reported mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>As single primary outcome</td>
<td>146 (20)</td>
<td>64 (26)</td>
</tr>
<tr>
<td>As co-primary outcome</td>
<td>64 (44)</td>
<td>34 (53)</td>
</tr>
<tr>
<td>As part of composite outcome</td>
<td>41 (28)</td>
<td>25 (39)</td>
</tr>
<tr>
<td>Reported serious morbidity</td>
<td>232 (32)</td>
<td>72 (30)</td>
</tr>
<tr>
<td>As single primary outcome</td>
<td>109 (47)</td>
<td>34 (47)</td>
</tr>
<tr>
<td>As co-primary outcome</td>
<td>90 (39)</td>
<td>32 (44)</td>
</tr>
<tr>
<td>As part of composite outcome</td>
<td>33 (14)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Reported functional status</td>
<td>25 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>As single primary outcome</td>
<td>12 (48)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>As co-primary outcome</td>
<td>11 (44)</td>
<td>0</td>
</tr>
<tr>
<td>As part of composite outcome</td>
<td>2 (8)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Reported quality of life</td>
<td>21 (3)</td>
<td>0</td>
</tr>
<tr>
<td>As single primary outcome</td>
<td>7 (33)</td>
<td>0</td>
</tr>
<tr>
<td>As co-primary outcome</td>
<td>14 (66)</td>
<td>0</td>
</tr>
<tr>
<td>As part of composite outcome</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Patient reported outcomes

![Graph showing the proportion of studies (%)](image-url)
Trend Over time

Proportion of studies (%)

Any clinically important outcome
Clinically important outcome reported as primary

Year

- Any clinically important outcome: $p = 0.28$ for linear trend
- Clinically important outcome reported as primary: $p = 0.27$ for linear trend
Timing of assessment

- Immediate: ≤ 7 days
- 8 - 30 days
- 1 - 3 months
- 3 - 6 months
- 6 - 12 months
- 12 months or more

Proportion of studies (%)
Impact on publication?

The bar chart shows the proportion of studies (%)

## Proportion of studies (%)

- **Top5 General Journals**
  - Any clinically important outcome
  - Clinically important outcome reported as primary

- **Top5 ICU Journals**
  - Any clinically important outcome
  - Clinically important outcome reported as primary

- **Other**
  - Any clinically important outcome
  - Clinically important outcome reported as primary
Interpretation

• At least a third of ICU clinical trials don’t report a “clinically important” outcome
  – Less than 50% of the time as primary
  – When reported, most of the time short-term

• No change over 15 years

• Patient reported outcome rarely reported
What now?

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Factors considered to select an outcome

• Appropriateness of outcomes with the trial objectives
• Objectivity of the outcome
• Internal validity
  – Measures what it is intended to measure
Factors considered in choice of outcomes

• Reproducibility
  – External validity
• Availability as part of routine care?
• Feasibility
• Efficiency (time, cost)
Challenge!

All Possible Outcomes

Resource Limitations
Recommendations?

• Use a two-step approach?
Principle 1

- Should we agree to a minimum set of outcomes in clinical research?
  - And use a systematic and methodical approach to identify them
Principle 2

• Solicit input from stakeholders
  – Has to remain realistic
  – Help prioritize
  – Help select the most appropriate outcome given social, ethical, financial or other issues…
What now?

• As clinicians:
  – In addition to usual “methodology assessment” of clinical trials
    • Consider how important the outcome is for everyone involved
    • Should we focus practices changes on trials with “clinically important outcomes”?
What now?

• As a researcher:
  – Despite very limited resources and increased complexity of conducting trials, importance of careful outcome selection
    • Patient-oriented
    • Practice changing
    • Input from stakeholders
  – Work towards minimal outcomes in ICU clinical research?
First trial by James Lind (1747):

Population: 12 sailors, 6 pairs

Interventions (same diet):
1) Cider vs 2) sulfuric acid vs 3) vinegar vs 4) sea water vs 5) oranges and lemon vs 6) barley water

Outcome: Scurvy yes/no

Clinically important outcome!

Result?
Group 5 cured
Some improvement in group 1